Appendix 6-A

Clinical Protocol

A phase II, randomized, placebo-controlled, double blind, cross-over, study of the effects of Gabapentin on chronic irritability in neurologically impaired children.

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Funding Sponsor:	Medical Education and Research Association (MERA) Gillette Children's Specialty Healthcare 200 University Ave E St. Paul, MN 55101 Attn: Joyce Trost 651-229-1745
Study Product:	Gabapentin (Neurontin®)
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List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
IDS	Investigational Drug Service
IRB	Institutional Review Board
ITT	Intent to Treat
NCCPC-R	Non-Communicating Children's Pain Checklist-Revised
PHI	Protected Health Information
REPA	Report of External Professional Activities
SAE	Serious Adverse Event
UPIRTSO	Unanticipated Problems Involving Risk to Subjects or Others

Study Summary

Title	A phase II, randomized, placebo-controlled, double blind, cross-over, study of the effects of Gabapentin on chronic irritability in neurologically impaired children
Short Title	Effects of Gabapentin on chronic irritability in neurologically impaired children.
Phase	Phase II
Methodology	The study is a randomized, placebo-controlled cross-over.
Study Duration	The estimated duration of the study is 12 months
Study Center(s)	This is a single center study to be conducted at Gillette Children's Specialty Hospital, 200 University Ave. E., St. Paul, MN 55101.
Objectives	To determine if gabapentin provides symptom relief for chronic irritability in neurologically impaired children despite medical management for identified sources of symptoms or if no etiology is identified.
Number of Subjects	40 evaluable subjects
Diagnosis and Main Inclusion Criteria	Neurological impairment and chronic irritability suggesting pain.
Study Product, Dose, Route, Regimen	Gabapentin (Neurontin®), to be administered as an oral solution titrated over a 22 day period, followed by a 7 day stable dose period (40 mg/kg/day over 3 dosages), followed by a 9 day taper and washout period
Duration of administration	Subjects will receive drug for 34 days, and placebo for 34 days, with a 3 day washout period in between.
Reference therapy	Reference therapy for this study is the placebo as there is no standard of care.
Statistical Methodology	The study will utilize non-parametric descriptive statistics to compare subject questionnaire responses after drug and placebo exposures.

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1.0 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (21 CFR 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Irritability in nonverbal neurologically impaired children (neuro-irritability) is often considered to indicate pain in such children. Children with neurological impairment experience pain more frequently than the general pediatric population". In one study, 44% of children with severe cognitive impairment were reported by caregivers to experience pain each week during a four-week interval. Pain frequency was highest in the most impaired group of children.[2] Caregivers of children with moderate to severe cerebral palsy reported over a 4-week interval that 26% experienced pain or discomfort "once or twice", 19% "a few times", 10% "fairly often", 2.5% "very often", and 8% "every/almost every day".[3] In a study of nonverbal cognitively impaired children, caregivers reported that 62% experienced five or more separate days of pain, and 23.5% experienced pain almost daily.[4]

Identifying a source of pain in a nonverbal child with neurological impairment poses a unique and significant challenge. Common recognized pain sources in these individuals include acute sources such as fracture, urinary tract infection, or pancreatitis and chronic sources such as gastroesophageal reflex (GER), constipation, feeding difficulties from delayed gut motility, positioning, spasticity, hip pain, or dental pain. Table 1 outlines etiologies of acute and chronic pain to consider.

Pain in neurologically impaired children is typically thought to be nociceptive in origin. Experience shows that a pain source may not be identified or pain may continue despite treatment of an identified source. Greco et al[5] identified the category "Screaming of unknown origin" to indicate children with neurologic disorders, severe developmental delay, neurodegeneration, or severe motor impairments with persistent agitation, distress, or screaming. Evaluation may identify a specific nociceptive cause but in many other cases, these evaluations can be frustrating for patients, families, and clinicians. In the chapter "Pain and Children with Developmental Disabilities", Oberlander and Craig review that pain in neurologically impaired children is typically thought to be nociceptive in origin; however, after repeated injury or surgery, neuropathic pain may also occur.[6] Because of the confusing neurologic and clinical picture, identification of neuropathic pain is challenging. Neuropathy may be another source of ongoing and poorly treated pain in such children.

Parents commonly identify the gastrointestinal tract as a source of pain in neurologically impaired children. Breau et al" [7] identified gastrointestinal as the second most common pain source category, after accidental causes, yet the most frequent source of all episodes of pain in children with severe cognitive impairment. Roughly half with gastrointestinal pain experienced pain classified as 'bowels' but not due to constipation and a similar number experienced episodes classified as 'digestive' due to 'gas' or `gastrointestinal' problems without identification of cause or 'location. Pain of unknown cause was the most intense, followed by pain attributed to the bowels, gastrointestinal tract and digestive pain. Houlihan et a1[3] reported significantly higher rates of pain in children with a gastrostomy tube and those taking medications for feeding, gastroesophageal reflux or gastrointestinal motility.

Table 1. Etiology of pain/irritability in nonverbal neurologically impaired children

Head, Eyes, Ears, Nose, Throat (HEENT)
Acute otitis media, pharyngitis, sinusitis, dental abscess/gingival inflammation, corneal abrasion, glaucoma, ventriculoperitoneal shunt malfunction
Chest
Pulmonary aspiration/pneumonia, esophagitis, pericardial effusion, supraventricular tachycardia, cardiac ischemia
Abdomen
Gastrointestinal: gastroesophageal reflux disease, gastritis/gastric ulcer, peptic ulcer disease, food allergy, appendicitis, intussusception, constipation, delayed/impaired motility, rectal fissure, visceral hyperalgesia
Liver/gallbladder: hepatitis, cholecystitis
Pancreas: pancreatitis
Renal: urinary tract infection, nephrolithiasis, neuropathic bladder, obstructive uropathy
Genitourinary: inguinal hernia, testicular torsion, ovarian torsion/cyst, menstrual cramps
Skin
Pressure sore/decubitus ulcer
Extremities
Fracture, hip subluxation, osteomyelitis, hair tourniquet
Psychosocial
Loss of caregiver, change in home environment, non-accidental trauma
General
Medication toxicity, sleep disturbance

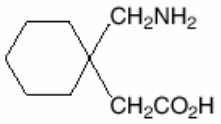
The association between pain and the gastrointestinal tract led to speculation that visceral hyperalgesia is a source of chronic irritability and agitation in neurologically impaired children. Zangen et al[8] identified visceral

hyperalgesia as a source of feeding difficulty in 12 of 14 neurologically impaired children with refractory, persistent food refusal, retching and vomiting despite maximal medical therapy and Nissen fundoplication. All patients had gastrointestinal motility and/or sensory abnormalities. Twelve of the 14 patients showed a low threshold for gastrointestinal sensory symptoms. Seven patients demonstrated both motility and sensory impairment. Only two patients had abnormal motility without sensory involvement. Tricyclic antidepressants and gabapentin successfully managed the symptoms identified in these patients. In a retrospective series of nine neurologically impaired children who experienced significant unexplained pain and irritability, marked symptom improvement was identified when the children received gabapentin therapy titrated to standard doses.[9] For such children with persistent irritability, we suggest use of medications, such as gabapentin, that have demonstrated benefit for neuropathic pain syndromes.

Gabapentin is a medication utilized for treating neuropathic pain and has the safest side effect profile of medications used for neuropathic pain. These investigators have observed benefit without harm in use of gabapentin for neurologically impaired children with chronic irritability. There is no standard of care for this problem.

1.2 Investigational Agent

Gabapentin (Neurontin®) is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of C_9Hi_7NO2 and a molecular weight of 171.24. The structural formula of gabapentin is:



Gabapentin is a white to off-white crystalline solid with a pK_ai of 3.7 and a pKa2 of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is —1.25. The oral solution contains 250 mg/5 mL of gab apentin. The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.

The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (e.g. spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test).

Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.

All pharmacological actions following gabapentin administration are due to the activity of the parent compound as gabapentin is not appreciably metabolized in humans. Adult subjects with compromised renal function require dosage adjustment. Pediatric subjects with renal insufficiency have not been studied. Dosage adjustment is also required for subjects undergoing hemodialysis. The apparent oral clearance of gabapentin decreased with increasing age, largely due to age related decline in renal function. Although formal studies comparing gender and race have not been studied, no significant gender or race differences are expected.

1.3 Pre-Clinical Data

In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day.

The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately $^1/_2$ of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times and approximately equal to the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 30 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4

times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300, and 1500 mg/kg/day, or less than approximately 'A to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

1.4 Clinical Data to Date

Neurontin® was evaluated for the management of postherpetic neuralgia (PHN) in 2 randomized, double-blind, placebo-controlled, multicenter studies; N=563 patients in the intent-to-treat (ITT) population (Table 2). Patients were enrolled if they continued to have pain for more than 3 months after healing of the herpes zoster skin rash.

TABLE 2. Controlled PHN Studies: Duration, Dosages, and Number of Patients

Study	Study Duration	Gabapentin (mg/day)* Target Dose Given in 3 divided doses (TM)	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3600	113	116
2	7 weeks	1800, 2400	223	111
		Total	336	227

Each study included a 1-week baseline during which patients were screened for eligibility and a 7- or 8-week double-blind phase (3 or 4 weeks of titration and 4 weeks of fixed dose). Patients initiated treatment with titration to a maximum of 900 mg/day gabapentin over 3 days. Dosages were then to be titrated in 600 to 1200 mg/day increments at 3- to 7-day intervals to target dose over 3 to 4 weeks. In Study 1, patients were continued on lower doses if not able to achieve the target dose. During baseline and treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). A mean pain score during baseline of at least 4 was required for randomization (baseline mean pain score for Studies 1 and 2 combined was 6.4). Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication). Both studies showed significant differences from placebo at all doses tested.

A significant reduction in weekly mean pain scores was seen by Week 1 in both studies, and significant differences were maintained to the end of treatment. Comparable treatment effects were observed in all active treatment arms. Phannacokinetic/pharmacodynarnic modeling provided confirmatory evidence of efficacy across all doses. Figures 1 and 2 show, these changes for Studies 1 and 2.

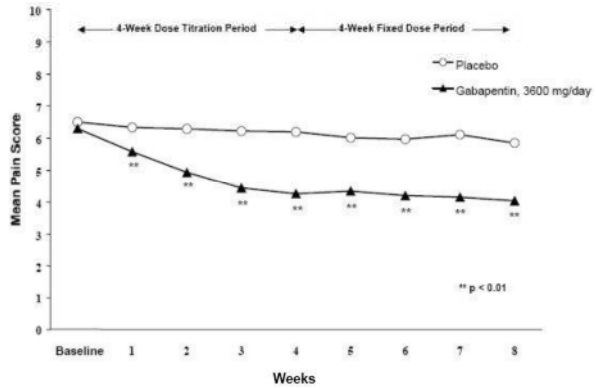


Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

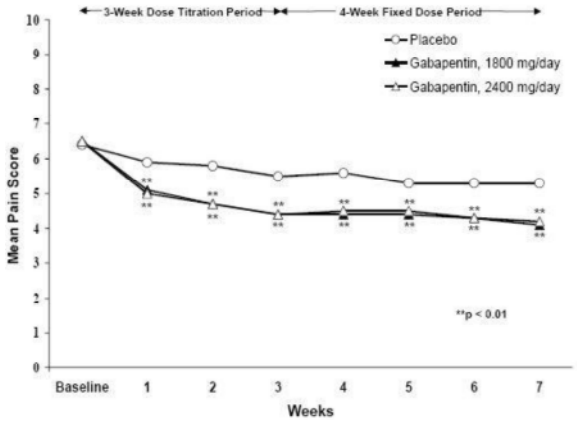


Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

The proportion of responders (those patients reporting at least 50% improvement in endpoint pain score compared with baseline) was calculated for each study (Figure 3).

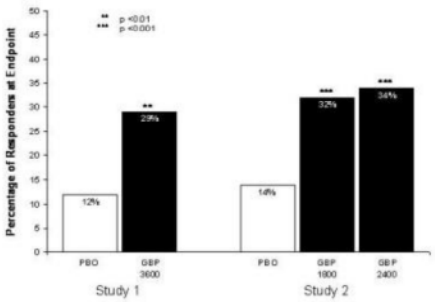


Figure 3. Proportion of Responders (patients with >50% reduction in pain score) at Endpoint: Controlled PHN Studies

No other clinical research information could be found to date for pain or irritability in non-verbal children.

1.5 Dose Rationale and Risk/Benefits

The dose protocol (see Section 5.2.) is based upon ideal dosing ranges, with sensitivity paid to titrating up and down slowly to minimize potential side effects and withdrawal symptoms. Additionally, the rationale of the increased dose in the evening is related to the known effect of inducing tiredness in some individuals. The decision to use the liquid form is to allow for tight titration of medications, and to prevent the need for "pill-splitting" to achieve precise dosing. Additionally, the liquid form may be easy to administer to patients with gastrostomy tubes. Finally, the liquid form will also be better tolerated by those patients without gastrostomy tubes but have difficulty manipulating pills.

Potential risks of Gabapentin include (from most common to least common): somnolence, dizziness, increase in hostility, nausea/vomiting, increased chance for viral infections and fevers, ataxia, fatigue, emotional lability, increased weight, and hyperkinesia.

Risks to unborn children are unknown. Therefore, parents of females who have reached puberty will be asked to allow a pregnancy test to be done. If applicable, a urine pregnancy test will be done on Day 0.

There is a risk for loss of privacy; however, study personnel will take precautions to prevent loss of privacy.

The risks of the medication are expected to be minimal compared to the benefit of relief from distressing symptoms (neuroirritability). Establishment of Gabapentin as an effective therapy for neuroirritability will help many children in the future be appropriately treated for the underlying condition without the need for other more dangerous medications (benzodiazepenes).

The patient population for this study is comprised of severely cognitively and often developmentally impaired children. Therefore, it is not applicable to screen for suicidality in this population.

2.0 Study Objectives

Primary Aim: To determine if gabapentin provides symptom relief for chronic irritability in neurologically impaired children despite medical management for identified sources of symptoms or if no etiology is identified,

Primary Hypothesis: Gabapentin is beneficial and safe for neurologically impaired children with chronic irritability that persists despite identification and appropriate management of symptom sources.

3.0 Study Design

3.1 General Study Design

The design of this study is a prospective, randomized, double blind, placebo-controlled, crossover clinical trial. The study will involve a 22-day medication/placebo titration period, 7-day stable dosing, 9-day taper and washout, followed by crossover, The length of the study is 12 months.

3.2 Primary Study Endpoints

Evaluation and Outcome Measures:

- Frequency and results of diagnostic studies obtained for evaluation of cause of pain/irritability with analysis of yield of testing
- Parental reporting of frequency and duration of pain episodes
- Parental reporting of associated gastrointestinal and sleep problems
- Symptom assessment using the NCCPC-R (Non-Communicating Children's Pain Checklist-Revised), a standardized pain assessment tool for nonverbal neurologically impaired children, validated to be significantly related to pain intensity ratings provided by caregivers, consistent over time, and sensitive and specific to pain
- Parental satisfaction

3.3 Secondary Study Endpoints

Secondary Aims:

- To describe results of diagnostic studies obtained in neurologically impaired children with chronic irritability
- To identify associated gastrointestinal and sleep problems
- To determine if start or escalation of symptoms is temporally related to surgical interventions

Secondary Hypotheses:

- Repeating diagnostic studies when irritability persists adds limited benefit
- Gastrointestinal symptoms (feeding intolerance and symptoms associated with gas and bowel movements) and disrupted sleep are frequently associated with chronic irritability and improve with gabapentin

Escalation of symptoms often has a temporal relationship with a surgical procedure.

4.0 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Subjects are eligible to participate in the study if all of the following conditions exist:

1. Male or female, age 1 month to 16 years at enrollment
2. Neurological impairment defined as subnormal (-2 S.D.) motor and/or cognitive ability from a variety of etiologies
3. Chronic irritability defined as symptoms suggesting pain to the child's caregiver occurring recurrently over a 4-week or greater time period
4. Subject must have an acceptable surrogate capable of giving consent on the subject's behalf

4.2 Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

1. Children with resolved symptoms after treatment of identified sources
2. Identified potential source of irritability without adequate trial of appropriate management
3. Ketogenic diet
4. Renal insufficiency or failure
5. Current treatment with gabapentin or pregabalin for another existing condition

4.3 Exit Criteria

Subjects will exit the study if any of the following conditions exist:

1. Subject voluntarily withdraws from the study.
2. Subject death.
3. Subject acquires any of the listed exclusion criteria.
4. Subject completes the protocol.
5. Subject is non-compliant with the study protocol. Subject non-compliance is defined in Section 5.5.

Subjects exiting the study prior to completion of the protocol will be withdrawn as per Section 4.5.

4.4 Subject Recruitment and Screening

Gillette Children's Specialty Healthcare clinicians and nurses that treat children with neurological impairment will be infoinied of the study. Targeted clinics within Gillette include pediatric neurology, pediatric gastroenterology, and pediatric pain, along with other pediatric clinics that provide a model of chronic care for children with chronic complex medical conditions. If a patient is seen within a clinic that has been informed of the study, an introduction letter for the study will be handed out to potential candidate families. Database searches will also be conducted for potential

subjects. If a candidate is found in a database search, that family will be mailed the introduction letter, and receive a follow-up telephone call two weeks later to determine if the family is interested. The introduction letter will also contain contact information for the investigators and the clinical research coordinator.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subjects

Subjects may withdraw from the study at any time by withdrawing their consent. They must agree to be contacted (for safety reasons) for survival data. Subjects who do not adhere to the study drug dosing may also be withdrawn from the study to preserve the data collection.

If the subject withdraws from the study, it will be recommended to titrate off the medication per the chart depending on current dose.

4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who are withdrawn from the study will be contacted for survival data. At least 5 phone calls will be attempted, after which 3 letters will be sent from the site. Subjects who do not answer these calls or letters will be considered lost to follow-up. We will attempt to determine any deaths via our databases, newspaper announcements, and telephone listings for parents.

5.0 Study Drug

5.1 Description

The study drug is the commercial product, Neurontin® (gabapentin) 250 mg/5 ml by Pfizer/Parke Davis. The active drug is in a flavored glycerin based solution.

The placebo will be also be a glycerin based clear solution that is flavored similar to the commercial product (see Section 5.4 below).

5.2 Treatment Regimen

Doses will be given in liquid form through gastrointestinal tubes (if the child already has one) or orally. Children will be put on the following dosage regimen:

Day	Morning	Afternoon	Evening
1 - 3			5 mg/kg
4 - 6	2.5 mg/kg	2.5 mg/kg	5 mg/kg
7 - 9	2.5 mg/kg	2.5 mg/kg	10 mg/kg
10 - 12	5 mg/kg	5 mg/kg	10 mg/kg

13 - 15	5 mg/kg	5 mg/kg	15 mg/kg
16 - 18	7.5 mg/kg	7.5 mg/kg	15 mg/kg
19 - 21	7.5 mg/kg	7.5 mg/kg	20 mg/kg
22 - 28	10 mg/kg	10 mg/kg	20 mg/kg
29	7.5 mg/kg	7.5 mg/kg	20 mg/kg
30	7.5 mg/kg	7.5 mg/kg	15 mg/kg
31	5 mg/kg	5 mg/kg	15 mg/kg
32	5 mg/kg	5 mg/kg	10 mg/kg
33	2.5 mg/kg	2.5 mg/kg	10 ing/kg
34			5 ing/kg
35 - 37	off for 3 days then crossover		

Weight			
Day	Morning	Afternoon	Evening
1 - 3			5 mg/kg
4 - 6	2.5 mg/kg	2.5 mg/kg	5 ing/kg
7 - 9	2.5 mg/kg	2.5 mg/kg	10
10 - 12	5 mg/kg	5 mg/kg	10 mg/kg
13 - 15	5 mg/kg	5 mg/kg	15 ing/kg
16 - 18	7.5 mg/kg	7.5 mg/kg	15 mg,/kg
19 - 21	7.5 mg/kg	7.5 mg/kg	20 mg/kg
22 - 28	10 mg/kg	10 mg/kg	20 mg/kg
29	7.5 mg/kg	7.5 mg/kg	20 mg/lcg
30	7.5 mg/kg	7.5 mg/kg	15 mg/kg
31	5 mg/kg	5 mg/kg	15 mg/kg
32	5 mg/kg	5 mg/kg	10 mg/kg

5.3 Method for Assigning Subjects to Treatment Groups

A randomization table will be made before the study begins. Each patient added will be entered into their group as the randomization table dictates. This table will be kept in the pharmacy, and a copy will be maintained by the research coordinator to keep track of which group each subsequent subject will be assigned. Access to the table with patient names and doses of drug or placebo will be available in the pharmacy 24 hours x 7 days per week for safety precautions and unblinding.

5.4 Preparation and Administration of Study Drug

The study drug and the placebo will be prepared in the Gillette Hospital Pharmacy. The study will also be registered with the Investigational Drug Service (IDS) pharmacy IDS #4109RO.

Neurontin (gabapentin) Oral Solution 250 mg/5 ml by Pfizer Labs

Appearance:	clear solution
Inactive ingredients:	glycerin, xylitol, purified water and artificial cool strawberry anise flavor.
Storage Requirements:	Must be refrigerated

Placebo formulation:

Appearance:	clear solution
Inactive ingredients:	see below
Storage Requirements:	Must be refrigerated

Placebo Ingredients

Ora Sweet Sugar Free (Paddock Labs)	0.5 ml
Strawberry Flavoring (Gallipot Labs)	0.2 ml
Licorice Flavoring (LorAnn Oils, Inc.)	0.05 ml
Raspberry Flavoring (Gallipot Labs)	2 ml
Sterile Water (Baxter)	15ml

Compound Instructions

1. Mix all flavoring ingredients and Ora Sweet Sugar Free in a prescription vial.
2. Add the sterile water and shake well.
3. Label and refrigerate with a 60 day expiration date

Stock Supply Label: Gabapentin Placebo Oral Solution
Refrigerate Control #
Exp: (60 days from compounding)

A sufficient amount would be dispensed for a 34 days' supply dependent on the weight of the patient.

The active or placebo drug will be dispensed on a randomized manner. A log of the patient name/weight/address/phone # 1 will be kept together with the control # of the active drug and placebo.

The blinded study code can only be broken upon a request of the Principal Investigator.

A dosing chart will be printed out for patient's family/caregiver for both the active drug and the placebo. Only a 34 days' supply will be dispensed at one

time: So if the placebo was dispensed for the first 34 days the next supply for 34 days (active drug) - the family would have to pick up the new supply.

The study treatment will be administered orally or via a gastrointestinal tube 3 times daily, with dose specified for the parent or guardian in a customized table for each study subject.

5.5 Subject Compliance Monitoring

Compliance will be monitored by having the parents of the subject bring any unused drug back to Gillette Children's Specialty Healthcare each time they visit for the study. Amount of unused drug will be measured by the pharmacy before the subjects can get their next supply of study drug. Subjects will also be called every two weeks to assess any AEs and any positive effects subjects are experiencing. They will be asked how the customized drug plan for them is working. If a subject is found to be noncompliant with the study drug, the subject will be withdrawn from the study, with all withdrawal procedures followed. A subject will be defined as noncompliant if more than three days of doses of drug are missed.

5.6 Prior and Concomitant Therapy

During the history and physical, it will be determined if the patient is now or has been treated with Gabapentin or pregabalin. If currently receiving Gabapentin or pregabalin, the patient will be excluded from the study. No restrictions on other medications and therapies will be placed on the patient other than the ketogenic diet, and use of Gabapentin or pregabalin.

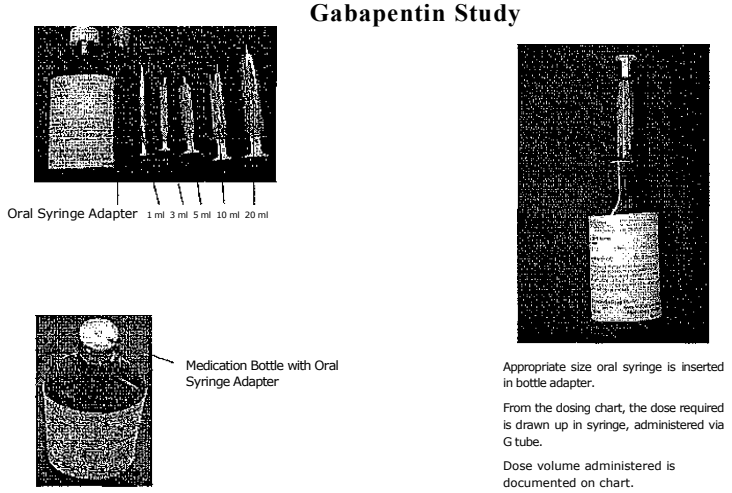


Figure 4. Study Drug Packaging

5.7 Packaging

The study drug or placebo will be packaged as a 34 day supply in an amber bottle with an oral syringe adapter and accompanying appropriately sized syringes. The bottles will be labeled with the subject's name, address, date, control number, expiration date, storage requirements and dosing instructions.

5.8 Blinding of Study Drug

The Gillette Children's Specialty Healthcare pharmacy will assign subjects to either the study drug or placebo as per the randomization table as described in Section 5.3. The pharmacy will prepare and label the study drug or placebo with a coded control number indicating group assignment.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The study drug is Nuerontin (gabapentin) 250 mg/5 ml 470 ml bottle solution by Pfizer/Parke Davis Pharmaceutical Company. It will be obtained by Gillette Hospital Pharmacy commercially from McKesson Wholesaler in St. Paul, MN

5.9.2 Storage

Nuerontin Solution must be stored in a refrigerator between 2-8 °C or 36-46 °F. The commercial bottle is an amber light resistant glass container. It will be placed in a special labeled container in the refrigerator "Gabapentin Study Drug".

5.9.3 Dispensing of Study Drug

Each patient will have its own unique record with the patient's clinical information together with address, parent or care giver's name & phone. The drug is prescribed on a mg/kg basis with 22 day medication/placebo titration period, 7-day stable dosing, 9-day taper and washout. The drug or placebo will be labeled identically except for a unique control number on the label. The label will state that the drug must be kept in the refridgerator.

Each study patient will have a chart with each day dosing given in the morning, afternoon and evening be printed with the volume (ml's) to be administered. Example: a 10 kg child on day #4 needs 2.5 mg/kg (25 mg) in morning and afternoon plus a 5 mg/kg (50 mg) in evening. The dosing chart would have on day #4 to give 0.5 ml (25 mg) in the morning and afternoon plus 1 ml (50 mg) in the evening. Gabapentin solution is 250 mg/5m1 or 50 mg/ml. This dosing chart is included with this application.

The total volume need for this 10 kg patient for the entire 34 day study would be less than 15 ml. We could dispense 20 ml in a 30 ml container with a oral syringe dispense cap.

The care giver would document each dose administered on this chart so we can reconcile the amount in the container plus the doses administered be the amount dispensed.

5.9.4 Return or Destruction of Study Drug

All study drug/placebo left over will be returned to Gillette Pharmacy for final reconciliation and destruction.

6.0 Study Procedures

Outline of procedure plan

1. Recruitment from clinics including: chronic care, neurology, gastroenterology, and pain
2. History and physical examination completed as part of routine assessment and management for chronic irritability
3. Determine if evaluation for potentially treatable causes of chronic irritability has been completed.
4. Parental consent
5. Parental questionnaire #1 and NCCPC-R rating 3 typical irritable events
6. Randomization: gabapentin or placebo
7. Titration schedule
8. Day 6 — phone call by study staff (or closest week day)
9. Day 13 — NCCPC-R, questionnaire #2, and phone call follow-up (or closest week day)
10. Day 24 — NCCPC-R, questionnaire #2, and phone call follow-up (or closest week day)
    If no improvement (dose 40 mg/kg/day) begin taper early(step #11) and set up visit with Research Coordinator (Step #12)
11. Day 29 — Begin medication taper
12. Day 34 to 38 — Family comes in to meet with the Research Coordinator. Subject is weighed. Perceived benefits and side effects of the drug are discussed. Report any concerns to the PI, if any. Subject is provided new drug at this visit. The old bottle will be taken back, along with the dosing chart. Remaining drug will be measured.
13. Day 38 — Crossover
14. Repeat steps 7 —11
15. At completion Research Coordinator contacts family by telephone to discuss perceived benefits/side effects of round 2 drug. Reports concerns to PI, if any

Parents complete one questionnaire #1, four questionnaires #2, and six NCCPC-R

Questionnaire # 1: includes 60 questions that require identifying the appropriate response from the items listed and 5 questions that require a written response.

Information obtained includes: frequency and duration of pain episodes along with associated gastrointestinal symptoms and sleep disturbance. The questionnaire takes approximately 15 minutes to complete.

Questionnaire #2: includes 24 questions that require identifying the appropriate response from the items listed and 2 questions that require a written response. Information obtained includes: frequency and duration of pain episodes along with associated gastrointestinal symptoms and sleep disturbance. The questionnaire takes approximately 5 minutes to complete.

NCCPC-R: Pain behavior in nonverbal neurologically impaired children can be measured using the Non-Communicating Children's Pain Checklist-Revised (NCCPC-R).[10, 11] The scale consists of seven domains including Vocal, Eating/Sleeping, Social/Personality, Facial Expression, Activity, Body/Limbs, and Physiological. The NCCPC-R has shown validity and reliability for everyday pain among children with developmental disabilities and was applied to study the incidence of pain in children with severe neurological impairments. Cut-off scores based on receiver operating characteristics suggest a score of 7 or greater on the NCCPC-R as indicative of pain in such children. The NCCPC-R takes approximately 5 minutes to complete.

Schedule of Events

Day	Pre-screen	Informed Consent	Medical History	Physical Exam	Phone Check	NCCPC-R	Ql	Q2
0	X	X	X	X		X	X	
6					X			
13					X	X		X
24					X	X		X
28					X			
34-37			X			X		X
38					X			
44					X			
51					X	X		X
62					X	X		X
76					X			

The Day 0 visit occurs as an office visit at the Gillette Children's Specialty Healthcare facility. A medical history and physical examination will be completed as part of routine assessment and management for chronic irritability. Determine if evaluation for potentially treatable causes of chronic irritability has been completed. The first round of drug will be dispensed. Families will be asked to mark off each dose they take out of the bottle with an X on the dosing sheet. Another visit with the research coordinator will occur once the drug has been tapered, during the washout period. During that visit, the subject will be re-weighed, the old drug bottle will be taken and the remaining drug measured, and

the old dosing sheet will be taken. Any benefits or side effects will be discussed at this visit, and the new drug bottle will be dispensed. Once drug has been tapered the second time, patients will be instructed to return the bottle when they return for their next standard of care appointment at Gillette Children's Specialty Healthcare.

Unscheduled visits
If any unscheduled visits occur due to side effects, another physical exam will be done and side effects will be recorded. Standard of care treatment will be administered for side effects. The NCCPR-C and Questionnaire #2 will be done as well.

7.0 Statistical Plan

7.1 Sample Size Determination

Power Calculations: A minimum sample size of 40 patients was determined by estimating a 15 point difference using the NCCPC-R pain assessment tool (90 points total) pre and post gabapentin, with a SD of 25 and within-person correlation of 0.6, accounting for recruitment and retention.

7.2 Statistical Methods

Simple descriptive statistics will be utilized to compare differences between the treatment and placebo groups with respect to frequency and duration of pain episodes, and frequency of gastrointestinal and sleep problems. Parent/caregiver reported questionnaires will be compared between groups. The NCCPC-R assessments will be scored and compared between groups, with a 15 point difference considered a significant difference.

7.3 Subject Population(s) for Analysis

The subject population to be analyzed includes all protocol compliant subjects. Subjects who are not compliant with the protocol will be withdrawn as described in Section 5.5

8.0 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal.
- is associated with a serious adverse event.
- is associated with clinical signs or symptoms.
- leads to additional treatment or to further diagnostic tests.
- is considered by the investigator to be of clinical significance.

Serious Adverse Event
A ***serious adverse event*** *(SAE)* is any AE that is:

- fatal.
- life-threatening.
- requires or prolongs hospital stay.
- results in persistent or significant disability or incapacity.
- a congenital anomaly or birth defect.

Important medical events may be considered SAEs. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug; more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor by telephone within 24 hours of the event. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Scott Schwantes, MD 651.229.3818 (phone)
651.265.7416 (fax)

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current Status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

8.3.3 FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit

the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

8.4 Unblinding Procedures

Unblinding of this study can be done by calling or contacting Gillette Pharmacy 24 hrs a day x 7 days a week. Only the approved providers can get access to this code.

8.5 Stopping Rules

The study will be interrupted or stopped in the following circumstances:

1. A separate body (e.g. FDA) deems Gabapentin to be unsafe for human use
2. The identification of a serious adverse event (fatality, life-threatening event, increased seizure activity, prolonged hospital stay), attributable to Gabapentin.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.0 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". Al] entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated, DO NOT ERASE OR WHITE OUT ERRORS, For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.0 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored by the Clinical and Translational Science Institute's Clinical Monitoring Service (CTMS) in accordance with the

attached Clinical Trial Monitoring Plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11.0 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the Gillette Children's Foundation Medical Education and Research Association (MERA).

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Subjects will receive a Target gift card for $50 at the end of the study for their time. Families will also receive parking vouchers for each visit completed. If a subject leaves the study early, that family will receive parking vouchers for each visit they completed.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 References

1. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LW, Passchier J, van der Wouden JC. Pain in children and adolescents: a common experience. Pain 2000;87(1):51-58.
2. Breau LM, Caulfield CS, McGrath PJ, Finley GA. The incidence of pain in children with severe cognitive impairments. Arch Pediatr Adolese Med 2003;157(12):121926.

3. Houlihan CM, O'Donnell M, Conaway M, Stevenson RD. Bodily pain and health-related quality of life in children with cerebral palsy. Dev Med Child Neurol. 2004;46:305-310.
4. Stallard P, Williams L, Lenton S, Velleman R. Pain in cognitively impaired, non-communicating children. Arch Dis Child 2001;85(6):460-2.
5. Greco C, Berde CB. Pain Management for the Hospitalized Pediatric Patient. Pediatr Clin N Am 2005;52:995-1027.
6. Schechter, NL, Berde, CB, Yaster. Pain in Infants, Children, and Adolescents. r[i] ed. Lippincott Williams and Wilkins; 2003.
7. Breau LM, Camfield CS, McGrath PJ, Finley GA. Risk factors for pain in children with severe cognitive impairments. Dev Med Child Neurol 2004;46(6):364-71.
8. Zangen T, Ciarla C, Zangen S, Di Lorenzo C, Flores AF, Cocjin J, et al. Gastrointestinal motility and sensory abnormalities may contribute to food refusal in medically fragile toddlers. I Pediatr Gastroenterol Nutr 2003;37(3):287-93.
9. Hauer I, Wical B, Chamas L. Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment. Pediatrics. 2007;119(2):e519-22.
10. Breau LM, Camfield C, McGrath PJ, Rosmus C, Finley GA. Measuring pain accurately in children with cognitive impairments: refinement of a caregiver scale. I Pediatr. 2001 May;138(5):721-7.
11. Breau LM, McGrath PJ, Camfield CS, Finley GA. Psychometric properties of the non-communicating children's pain checklist-revised. Pain. 2002 Sep;99(1-2):349-57.

15 Attachments

Dosing Chart
Questionnaire #1
Questionnaire #2
NCCPC-R
Clinical Monitoring Plan: Clinical and Translational Science Institute