Excessive crying in children with cerebral palsy and communication deficits - a fixed-sequence, crossover clinical trial

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Research Article

Keywords: childhood-onset dystonia, dysphagia, hyperalgesia, muscle spasticity, neuropathic pain

Posted Date: June 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1666292/v2

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Abstract

**Aim:** To study epidemiology, response to drug therapy, and a drug taper after 250 days of treatment of excessive crying in children with cerebral palsy with communication deficits (ECCCPCD). **Methods:** This was a fixed-sequence crossover study of 131 consecutive subjects <15 years with >7.5 hours crying duration/day for 30 straight days. Outcome measures were epidemiological data, measurement of means of total and unexplained ECCCPCD durations (TECCPCD and UECCPCD) while on the placebo (M1), while on treatment (M2-M5), and the effect of a drug taper (M4). **Results:** 74% were <2 years; 65% were males. Paired t-tests between TECCPCD of M1-M2 yielded a mean difference of -3.67 (95% CI -3.80 to -3.53), p<0.001; between UECCPCD of M1-M2, -3.04 (95% CI -3.16 to -2.93), p<0.001. Wilcoxon tests between TECCPCD of M1-M5 yielded medians of 9.98 (95% CI 9.73 to 10.16) and 2.67 (95% CI 2.53 to 2.82), p<0.001. Wilcoxon tests between UECCPCD of M1-M5 yielded medians of 8.22 (95% CI 8.02 to 8.39) and 2.16 (95% CI 2.04 to 2.28), p<0.001. The dosage could be tapered in 51.15% of participants. **Conclusions:** Treatment of spasticity, dystonia, visceral, and neuropathic pain reduced crying. The drug requirement was less after 250 days of treatment.

Keynotes

- Pain/discomfort is an under-suspected/underdiagnosed cause of Excessive Crying in Children with Cerebral Palsy and Communication Deficits (ECCCPCD).
- Delay in making an etiopathologic diagnosis and instituting appropriate treatment results in a vicious cycle of spasms-pain-spasms.
- Treatment of spasticity, dystonia, visceral, and neuropathic pain reduced crying. The drug requirement was less after 250 days when the vicious cycle of spasm-pain-spasm was broken.
- Parents/caregivers reported improvement in dysphagia/drool when ECCPCD was treated.

A. Introduction

**Background:**

Cerebral Palsy (CP) can be diagnosed in the first year[s] of life. Comorbidities are frequent in CP: Among children with CP, 3 in 4 (75%) are in pain; One in 2 (50%) has an intellectual disability; One in 4 (25%) cannot talk. The prevalence of co-existing disorders often varies with the severity and type of cerebral palsy. Older children with CP who could communicate reported that pain was due to many comorbidities besides spasticity and dystonia (Table. 1).

Muscle spasm leads to ischemic pain, which in turn exaggerates spasms resulting in a vicious cycle.

**Acute pain** [and following crying] draws the caregiver’s attention to an area of injury to seek Medicare for healing. Diagnosis and management of nociceptive pain at the earliest are essential because, unlike touch, pain does not develop tolerance. Untreated, under-treated, or mistreated acute pain lowers the threshold to both noxious and non-noxious stimuli and may lead to chronic pain states by hypersensitization. Chronic pain is disabling and results in chronic dysfunction rather than healing. Adaptive plasticity can be misdirected or unadapted, thus becoming counterproductive and harmful. Neuropathic pain is a typical example of “unsuccessful” cortical plasticity. Deranged plasticity in the primary motor and sensory cortices causes dystonia, chronic pain, and hyperreflexia. Plasticity occurs in both the central [brain and spinal cord] and peripheral nervous systems. Pain disrupts structural and functional brain connectivity, which can be restored with effective treatment. Since several neural pathways carry pain sensation; neurosurgical interruption of a single pathway is unlikely to alleviate pain. Invasive procedures are not effective beyond a sham in chronic pain. So, the treatment of choice is medical. Currently, evidence-based neuropathic pain treatment options include anti-epileptic drugs, anti-depressants and gabapentanoids. Their impacts are partial.

Excessive crying in infants is a challenge. Identifying the cause of Excessive Crying in Children with Cerebral Palsy and Communication Deficits [ECCCPCD], either because of their age or global developmental delay/profound intellectual retardation, is more challenging. It is difficult to distinguish discomfort, pain, and distress in such children.

The interaction of the sensory and emotional aspects of pain may lead to hypersensitivity and hyperalgesia. A variety of sleep disorders may be associated with pain.

Pain and distress, if not diagnosed in time, result in suboptimal management.

Pain treatments in children who cannot communicate are frequently hit or miss or trial & error, or not offered. This has an impact on the quality of life of both the child and their families.

Our study is an attempt to improve the quality of life of excessively crying children with CP and their families because knowing the likely etiology, and the treatment reduces a parent’s anxiety and distress.
Hypothesis:

It was hypothesized that,

1. ECCCPCD may be caused by pain/discomfort due to multiple causes at multiple levels like visceral hyperalgesia, neuropathic [which includes peripheral and central] pain in addition to spasticity, and dystonia of skeletal muscles [Table. 1].

2. Treatment of pain/discomfort may reduce ECCCPCD.

3. The vicious cycle of spasm-pain-spasm induced by hypertonia [Table. 1] may disappear after a few months of successful treatment. So, it may be possible to reduce the dosages.

Objectives:

To study

1. the epidemiologic data (age, sex), the Gross Motor Function Classification System [GMFCS] levels, and the Modified Ashworth Scale [MAS] scores (to be recorded after excluding the factors aggravating the MAS) of ECCCPCD. The GMFCS levels and MAS scores recorded at the time of enrollment shall be used for the study.

2. The response of participants with ECCCPCD, to oral drug treatment based on
   a. the predominant subtype of CP,
   b. presumed etiology & pathophysiology of pain/discomfort,
   c. clinical findings,
   d. ElectroEncephaloGraphy [EEG],
   e. neuroimaging,
   f. mechanism of action of the drug,
   g. associated problems,
   h. side effects of the drug,
   i. and allergies.

3. The response of ECCCPCD to reducing the drug by 5% weekly from the 251st day until the cry duration started increasing.

4. Additional observations, if any, volunteered by the caregivers [secondary outcomes].

B. Participants And Methods

Trial design:

This clinical trial was a single-Center, interventional, placebo-controlled, two-period, two-treatment, fixed-sequence crossover study. It was double-blind for the initial 110 days and was followed by open-label for the next 290 days, [Figure. 1, Figure. 2.].

Inclusion criteria:

A child with cerebral palsy under the age of 15 years and could not communicate the reason for excessive crying because of young age or global developmental delay/profound intellectual retardation. The inclusion criteria in detail are shown in Table. 2.

Exclusion criteria:

1. Medicines used in the study were used in the previous 30 days, and it was impossible to taper off the drugs without worsening of symptoms.

2. Excessive crying due to known causes.


Participants:

One hundred and thirty-two consecutive participants were enrolled. One participant was lost to follow-up due to death caused by accident [Figure. 2]. One hundred and thirty-one participants aged <15 years of both sexes from various states of India [109], countries from the Middle East [13], and the far east [9] completed the study.

Settings and location:
All the caregivers sought treatment in XXX Clinic, India, when other doctors, caregivers, the staff of physiotherapy centers and institutes for the empowerment of people with intellectual disabilities referred the participants when symptomatic treatment, rehabilitation therapy, and other strategies to reduce crying did not give relief. Participants and caregivers were not given any incentive for participating.

The study period was from December 7, 2005, to August 4, 2020.

**Interventions:**

*The Placebo:*

The placebo contained fructose powder. The pharmacist prepared medicines and placebo, which were identical in quantity, color, and packing (white, red, green, yellow, blue, gray, black, striped red/white, and blue/white wrappers).

**Placebo period:**

Placebo period was used not only to confirm the diagnosis of the etiology of crying and collect the baseline data but also to confirm that the study criteria were satisfied, there were no placebo responders, the subject was not receiving any unnecessary drugs (like vitamins without any indication or medicines prescribed by other systems’ practitioners like Homeopathy, Ayurveda, Unani, etc.) This was done to avoid any interference/interaction with the study results.

**Medication:**

Phase of clinical research:

This was a phase IV study. To avoid unethical issues and protect our subjects, only the drug[s] that would have been prescribed even if the child had not been enrolled into the study was/were prescribed. No necessary drug was refused, and no unnecessary drug was administered to any subject at any stage of the study. If a child received the medicines used in the study in the previous 30 days, and it was impossible to taper off the drugs without worsening of symptoms, the child was treated and excluded from the study.

Ethical choices, between one good and another good (not between good and evil), were made in the best interest of the subject to protect them from long-term consequences of decisions in which they did not participate. Due to the importance of work in human studies and the need to preserve the life and safety of participants, all the drugs that were used in this study were picked up from drugs that are already being used in pediatrics for decades. All subjects received only the drugs they needed as per the accepted indications. Their parents/caregivers were informed of the reason for using the particular drug and the expected response and side effects. Oral medication was used for reducing hypertonia and hypothesized pain/discomfort caused by excessive stimulation of nociceptors/visceral hyperalgesia/smooth muscle spasms/neuropathic pain. The drugs included baclofen, diazepam, clonazepam, trihexyphenidyl, tetrabenazine, gabapentin, topiramate, lamotrigine, and amitriptyline. Antiepileptic drugs were added for epilepsy.

**Study Algorithm [Figure. 1, Figure. 2.]:**

‘Placebo Run-In Period’ [PRIP] lasted 15 days [-R14-R0]. The caregiver was trained for five hours by an experienced nurse on the first two days [-R14 & -R13] to measure the cry duration accurately. They were educated regarding the possibility of any clinically unobvious noxious stimuli [like yawning, transferring, touching with a hand or a bed cloth] increasing ECCCPCD. During the last two days of the run-in period [-R1 to R0], the cry duration was measured by the caregivers sitting in a side room. Their accuracy of measurement, reliability, and compliance was checked by a research nurse watching through a closed-circuit television/web camera. A notice was displayed in the clinic that the clinic was under video surveillance.

The reasons for using PRIP are shown in Table. 3.

A senior pediatric neurologist (>25 years teaching and consultancy experience at the beginning of the study) screened the participants for eligibility for the study.

The participant dropout risk was minimized by explaining the possible side/overdosage effects [Table. 4], reviewing monthly & as and when necessary. A doctor’s emergency contact phone number was provided.

The drugs, their dosage adjustments [Table. 4] and the sequence of medications used [Table. 5] to reduce crying were guided by the predominant subtype of CP, presumed etiology & pathophysiology of pain/discomfort, clinical findings, EEG, neuroimaging, mechanism of action of the drug, associated problems, side effects of the drug, and allergies [Table. 4]. When there was no clinical lead [like spasticity, dystonia, or seizures], but Magnetic Resonance Imaging [MRI] showed damage to the basal ganglia, thalami, perisylvian area, insula, or putamen, “gabapentin,” or “topiramate,” or “lamotrigine,” or “amitriptyline” was used in that order because visceral hyperalgesia or neuropathic pain were the possibilities causing ECCCPCD. Gabapentin was used in young infants because it has already been used for visceral hyperalgesia (which is not rare in infants). When gabapentin failed in older infants, topiramate was used empirically because it has multiple mechanisms of action in controlling neuropathic pain [Table 4]. Lamotrigine was the next choice because it acts only on sodium channels to control neuropathic pain. Though amitriptyline is effective for neuropathic pain, it was the last to be used because experience with the drug in
children is minimal. Caregivers were advised to inform the doctor if they were taking any other drug for any other problem. Caregivers were also advised not to stop the medicine suddenly.

Drugs were used either singly or in combination. The lowest dose that elicited the optimal response was used. From the 251st day of treatment, the dose was reduced by 5% weekly until ECCPCD started to increase. This dose was maintained until the subsequent measurement between T-311 and T-320. Then the dosages were adjusted as necessary. Drug adverse effects were recorded [Table. 4].

Treatments by all other specialists [orthopedic surgeons, gastroenterologists, physiotherapists, etc.] were continued during the study period.

Investigations:
All participants had a structural MRI scan of the brain before enrollment. EEG was planned if seizures were clinically diagnosed/suspected.
All participants were followed up until the completion of the study.

Outcomes:

Primary outcomes:
1. Epidemiologic data, the GMFCS levels, the MAS scores were noted.
2. Caregivers measured both Total and Unexplained ECCPCD [TECCPCD and UECCPCD] durations with a digital watch or a mobile phone in hours: minutes: seconds over five ten-day periods. MM1 was while on placebo days 6-15 [P6-P15], and four measurements MM2 to MM5 while on treatment days 61-70 [T61-70], 241-250 [T241-250], 311-320 [T311-320], and 351-360 [T351-360]. The statistician calculated one day’s mean/median values of M1 to M5 for statistical calculations. Total cry duration had the suffix ‘t,’ and unexplained cry duration had ‘u.’

Secondary outcomes:
Any other changes observed during the study period were reported by the caregivers.

Sample size:
127 participants were required for this study [probability= 90%, for a 2-tailed 0.05 significance level, if the true difference between treatments= 0.41 units, based on the assumption that the within-patient standard deviation of the response variable= 1]. So, it was planned to enroll 140 participants for the study to compensate for dropouts.

Enrollment:
The sample was based on consecutive clinical enrollment.

Blinding:
As it is well known, the best and most reliable form of research is a double-blind, placebo-controlled study that would eliminate the power of suggestion and prevent bias when patients’ outcomes are evaluated thereby improving the reliability of clinical trial results.

Our study was double-blind initially for 110 days until the 70th day of treatment [Figure. 1, Figure. 2]. The caregiver of the participant was unaware of the drug(s) and other participants’ details. There was no contact between the research nurse, the pharmacist preparing the medicines, and the outcome data collecting nurse. None of them knew the drug or drug combination and the dosage.

Later, it was an open-label study for 290 days because double blinding for the total period of 400 days may not serve any additional purpose. The open-label part of this study is like open-label extension studies reported by many.

Consent:
Informed consent was obtained. The parents [who had the authority and competency] were given information about the problem their child has, expected benefits and risks, and the likelihood (or probability) that the benefits and risks would occur with the particular treatment or test [in a language and terminology they could understand] to let them decide whether to let or not let their child undergo the treatment, procedure or any test that may be
necessary. They were informed about the approximate cost of drug therapy for the open-label part of the study lasting 290 days. They were informed about the availability of alternative treatments, procedures, or tests and their relative benefits and risks. They were also informed about the consequences of refusing the test, procedure, or treatment. They were specifically informed that they have the right to make decisions about the treatment and tests and the decision to enter the study is voluntary without coercion or duress and can leave the study any time if they so desired.

Written consent was signed by the parent/s/caregivers and the doctor and a copy was given to the parent/s/caregivers before the study initiation.

**Complying with Ethics of Experimentation:**

The study protocol was reviewed and approved by the ethics committee of XXX, and the clinical trial was registered retrospectively.

**Statistical methods:**

One hundred and thirty-one participants who completed the study were analyzed. Summary statistics were calculated for all measurements.

A 2-tailed p-value of <0.05 was considered statistically significant. Data were given as mean/median with Confidence Intervals [CI].

Epidemiological data were analyzed. GMFCS level and MAS scores recorded at the time of enrollment were used for the analysis.

Box and Whisker plots and scatter diagrams with heat maps & trend lines of TECCPCD and UECCPCD while on placebo versus treatment for various periods were drawn. The Shapiro-Wilk test was used to check the normal distribution of the results. Paired t and Wilcoxon's signed-rank tests for paired samples were done to compare continuous variables between the two groups, assuming no sequence effect, no carryover effect, and no period effect. MedCalc v19.4.1 64-bit was used for statistical analysis.

**C. Results**

Out of a total of 7561 children with cerebral palsy screened, 260 [16.1%] satisfied the inclusion criteria [Figure. 2, Figure. 3]. Participants excluded from the study as per exclusion criteria were 1355 [Table. 6].

Participant flow is shown in Figure. 1 and Figure. 2. Two hundred and sixty participants were enrolled; 128 [49.23%] were excluded during the PRIP. The reasons for exclusions were symptom instability [59], noncompliance to placebo administration on time [32], noncompliance to data collection [22], placebo responders [9], missed appointments without any explanation, and resulting lack of data [6].

One hundred and thirty-two subjects entered the study. One participant died in an accident during the washout period. One hundred and thirty-one participants completed the study. Losses and exclusions, along with reasons at various stages, are illustrated in Figure 2, Figure. 3, and Table. 6.

Recruitment was from December 7, 2005, to June 21, 2019.

**Time frame:**

Three hundred eighty-five days, excluding the run-in period of 15 days.

**Outcomes:**

**Primary Outcomes:**

**Data:**

Epidemiological data are presented in Table 7 and Figure. 4. Results are summarized in Table. 8.

**Secondary outcomes:**

Caregivers volunteered about improvements in swallowing and drooling [Table. 9].

**Statistical analysis:**

**Primary outcomes:**
Epidemiological data: [Figure 4]. 74% were <2 years. Males were more affected. 85 (65%) were male and 46 (35%) were female. GMFCS levels affected were V [63.36%] and IV [36.64%]. MAS scores varied from 0 to 4. TECCCPCD and UECCCPCD were obtained [Figure 5, Figure 6] Summary statistics of M1 to M5 of TECCCPCD and UECCCPCD, including effect sizes, and their precision [95% CI], the medians and data distributions through their quartiles and outliers of various means at different periods [Table 8, Figure 5, Figure 6, A to F], epidemiological data [Figure 4], GMFCS levels [Figure 4, B], MAS scores [Figure 4, C], GMFCS levels versus MAS scores [Figure 4, D], the Shapiro-Wilk test results, paired t, and Wilcoxon tests [Table 8] are presented. Treatment was associated with a significant reduction in the mean/median of TECCCPCD and UECCCPCD [p = <001].

Response to drugs:
The number of participants who responded to each drug is illustrated in Table 5.

EEG was done on 16 participants. Nine had epileptic [infantile] spasms & seven had Lennox-Gastaut syndrome with tonic seizures. They required the addition of appropriate treatment, and then ECCPCD responded.

35 [26.72%] very young participants without obvious hypertonia who had perisylvian, thalamic/basal ganglionic damage responded to “gabapentin,” “topiramate,” “lamotrigine,” “amitriptyline.” Adding “baclofen” or “trihexyphenidyl” on suspicion alone before spasticity or dystonia appeared clinically reduced ECCPCD in 11 [8.4%] participants. When hypertonia clinically appeared in 22 participants, it was treated.

Dose reduction:
When the dose was reduced up to 30%, 51.15% [67/131] continued to improve [Figure 7, A], but 48.85% [64/131] worsened [Figure 7, B]. Five-percent dose could be reduced in 25 participants [19.08%], 10% in 17 [12.98%], 15% in 9 [6.87%], 20% in 7 [5.34%], 25% in 5 [3.82%], and 30% in 4 [3.05%]. More than 30% reduction of doses worsened all participants. Therefore, the drug taper was stopped at 30%.

Three participants had ECCPCD on touching or covering with a bed cloth.

Secondary outcomes:
61.83% [81/131] had dysphagia [Figure 8, A]. Of them, 61.73% [50/81] responded to treatment [Figure 8, B]. 67.18% [88/131] had drool [Figure 8, C]. Of them, 63.64% [56/88] responded to treatment [Figure 8, D].

Adverse effects:
Three participants had adverse effects; one had skin rashes with lamotrigine at a dose of 7 mg/kg/day. Skin rashes are caused by a hypersensitivity reaction to lamotrigine. So, lamotrigine was withdrawn. One participant was sleepy with baclofen at a dose of 2 mg/kg/day. Reduction of the dose to 1.5 mg/g/day solved the sleepiness problem. Another participant had anhidrosis and heat intolerance with trihexyphenidyl at a dose of 0.6 mg/kg/day. The side effects disappeared when the dose was reduced to 0.4 mg/kg/day.

D. Discussion
The study design:
All subjects were in a single group and received the placebo initially followed by the drug therapy [Figure 1, Figure 2.]. The single group functioned as the control group initially [during the placebo period] and as the experimental group [during the treatment period] later.

Reasons for not using randomization in this study:
The treatment arm had to be long (360 days) to achieve the full effect of the drug(s) used because many drugs used in the study required many weeks to months of treatment to show their efficacy in resolving the problem of crying. Using the placebo for such a prolonged period in the control group is unethical. So, the placebo arm period and the treatment arm period had to be unequal. Withdrawing drug therapy in one group after an initial 15-day period and giving the placebo for 360 days would make the study unreliable and unethical. It would be unreliable because the full drug effect cannot be attained in 15 days. It would be unethical because it would increase the suffering and the resultant crying of the subjects, and all subjects in the group would then drop out of the study. Therefore, the fixed-sequence crossover study which has only one group and so does not require randomization to two groups, and does not require any withdrawal of drug therapy for the study’s sake, once started, was used.

Addressing potential weaknesses of crossover design:
Potential weaknesses of crossover design were addressed. Carryover and sequence effects were unlikely because of the prolonged washout period of ten days (144 times the necessary period). The period effect was eliminated by including only CP [a static encephalopathy] cases undergoing treatment. The observation that the drug dose could be reduced with continued improvement in 51.15% [Figure. 7, A] also excluded a period effect. This study's other strengths include blinding study treatments for the initial 110 days and crossover design, where participants were exposed to both treatments in similar health states. A crossover design allowed for detecting differences not confounded by differences in health states and for each participant to act as his own control.

**Reasons for changing from double-blind study of 110 days to open-label study for the next 290 days:**

i. Participants had to travel long distances from other states and countries spending a lot of money and time to collect drugs. This would increase the dropout rate.

ii. The cost of drugs and logistics of double-blinding was too expensive to continue double-blinding because it was an unfunded study.

iii. by the end of 110 days of study (70 days of treatment), the treatment was finalized and the response to treatment was clear to both parents/caregiver and the doctor. So, continuing double-blinding would not have served any additional purpose.

**Addressing the negative aspect of the open-label period which followed a double-blind period:**

The open-label part of this study is like open-label extension studies reported by many. They are useful and legitimate if the open-label extension study is designed, executed, analyzed, and reported competently.

The negative aspect of the open-label extension study (that it may be used as a significant marketing tool) can be safely excluded in this study because the drugs used in this study have been in the market for many decades.

**Additional reasons:**

Additional reasons for choosing this design are shown in Table. 10.

**Frequencies**

Managing known causes and provoking factors of spasticity reduced crying in most cases [Table. 6]. ECCPCD was more frequent than progressive encephalopathies with excessive crying. ECCPCD was more frequently because of known causes rather than unknown causes.

**Infancy**

Derangements in evolving plasticity [Table. 1] may be responsible for the higher frequency (74%) of pain and ECCPCD in infants. Since the inhibitory nervous system develops later than the afferent excitatory system, infants probably experience more intense pain than children.

**Epidemiology**

The male preponderance [1.848:1] is higher than that of CP [1.41:1] and maybe partly because of the better attention male babies get in these regions. This contrasts with another study where girls (age range-4-18 years) reported pain with a higher frequency and intensity than boys. Whether this is related to the sex-dependent differential nervous system maturation has to be investigated.

Only GMFCS levels IV and V had ECCPCD. It indicates that the more damage to the brain, the higher the risk of ECCPCD. Increased frequency and severity of pain have been reported in children with more extensive disability. Both GMFCS levels (IV and V) had variable MAS scores indicating that all MAS scores are associated with ECCPCD and are probably because of the occurrence of ECCPCD in all subtypes. This is expected because GMFCS is indeed a classification though MAS not, since it is influenced by other factors such as pain and is not a classification or a "state."

**Treatment effect:**

Treatment was associated with a significant reduction in the means/medians of TECCPCD and UECCPCD \( p < 0.001 \) [Table. 8]. To conclude that this decrease was due to the medicine[s], we have to use auxiliary data, information, and assumptions.

Because the placebo was given to the participants and the TECCPCD and UECCPCD recordings were made by the caregivers, endorphin-mediated relief can be excluded. Additionally, placebo responders were excluded during the PRIP itself.
Highly significant p-values quantified the effect size, and the joint distribution while on placebo versus treatment confirmed the precision/significance of the trial [Table. 8, A. B and C, Figure. 5, Figure. 6, A-F]. Scatter diagrams of TECCCPCD and UECCCPCD demonstrated the highly significant effects of the treatment and its distribution [Figure. 6, A-F]. Box plots and scatter charts showed homogeneous distribution of results in all measurements except clustering into different groups at 61-70 days [Figure. 5, Figure. 6, A and B]. Clustering probably suggested the necessity for better drug selection and dosage titration during the first 70 days of treatment in 35 [26.72%] participants who did not have hypertonia or seizures at the time of enrollment.

Though in this crossover trial, the groups were truly comparable in all aspects, including a genetic perspective, because of the long period of the study, the ambient temperature at the time of measurement would have been different for different participants recruited at different periods. However, because the study lasted 385 days [plus a 15-day run-in period], every participant went through all seasons, and the child was exposed to the same weather changes before and during the study. So, it is unlikely that the weather would have affected ECCPCD.

**Comparison with the earlier study:**

ECCPCD, which responded to hypertonia treatment, was reported in 1998 [Figure. 3, data B]. The percentage of children with ECCPCD among CP and its subtypes are almost the same in the present study [3.44%] compared to the 1998 study [3.28%] [Figure. 3, data B], except its higher incidence in dyskinetic type in the present study [5.5% versus 4.98%].

**Drug indications:**

Baclofen, diazepam, and clonazepam were frequently useful probably because they act for both spasticity and dystonia. Trihexyphenidyl and tetrabenazine were useful for ECCPCD associated with dystonia.

Relief of ECCPCD after the addition of antiepileptics in sixteen participants suggested that infantile spasms/tonic seizures aggravated them. The higher frequency of infantile spasms/tonic seizures in our study maybe because of the frequent requirement of specialist management for their control.

Gabapentin was used in neonates to treat agitation and refractory pain, including visceral pain. In the present study, the response of 26.72% of very young participants, without hypertonia, with perisylvian or thalamic or basal ganglionic damage, to “gabapentin,” “topiramate,” “lamotrigine,” “amitriptyline.” suggested that visceral hyperalgesia with abdominal pain or injury to neural pathways was responsible for their pain/discomfort. The necessity to add baclofen/diazepam/trihexyphenidyl before spasticity or dystonia appeared clinically in 8.4% of cases suggested unnoticed/undiagnosed spastic or dystonic spells.

**Dose reduction after breaking the vicious cycle of spasm-pain-spasm.**

The dose could be reduced with continued improvement in 51.15% [Figure. 7, A]. This observation excluded a period effect. An increase in ECCPCD when the dose was decreased in 48.85% of participants [64/131] indicated that drug treatment was responsible for the improvement. Therefore, the crossover design was justified because of the transient effect of drugs. The dose could be tapered only up to 30% from 251 to 310 days in 51.15% without worsening, which probably,

1. excludes the impact of a period effect [hypotonia evolving into hypertonia, development of dystonia, or development/maturation of the nervous system].
2. indicates the spasm-pain-spasm vicious cycle's resolution, which reduced the dose required to stop spasms and the resulting ischemic pain.

Because treatment by all other specialists [orthopedic surgeons, gastroenterologists, physiotherapists, etc.] was continued, it may be argued that the improvement in ECCPCD maybe because of their treatment. ECCPCD decreasing with drug therapy, increasing with dosage taper, and decreasing again with an increase in dosages [Figure. 7, B, Table.8, C] excludes all other crying causes, including the possibility of all other specialist treatments.

**Allodynia:**

ECCPCD on touching or covering with a bed cloth suggesting allodynia [evidence of neuropathic pain, central or peripheral] responded to gabapentin.

**Dysphagia and drool:**

The response of dysphagia to baclofen is known. Insufficient relaxation of the cricopharyngeal muscle is an important cause of dysphagia, which responds to oral baclofen. Baclofen reduces gastroesophageal reflux episodes by decreasing the number & the duration of attacks and the frequency of the lower esophageal sphincter's transient relaxation.

Dysphagia, feeding problems, and drooling are frequent in CP. The response of dysphagia to trihexyphenidyl/tetrabenazine suggested that the dystonia was probably the cause of dysphagia. Transfer dysphagia responds to trihexyphenidyl/tetrabenazine. Trihexyphenidyl also controlled drool, resulting from dysphagia or lack of lip control, or excessive secretions.
Chromically experiencing pain disturbs sleep and initiates depression and anxiety. All the drugs used here have an anxiolytic effect. Whether this [side] effect also contributed to the reduction of ECCCPCD is debatable.

**Adverse reactions:**

Side effects were seen in three participants [3/131 participants, 2.29%]. The offending medicine was changed [lamotrigine], or the dosage was reduced [baclofen, trihexyphenidyl], and treatment continued.

**The Limitations of the study**

The limitations of the study are presented in Table. 11. All these limitations are unlikely to be significant because both p-values, data, their CI, and distribution show very high significance both statistically and clinically [Table. 8, Figure. 5, Figure. 6, A-F].

**E. Conclusions**

After excluding known causes of crying, ECCCPCD must be suspected when GMFCS levels are high [IV and V].

The oral drugs and their order of usage depend on the predominant subtype of CP, presumed etiology & pathophysiology of pain/discomfort, clinical findings, EEG, MRI, mechanism of action of the drug, associated problems, side effects of the drug, and allergies. For preterm babies, spasticity or MRI evidence of periventricular leukomalacia, "baclofen" "benzodiazepines" are useful, and for dystonia, "baclofen" "benzodiazepines" "trihexyphenidyl" "tetrabenazine" in that sequence. The antiepileptic of choice must be added for seizures. When there is no clinical lead to guide drug selection, or MRI shows damage to the basal ganglia, thalami, perisylvian area, insula, or putamen, "gabapentin," "topiramate," "lamotrigine," "amitriptyline." must be used in that sequence because visceral hyperalgesia/neuropathic pain is the likely cause. They probably reduce pain/ discomfort and, consequently, ECCCPCD.

Dysphagia and drooling in some cases respond to the same treatment.

Relief from ECCCPCD improves the life of the participant, its caregiver, and the family.

Cry intensity was defined for this study. However, even lesser cry intensities/durations can be treated with the same drugs.

These results can be extrapolated to treat excessive crying in progressive encephalopathies because the pathophysiology of crying is likely to be the same.

**Declarations**

**F. Funding/Support:**

No funding was secured for this study.

**G. Conflict of interest:**

No conflicts of interest.

**References**


38. David Schoenfeld PD. Statistical considerations for a cross-over study where the outcome is a measurement USA2020 [Available from: http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html.


Tables
Table 1. Etiology, pathogenesis, and treatment.

A. Etiology of Pain in CP

<table>
<thead>
<tr>
<th>A. S.No</th>
<th>B. Causes</th>
<th>C. Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Types</td>
<td>Pain can be nociceptive, visceral, neuropathic, or central.</td>
</tr>
<tr>
<td>2</td>
<td>Hypertonia</td>
<td>Hypertonic muscle (as in spasticity, dystonia) tends to contract, resulting in spasms, which provoke ischemia (due to vascular compression and excessive oxygen consumption), and ischemia stimulates the pain receptors in the muscles by releasing various chemicals and neurotransmitters, which cause more spasms resulting in a vicious cycle of spasm-pain-spasm, ultimately leading to injuries to tendons, bones, misaligned joints damaging the adjacent nerves (causing additional neuropathic pain), with consequential deformities, movement problems, and considerable functional impairment. Caregiving becomes challenging (e.g., positioning, hygiene). The child’s sleep is disturbed. Spasticity and the other forms of UMNS can be extremely painful (e.g., flexor and extensor spasms), and sometimes treatment is needed merely for analgesia rather than improvement of function. Noxious stimuli, as well as non-noxious stimuli (like yawning, transferring), can exacerbate spasticity. Pain and sensory phenomena are common in dystonia. 'Status dystonicus' can last minutes, hours, or days. Pain may occur from overactivity of affected muscles or may occur in muscles activated to compensate for dystonia. Pain may occur in a different location from involuntary movements.</td>
</tr>
<tr>
<td>3</td>
<td>Visceral hyperalgesia</td>
<td>Visceral hyperalgesia [increased pain sensation in response to gastrointestinal sensory stimulus] is a neuropathic pain source even in premature infants.</td>
</tr>
<tr>
<td>4</td>
<td>Smooth muscle</td>
<td>Pain due to smooth muscle spasm is possible because baclofen, an anti-spasticity drug, probably also acts on smooth muscle, evidenced by its side effects (gastrointestinal disturbances, diarrhea, paralytic ileus, etc.) and the ability to suppress contractions in the longitudinal muscle of the jejunum. Trihexyphenidyl has blocking action on parasympathetic-innervated peripheral structures, including smooth muscle.</td>
</tr>
<tr>
<td>5</td>
<td>Dropouts are minimized by fixed-sequence crossover design.</td>
<td>Plasticity occurs in both the central (brain and spinal cord) and peripheral nervous systems. After brain damage, the developing brain’s plasticity improves the functional outcome, though there may be disturbances in target reinnervation, sensory localization, or fine motor control. Deranged plasticity in the primary motor and sensory cortices causes dystonia, chronic pain, and hyperreflexia. In the peripheral nervous system, plasticity and regeneration occur as axonal (re)growth and neuron addition.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Probable Mechanism</th>
<th>Treatment given (based on probable etiology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive pain</td>
<td>Prostaglandin E2</td>
<td>Nonselective inhibitors of cyclooxygenase. NSAIDs like acetaminophen, ibuprofen</td>
</tr>
<tr>
<td></td>
<td>Exhausting the supply of substance P in nerves</td>
<td>Capsaicin cream applied locally.</td>
</tr>
<tr>
<td>Visceral hyperalgesia</td>
<td></td>
<td>Gabapentin (calcium channel blocker)</td>
</tr>
<tr>
<td>Neurogenic Pain</td>
<td>Neuroplasticity leads to the evolution of acute pain into a chronic pain state.</td>
<td>1. Lamotrigine (sodium channel blocker). 2. Gabapentin (calcium channel blocker). 3. Tricyclic antidepressants (e.g., amitriptyline) block serotonin reuptake and thus enhance the action of this neurotransmitter at synapses and putatively facilitate the action of the intrinsic opiate analgesic system.</td>
</tr>
<tr>
<td>Neurogenic Pain†</td>
<td>It can be caused by lesions of the parietal lobe, thalamus, medial lemniscus, and posterior columns of the spinal cord. A lesion anywhere along the neuroaxis conducting and controlling pain can lead to Central Post Stroke Pain.</td>
<td></td>
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<td></td>
<td>Sensitization of central pain pathways in the spinal cord's dorsal horns results in an abnormal response to stimulation, causing hyperalgesia and allodynia.</td>
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<td></td>
<td>The immature descending inhibitory system increases the intensity of pain perceived.</td>
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</tr>
<tr>
<td></td>
<td>Loss of the descending inhibitory system as in stroke, trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serotonergic neurons are involved.</td>
<td>Tricyclic antidepressants (e.g., amitriptyline)</td>
</tr>
<tr>
<td></td>
<td>An injury to the peripheral nerve in a limb can trigger microglia-mediated neurotoxicity in the CNS. They produce algesic (pain-producing) molecules.</td>
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<tr>
<td></td>
<td>Chronic neuropathic pain from an injured nerve remodels the entire pain-sensing pathway, including the cortex, the thalamus, the spinal cord's dorsal horn, and the dorsal root ganglia, and the damaged nerve itself.</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathic pain‡</td>
<td>Spontaneous activity in nociceptive C fibers causes burning pain.</td>
<td></td>
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<tr>
<td></td>
<td>Deafferentation of secondary neurons in the posterior horns or of sensory ganglion cells that terminate on them.</td>
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<td></td>
<td>Denervation hypersensitivity</td>
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<tr>
<td></td>
<td>Ectopic impulse generation all along the surface of injured axons and the possibility of ephaptic activation of unmyelinated axons.</td>
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<tr>
<td></td>
<td>Regenerating axonal sprouts forming in response to nerve injuries (neuroma) are hypersensitive to mechanical stimuli. Voltage-gated sodium channels gather at the site of injury and all along the axon, evoking ectopic and spontaneous activity of the sensory neuron and its axon.</td>
<td>Lamotrigine (sodium channel blocker)</td>
</tr>
<tr>
<td></td>
<td>Due to a peripheral lesion transmitting pain impulses to the spinal cord persistently, inhibitory interneurons modulating painful nerve impulses ultimately die.</td>
<td></td>
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<tr>
<td></td>
<td>The firing of large myelinated A-fibers produces dysesthetic pain induced by tactile stimuli.</td>
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</tbody>
</table>

*The term "neuropathic pain" was initially used for peripheral nerve injury symptoms but is currently adopted for the central nervous system pain also.

†During inflammation in neuropathy, nervi nervorum probably are responsible for the neuropathic pain.

‡Allodynia is the perception of touch as being painful. If the child cries on touching or when a cloth touches it, allodynia must be suspected. It is seen in peripheral neuropathic pain. Soaking limbs with nerve damage temporarily lessens allodynia and crying, but the disadvantage is that continuous soaking damages the skin, and chronic ulcers may develop.
Table 2. Inclusion Criteria.

1. A child with cerebral palsy under the age of 15 years and could not communicate the reason for excessive crying because of young age or global developmental delay/profound intellectual retardation.

2. Excessive crying of >7.5 hours daily for 30 consecutive days unresponsive to treatment by the pediatrician, orthopedic surgeon, gastroenterologist, and physiotherapists.

3. Minimum cry intensity for recording: If the intensity of crying was so high that the caregiver could not hear radio, TV, or another person talking to her [sitting near her], the cry duration was recorded.

4. History, clinical, and neuroimaging findings (structural MRI) were suggestive of chronic static encephalopathy.

5. Motor impairment could be explained by an insult that occurred in the developing fetal or infant brain.

---

Table 3. Reasons for using Placebo Run-In Period (PRIP).

**Placebo run-in period was used to:**

1. Increase the probability of detecting a potential treatment effect.

2. Reduce the number of subjects required to reach a statistically significant result.

3. Confirm that the study criteria were satisfied.

4. Ensure that all participants were in a stable condition.

5. The same group functions as the placebo group and experimental group they are truly comparable in all aspects (age, sex, health states, etc.), including a genetic perspective.

6. Exclude subjects with rapid fluctuation of cry duration because they are unlikely to have CP.

7. Exclude subjects absent for more than one day without a reasonable explanation to reduce missed appointments and resulting lack of data.

8. Dropouts are minimized by fixed-sequence crossover design.

9. Offer time before the actual trial, for parents/caregivers to change his/her decision about permitting their child to take part in the study [to reduce patient attrition].
**Table 4. Details of drugs used.**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name</th>
<th>Indications</th>
<th>Mechanism of action</th>
<th>Starting dose/increments</th>
<th>Maximum dose</th>
<th>The maximum dose used in this study</th>
<th>Biological half-life</th>
<th>Peak clinical effect was seen in</th>
<th>Side effects looked for</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baclofen</td>
<td>Spasticity, dystonia</td>
<td>GABA-B agonist. (GABAergic neurons are predominantly inhibitory interneurons in the central and enteric nervous systems. It reduces the tonic output of the spinal motor neurons. It relaxes the cricopharyngeal muscle and treats dysphagia. It suppresses contractions in the longitudinal muscle of the jejunum.</td>
<td>0.5 mg/kg per day in three divided doses. Weekly increments of 0.5 mg/kg per day. The onset of action ranges from hours to weeks.</td>
<td>2 mg/kg per day</td>
<td>1.8 mg/kg/day</td>
<td>3-5 hours</td>
<td>Two months</td>
<td>sedation; confusion; hypotonia; nausea; constipation, dysphoria, muscle weakness; urinary retention The sudden withdrawal of baclofen can cause serious side effects, including seizures and hallucinations.</td>
</tr>
<tr>
<td>2</td>
<td>The same group functions as the placebo group and experimental group they are truly comparable in all aspects (age, sex, health states, etc.), including a genetic perspective.</td>
<td>Spasticity</td>
<td>Facilitates GABA activity at GABA-A receptors located primarily in the brain stem and spinal cord; central nervous system depressant. Reduces hypertonia (spasticity &amp; dystonia), improves passive range of movement, and increases spontaneous movement in the short term.</td>
<td>Infant 1–11 months: Initially 250 μg/kg twice daily, Children 1–4 years: Initially 2.5 mg twice daily, Children 5–11 years: Initially 5 mg twice daily, Children 12–17 years: Initially 10 mg twice daily; maximum of 40 mg per day</td>
<td>40 mg per day</td>
<td>30-56 hours</td>
<td>Few days to few weeks</td>
<td>Sedation; depression; confusion; weakness, ataxi memory disturbances, an dependence</td>
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<tr>
<td>3</td>
<td>Clonazepam</td>
<td>Spasticity</td>
<td></td>
<td>0.01-0.03 mg/kg/day PO divided q8hr; increase by 0.25-0.5 mg/day q3Days</td>
<td>0.1-0.2 mg/kg/day PO divided q8hr</td>
<td>0.18 mg/kg/day</td>
<td>19-60 hours</td>
<td>Hours to weeks</td>
<td>Sedation; depression; confusion; dependence</td>
</tr>
<tr>
<td>4</td>
<td>Trihexyphenidyl</td>
<td>Dystonia</td>
<td>Blocks muscarinic receptors and suppresses cholinergic interneurons' overactivity in the striatum, reduces muscle tone, and controls sialorrhea. Treatment of transfer dysphagia.</td>
<td>0.02-0.06 mg/kg given two or three times daily, with weekly increases of 0.05-0.1 mg/kg increments.</td>
<td>0.75 mg/kg/day</td>
<td>0.5 mg/kg/day</td>
<td>3-3-4.1 hours</td>
<td>A few days to 9 months</td>
<td>Dose-dependent but decrease over time as tolerance develops. Dry mouth, blurred vision; exacerbation of acute-angle glaucoma; urinary retention constipation; memory problems; sedation; confusion; hallucinations;</td>
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<tr>
<td>5</td>
<td>Tetrabenazine</td>
<td>Hyperkinetic disorders, including dystonia</td>
<td>It is a reversible human vesicular monoamine transporter type 2 inhibitor. It promotes depletion of monoamine neurotransmitters serotonin, norepinephrine, and dopamine from stores within the basal ganglia. It also decreases uptake into synaptic vesicles. Treatment of transfer dysphagia.</td>
<td>0.75 mg/kg in 3 divided doses. Increase by 0.5 mg/kg every four weeks.</td>
<td>37.5 mg</td>
<td>10 hours</td>
<td>Four weeks</td>
<td>Anxiety, confusion, constipation, diarrhea, drowsiness, hypotension, insomnia, nausea, parkinsonism, vomiting, depression, dysphoria.</td>
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<tr>
<td>6</td>
<td>Gabapentin</td>
<td>Analgesic for Visceral hyperalgesia, Neuropathic pain, central pain, Antispastic, anxiolytic</td>
<td>The α2δ subunits are up-regulated in damaged sensory neurons resulting in a range of pain states associated with nerve damage and central pain. Gabapentin blocks calcium channels via interactions with the α2δ subunit. Lipid soluble and so crosses the blood-brain barrier, Reduces the low-threshold T-type Ca2+ current that provides the thalamus’s pacemaker activity. Decreases glutamate release. For painful dystonia. Smooth muscle relaxant.</td>
<td>Ten milligrams per kilogram once daily on day 1, then 10 mg/kg twice daily on day 2, then 10 mg/kg 3 times a day on day 3, then increased to 30–70 mg/kg daily in 3 divided doses, adjusted according to response and tolerance. Lower the dose in renal diseases. The absorption of gabapentin from the intestine depends on the L-amino acid carrier system and shows saturaability. So, increasing the dose does not proportionately increase the amount absorbed. Abrupt cessation may cause autonomic withdrawal symptoms like tachycardia, emesis, hyperactivity, irritability, and agitation.</td>
<td>50 mg/kg/day</td>
<td>45 mg/kg/day</td>
<td>4.7 hours. Excreted in the urine unchanged.</td>
<td>Several weeks</td>
<td>Sedation, headache, fatigue, dizziness, nystagmus, and weight gain. Avoid in pulmonary diseases that reduce lung function.</td>
</tr>
<tr>
<td>7</td>
<td>Topiramate</td>
<td>Both central pain and neuropathic pain.</td>
<td>Acts on voltage-gated Na+ channels, HVA Ca+ channels, GABA&lt;sub&gt;A&lt;/sub&gt; receptors, glutamate receptors, voltage-gated K+ channels, and</td>
<td>Initially 0.5–1 mg/kg once daily (maximum per dose 25 mg) for one week, at night, then increased in increments of 250–500 micrograms/kg</td>
<td>7.5 mg/kg twice daily</td>
<td>6 mg/kg BD</td>
<td>21 hours.</td>
<td>Four days</td>
<td>Sedation. Speech/language problems, impaired cognition, weight loss, nephrolithiasis, hyperchloremic metabolic acidosis.</td>
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<td>8</td>
<td>Lamotrigine</td>
<td>Both central pain and neuropathic pain.</td>
<td>Sodium channel blocker. Inhibits the generation of action potentials. Prolongs the inactivated state of the sodium channel. Also, it decreases neurotransmission by prejunctional neurons.</td>
<td>Without valproic acid: 0.6 mg/kg/day PO divided q12hr for 2 weeks, then 1.2 mg/kg/day PO divided q12hr for 2 weeks. At five weeks, increase by 1.2 mg/kg every 1-2 weeks to maintenance dose of 5-15 mg/kg/day PO divided q12hr</td>
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<td>Six weeks 400 mg/day divided q12hr</td>
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<td></td>
<td>Skin rashes, tremors, Stevens Johnson syndrome, aseptic meningitis, blood dyscrasias</td>
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<td>9</td>
<td>Amitriptyline</td>
<td>Chronic neuropathic pain</td>
<td>It acts centrally by inhibiting neuronal noradrenaline and 5-hydroxytryptamine uptake and is effective in relieving neuropathic pain.</td>
<td>0.1 mg/kg at bedtime increased every three weeks by the same dose.</td>
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<td></td>
<td>2 mg/kg 1 mg/kg 12-24 hours Days to weeks Sedation, constipation, dry mouth, tremor, blurred vision, sweating, weight gain, elevated LFTs, urinary retention.</td>
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</tbody>
</table>
**Table 5. The sequence of the drugs used*.**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Initial clinical presentation (number of subjects)</th>
<th>Initially treated for</th>
<th>Later treated for</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spastic (106)</td>
<td>Spasticity†</td>
<td>Neuropathic pain¶</td>
</tr>
<tr>
<td>2</td>
<td>Dystonia (23)</td>
<td>Dystonia‡</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>None. Initially, there was no spasticity or dystonia, or seizures§ (35). MRI showed damage to the basal ganglia, thalami, perisylvian area, insula, or putamen.</td>
<td>Visceral hypersensitivity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>() number of subjects treated</th>
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</thead>
<tbody>
<tr>
<td>Drugs were used either singly or in combination.</td>
</tr>
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</table>

*The drug's sequence used to reduce crying was decided by the initial clinical presentation, presumed etiology & pathophysiology of pain/discomfort, mechanism of action of the drug, associated problems, side effects of the drug, allergies, neuroimaging, and experience with the drug in that age group*.#*

†Baclofen (105), diazepam (44), clonazepam (18)
‡Baclofen (18), diazepam (14), clonazepam (11), trihexyphenidyl (17), tetrabenazine (4).
§When they developed hypertonia like spasticity or dystonia, or seizures, the appropriate drug was added. When the full clinical picture evolved, these cases were shifted into the other groups. Two subjects evolved into the mixed type of CP.
||Gabapentin (31)
|**Topiramate (15), lamotrigine (21), amitriptyline (10)**

*If there was a response, the drug was gradually increased till a response was achieved or side effects appeared. If there was no response within three weeks, another drug was added, and the first drug was tapered and stopped.*

Caretakers were advised to inform the doctor if they are taking any other drug for any other problem.

Caretakers were advised not to stop the drug suddenly.
Table. 6. Details of participants (who satisfied duration of crying criteria) excluded.

<table>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Medicines used in the study were used in the previous 30 days, and it was impossible to taper off the drugs without worsening of symptoms.</td>
<td>Symptomatic treatment must be given.</td>
<td></td>
<td></td>
<td></td>
<td>279</td>
</tr>
<tr>
<td>2</td>
<td>Cause of excessive crying was known like dysphagia (and the resulting hunger), gastroesophageal reflux, ulcers, constipation, hip dislocation/subluxation, musculoskeletal deformity, stretching exercises, physiotherapy, pain related to positioning, range of motion manipulation, the imbalance of muscle activation across joints resulting in atypical joint compression, cartilage damage leading to joint sensitization, subluxation, dislocations, contractures, musculoskeletal deformities like scoliosis, immobilization &amp; pain related to equipment (e.g., use of splints, braces, casts, and other devices), intramuscular botulinum neurotoxin A (BoNT-A) injections, serial casting, surgical procedures; infections, skin breakdown, headaches, dental and gingival disease, etc.</td>
<td></td>
<td></td>
<td>285</td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Crying responded to the treatment of provocative factors that increased spasticity (like tight clothing, poor positioning, medications, constipation, inflamed skin creases, pressure sores, tight orthoses, ingrown toenails, indwelling catheter or urinary tract infection), massage, stretching, transcutaneous electrical nerve stimulation (TENS), surgical procedures and use of analgesics like acetaminophen or ibuprofen.</td>
<td>To exclude chronic progressive encephalopathies caused by neurogenetic and neurometabolic masqueraders of CP. They require more work up for an accurate diagnosis to properly manage a treatable metabolic error and genetic counseling.</td>
<td></td>
<td></td>
<td></td>
<td>232</td>
</tr>
<tr>
<td>4</td>
<td>Red flags (some cases had multiple exclusion points).</td>
<td>To exclude chronic progressive encephalopathies caused by neurogenetic and neurometabolic masqueraders of CP. They require more work up for an accurate diagnosis to properly manage a treatable metabolic error and genetic counseling.</td>
<td></td>
<td></td>
<td></td>
<td>137</td>
</tr>
</tbody>
</table>

The same group functions as the placebo group and experimental group they are truly comparable in all aspects (age, sex, health states, etc.), including a genetic perspective.

i. Absence of risk factors for CP that may cause brain dysgenesis or injuries such as a hypoxic-ischemic insult during prenatal, natal, neonatal period or infancy, prematurity, low birth weight, multiple births, small for gestational age, too severe and prolonged neonatal hypoglycemia, jaundice and kernicterus, intrapartum asphyxia, intracranial hemorrhage, infection, toxins, congenital brain malformations, cerebral vascular accident or head injuries. 19

ii. Positive family history of CP consanguinity, 5

iii. Fluctuation in motor symptoms, paroxysmal symptoms in relation to the time of day, diet/fasting, or activity or illnesses, diurnal variation of symptoms 8

iv. Progressive neurological symptoms 89

v. Regression of milestones 78

b. in the examination

i. Dysmorphic features (e.g., abnormal head circumference, Progressive hydrocephalus) To exclude CP mimics 9

ii. Isolated motor dysfunction such as isolated ataxia or isolated hyptonia without dystonia or spasticity 7

iii. Peripheral nervous system abnormalities: absent reflexes, sensory signs To exclude genetic conditions 3

iv. Skin abnormalities: Café au lait spots, port-wine stain, nevus flammeus, vitiligo. 5

v. Eye movement abnormalities (e.g., oculogyria, oculomotor apraxia, or paroxysmal saccadic eye-head movements) 6

vi. Eye abnormalities (e.g., cataracts, optic nerve 5
hypoplasia, optic atrophy, retinal pigmentary degeneration, coloboma, chorioretinal lacuna).

vii. Rigidity

viii. Paraplegia 2

ix. Visceromegaly 2

c. Magnetic Resonance Imaging

i. MRI is normal. But history, physical examination, and investigations suggest a progressive neurologic disease. If MRI does not show a lesion, further investigations are necessary to exclude genetic causes.

17

ii. MRI—reveals a developmental brain malformation (e.g., lissencephaly, schizencephaly, or pachygyria) or frontal/temporal atrophy. Inborn errors of metabolism probably lead to neuronal migration defects and cerebral malformations. They require more work up for an accurate diagnosis to properly manage a treatable metabolic error and genetic counseling.

9

iii. Nonspecific abnormalities, such as isolated globus pallidus involvement. Isolated globus pallidus involvement can suggest methylmalonic aciduria.

3

iv. Imaging shows specific lesions inconsistent with perinatal brain injury but characteristic of a particular genetic disorder, such as leukodystrophies, features of glutaric aciduria type 1, or features of Joubert syndrome.

13

5 Neurogenetic/Neurometabolic diseases

a. Presented with spasticity 107

i. Arginase deficiency Elevated serum arginine and blood ammonia, no detectable arginase activity in red blood cells.

13

ii. Pyruvate dehydrogenase deficiency Deficient enzyme activity in cultured leukocytes.

2

iii. Adrenoleukodystrophy T2-weighted MRI showed high signal intensity in the periventricular white matter. Adrenal insufficiency was evidenced by a subnormal response to stimulation by the adrenocorticotropic hormone. The level of very-long-chain fatty acids in plasma was elevated.

2

iv. Ornithine transcarbamylase deficiency Deletion of the whole OTC gene.

8

v. Leigh syndrome Elevated blood concentrations of lactate and pyruvate. MRI of the brain showed a bilateral symmetrical hyperintense signal abnormality in the periaqueductal area of the brainstem and basal

14
<table>
<thead>
<tr>
<th></th>
<th>Condition</th>
<th>Diagnosis/Investigation</th>
<th>Case Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>Glutaric aciduria type 1</td>
<td>T2-weighted MRI of the brain showed bilateral frontotemporal atrophy with wide Sylvian fissure (<em>bat-wings</em> appearance). Urine gas chromatography/Mass Spectrometry revealed glutaric acid, glutarconic acid, and 3-hydroxy glutaric acid.</td>
<td>9</td>
</tr>
<tr>
<td>ii</td>
<td>Niemann-Pick disease type C</td>
<td>Mutation analysis</td>
<td>7</td>
</tr>
<tr>
<td>iii</td>
<td>Dopa-responsive dystonia</td>
<td>Response to a trial of carbidopa-levodopa. Dopa-responsive dystonia NGS panel Test.</td>
<td>2</td>
</tr>
<tr>
<td>iv</td>
<td>Lesch-Nyhan syndrome</td>
<td>Hyperuricemia and hyperuricosuria, hypoxanthine guanine phosphoribosyl transferase-1 deficiency in red blood cells.</td>
<td>5</td>
</tr>
<tr>
<td>vi</td>
<td>Undiagnosed</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Focal spasticity/dystonia</td>
<td>Botulinum toxin is the treatment of choice.</td>
<td>422</td>
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<tr>
<td></td>
<td>Total cases</td>
<td></td>
<td>1355</td>
</tr>
<tr>
<td>S.No.</td>
<td>Variable</td>
<td>Group</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td>1</td>
<td>Gender</td>
<td>Males</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>Age</td>
<td>&lt;2 years</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>16</td>
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<td>4</td>
<td>6</td>
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<td></td>
<td></td>
<td>14</td>
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<td>3</td>
<td>GMFCS levels</td>
<td>V</td>
<td>83</td>
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<td></td>
<td></td>
<td>IV</td>
<td>48</td>
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<td>MAS scores</td>
<td>4</td>
<td>19</td>
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<td>3</td>
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<td></td>
<td>2</td>
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<td></td>
<td>1+</td>
<td>14</td>
</tr>
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<td></td>
<td></td>
<td>1</td>
<td>32</td>
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<tr>
<td></td>
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<td>0</td>
<td>22</td>
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</table>
### Table 8. Results

#### A. Summary Statistics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arithmetic mean</th>
<th>95% CI for the Arithmetic mean</th>
<th>Median</th>
<th>95% CI for the median</th>
<th>Variance</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1t-P06-P15</td>
<td>10.02</td>
<td>9.84 to 10.2</td>
<td>9.98</td>
<td>9.73 to 10.16</td>
<td>1.05</td>
<td>1.02</td>
</tr>
<tr>
<td>M2t-T61-T70</td>
<td>6.35</td>
<td>6.3 to 6.41</td>
<td>6.27</td>
<td>6.25 to 6.29</td>
<td>0.1</td>
<td>0.31</td>
</tr>
<tr>
<td>M3t-T241-T250</td>
<td>2.83</td>
<td>2.71 to 2.96</td>
<td>2.84</td>
<td>2.68 to 3</td>
<td>0.52</td>
<td>0.72</td>
</tr>
<tr>
<td>M4t-T351-T360</td>
<td>The same group functions as the placebo group and experimental group they are truly comparable in all aspects (age, sex, health states, etc.), including a genetic perspective.</td>
<td>2.55 to 2.78</td>
<td>2.67</td>
<td>2.53 to 2.82</td>
<td>0.43</td>
<td>0.66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arithmetic mean</th>
<th>95% CI for the Arithmetic mean</th>
<th>Median</th>
<th>95% CI for the median</th>
<th>Variance</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1u-P06-P15</td>
<td>8.26</td>
<td>8.11 to 8.41</td>
<td>8.22</td>
<td>8.02 to 8.39</td>
<td>0.72</td>
<td>0.85</td>
</tr>
<tr>
<td>M2u-T61-T70</td>
<td>Dropouts are minimized by fixed-sequence crossover design.</td>
<td>5.17 to 5.26</td>
<td>5.14</td>
<td>5.12 to 5.16</td>
<td>0.07</td>
<td>0.26</td>
</tr>
<tr>
<td>M3u-T241-T250</td>
<td>2.29</td>
<td>2.19 to 2.39</td>
<td>2.29</td>
<td>2.17 to 2.42</td>
<td>0.36</td>
<td>0.6</td>
</tr>
<tr>
<td>M4u-T351-T360</td>
<td>2.15</td>
<td>2.06 to 2.25</td>
<td>2.16</td>
<td>2.04 to 2.28</td>
<td>0.3</td>
<td>0.55</td>
</tr>
</tbody>
</table>

#### B. Results. Paired sample t test results.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Test</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Remarks</th>
<th>Sample size</th>
<th>Total cry duration</th>
<th>Unexplained</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>paired sample t test</td>
<td>6-15 days on placebo</td>
<td>61-70 days on treatment</td>
<td>placebo vs. drug</td>
<td>131</td>
<td>-3.67</td>
<td>-3.80 to -3.53</td>
</tr>
</tbody>
</table>


### C. Results. Wilcoxon test (paired samples) results.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Test</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Remarks</th>
<th>Median</th>
<th>95% CI for the median</th>
<th>Median</th>
<th>95% CI for the median</th>
<th>p value</th>
<th>Sample size</th>
<th>Total cry duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wilcoxon test (paired samples)</td>
<td>6-15 days on placebo</td>
<td>241-250 days on treatment</td>
<td>placebo vs. drug</td>
<td>131</td>
<td>9.98</td>
<td>9.73 to 10.16</td>
<td>2.84</td>
<td>2.68 to 3.00</td>
<td>p &lt;0.001</td>
<td>8.22</td>
</tr>
<tr>
<td>2</td>
<td>6-15 days on placebo</td>
<td>351-360 days on treatment</td>
<td>placebo vs. drug</td>
<td>131</td>
<td>9.98</td>
<td>9.73 to 10.16</td>
<td>2.67</td>
<td>2.53 to 2.82</td>
<td>p &lt;0.001</td>
<td>8.22</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>241-250 days on treatment</td>
<td>311-320 days on treatment</td>
<td>The effect of drug taper-improved</td>
<td>67</td>
<td>2.99</td>
<td>2.79 to 3.16</td>
<td>2.91</td>
<td>2.74 to 3.04</td>
<td>p &lt;0.001</td>
<td>2.35</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>The effect of drug taper-worsened</td>
<td>64</td>
<td>2.57</td>
<td>2.36 to 2.90</td>
<td>2.7</td>
<td>2.51 to 3.04</td>
<td>p &lt;0.001</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 9. Secondary outcomes. Additional observations volunteered by caregivers.

1. The crying spells started initially during the daytime, and later nocturnal attacks appeared in 117 of 131 (89.31%). However, caregivers were concerned more about the nocturnal attacks and complained about them more frequently.

2. Improvements in dysphagia and drooling were reported when baclofen/trihexyphenidyl/tetrabenazine was given (Figure 7). The response varied in different subtypes of CP (Figure 7). Those who could not eat solids could, those who could not drink liquids could, and those who could not eat semisolids could. This improvement was lost when the drug dosage was reduced from the 251st day until the dose was increased again.

3. Dysphagia associated with spasticity responded to baclofen/diazepam given to control spasticity (Figure 7).

4. Decreased irritability, feeding tolerance, improved comfort, and sleep in 127 of 131 (96.95%).

### Table 10. Reasons for choosing the fixed-sequence crossover design.

The fixed-sequence crossover design was chosen because

1. The problem is chronic.

2. The treatment effects are reversible and short-lived.

3. Within-subject variation is less than the between-subject variation.

4. Fewer participants are required for a target effect size and type one error rate.

5. The same group functions as the placebo group and experimental group they are truly comparable in all aspects (age, sex, health states, etc.), including a genetic perspective.

6. Carryover and sequence effects do not occur.

7. The period effect is negligible in treated CP cases.

8. Dropouts are minimized by fixed-sequence crossover design.

9. It would be unethical to conduct trials for 400 days using some other design like randomized case-control or 2-sequence crossover or stepped wedge design or starting subjects on active therapy and performing randomized withdrawal.
Table 11. The limitations of the study.

1. The study was conducted over a long period of >14 years, raising concerns of a lot of heterogeneity in enrolled participants. But since CP itself is a heterogeneous neurodevelopmental disorder, and the study criteria were unchanged, it is improbable that the study results were altered because of the long duration.

2. There are many reasons for cry in the first two years of life than in any other period, and infants are not correctly communicating before two years old. The mechanisms for crying were speculative and unproven, which made medication selection partly empiric. The sequence of drugs used to reduce crying was decided by the initial clinical presentation, presumed etiology & pathophysiology of pain/discomfort, mechanism of action of the drug, associated problems, side effects of the drug, allergies, neuroimaging, and experience with the drug in that age group because there was no better way.

3. Nonprogressive refers to the brain's injury and not the symptoms and signs that change with the repair and recovery; tone, posture, and reflexes change over time, even in a static process. Plastic changes and myelination take months to evolve and delay the appearance of hypertonia and exaggerated deep tendon reflexes. Hypotonia is more frequent than hypertonia in infants under one year who eventually manifest CP. Spasticity may not be diagnosed until six months of age. Dyskinetic patterns are often not apparent until 18 months. Ataxia may not become evident until even later. So, plasticity or maturation of inhibitory pathways may have reduced ECCCP, resulting in a period effect. The unchanged study criteria (Table 3, Table 7), analysis of total & unexplained cry durations (Figure 3, Figure 4), and response to dose reduction (Figure 6) confirmed that drugs indeed were responsible for reducing ECCCP and not plasticity or maturation of the nervous system.

4. Substantial research has resulted in new methods for early identification and intervention, which could have affected the study because of the long duration. Since the study criteria were not changed, the study results were unlikely to be affected.

5. Similar to all pain investigations among nonverbal or communicatively impaired participants, the ECCCP reported were decided by caregivers' proxy report. In such studies, limitations of research design are unavoidable. Though every possible care was taken to explain, discuss, guide, and check the caregivers’ measurement of the duration, the weakest point of the study is that it relied totally on the caregivers' data collection of ECCCP. However, proxies' reports of pain are reported to be almost equal to self-reports. The box plots (Figure 3, Figure 6) and scatter diagrams (Figure 4 A-F) show that they have done it quite well.

6. The same group functions as the placebo group and experimental group they are truly comparable in all aspects (age, sex, health states, etc.), including a genetic perspective.

7. Though the period effect was minimized by including only CP (static encephalopathy) cases, we cannot assume it to be 100% accurate. Spasticity increases gradually up to the age of five years and then decreases slowly. Because 99 spastic participants were below that age, the slight increase in spasticity would have increased ECCCP, and seven spastic participants were above that age, probably decreasing ECCCP. If there were period effect operating at all, the net result would have been increased ECCCP, which would have reduced treatment response. Therefore, it is unlikely that the period effect would have altered the results and conclusions. Additionally, dose reduction between T251-T310 would not have been possible in 67/131 (51.15%) participants if the period effect increased spasticity and ECCCP significantly.

8. Unclear etiologies for crying and the use of so many different medications may limit the findings' practicality and application. So, an attempt was made to develop an algorithm based on pathophysiology to choose the drug (Table 6).

9. Dropouts are minimized by fixed-sequence crossover design.

Figures

**Figure 1**

Fixed-sequence crossover study

It has only one group.
Figure 2

The CONSORT Flow Diagram
Figure 3

The participant numbers of subtypes of cerebral palsy at various stages of the present study (data-A) compared to those of the 1998 study (data-B).
Figure 4
Epidemiology of Excessive Crying in Children with Cerebral Palsy and Communication Deficits [ECCCPCD]. A. Frequencies chart showing the age wise distribution of participants of ECCCPCD versus rounded-up age. B. Frequencies chart showing the distribution of participants between Gross Motor Function Classification System (GMFCS) levels. C. Frequencies chart showing the distribution of participants among modified Ashworth Scale (MAS) scores. D. Frequencies chart showing the distribution of MAS scores of participants between GMFCS levels.

Figure 5
Box and whisker plots displaying the medians and data distributions of Total and Unexplained Excessive Crying in Children with Cerebral Palsy and Communication Deficits [TECCCPCD and UECCCPCD] through their quartiles and outliers of various means at different periods. The clustering into different groups in M2t and M2u data probably suggests the necessity for better drug selection and dosage titration in 35 (26.72%) participants who did not have hypertonia or seizures at the enrollment time. Means of cry duration in hours per day (M1, M2, M3, and M5) were calculated from 10-day period measurements while on placebo, MM1, on days Placebo-6 to Placebo-15 (P6-P15), and MM2, MM3, and MM5 while on treatment T61-70, T241-250, and T351-360. Total cry duration has the suffix ‘t’, and unexplained cry duration has ‘u’. M4 data are not shown here because they represent means after the reduction of the dose.
Figure 6

Scatter diagram with heat maps & trend lines of Total and Unexplained Excessive Crying in Children with Cerebral Palsy and Communication Deficits (TECCPCD and UECCPCD) duration while on placebo versus treatment. Pure green is the lowest value, pure red is the highest value, and pure yellow is precisely in the middle. All parts of the grid that have a value of 0 remain transparent. Total cry duration has the suffix ‘t’. Unexplained cry duration has the suffix ‘u’.

A. M1t, on days Placebo-6 to Placebo-15 (P6-P15) versus M2t while on treatment (T61-70), B. M1u, on days Placebo-6 to Placebo-15 (P6-P15) versus M2u while on therapy (T61-70). The clustering into different groups in A and B probably suggests the necessity for better drug selection and dosage titration in 35 (26.72%) participants who did not have hypertonia or seizures at the time of enrollment. C. M1t, on days Placebo-6 to Placebo-15 (P6-P15) versus M3t while on treatment (T241-250), D. M1u, on days Placebo-6 to Placebo-15 (P6-P15) versus M3u while on therapy (T241-250), E. M1t, on days Placebo-6 to Placebo-15 (P6-P15) versus M5t while on treatment (T351-360), F. M1u, on days Placebo-6 to Placebo-15 (P6-P15) versus M5u while on therapy (T351-360).

M4 data are not shown here because they represent means after the reduction of the dose.
Figure 7

Box and Whisker Plots displaying the medians and data distributions of Total and Unexplained Excessive Crying in Children with Cerebral Palsy and Communication Deficits [TECCPCD and UECCPCD] through their quartiles of various means at different periods. Means of cry duration in hours per day (M3, M4, and M5) were calculated from three 10-day period measurements: MM3 (day treatment-241 to treatment-250 (T241-250), MM4 treatment-311 to treatment-320 (T311-320), and MM5 treatment-351 to treatment-360 (T351-360) while on treatment. Total cry duration has the suffix ‘t’, and unexplained cry duration has ‘u’. A. Data of 67 participants (51.15%), who continued to improve on dose reduction up to 30%. B. Data of 64 participants (48.85%) who worsened on dose reduction up to 30%.
Figure 8

Secondary outcomes. A. Frequencies of dysphagia in various subtypes of CP. B. Improvement in dysphagia reported (percentages) in different subtypes of CP. C. Frequencies of drool in various subtypes of CP. E. Improvement in drool reported (percentages) in various subtypes of CP.

Supplementary Files

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- checklist.docx