Trial Design Considerations for Acute Pain in Neonates and Infants: Industry Perspective

FDA/Univ of Maryland CERSI Workshop
October 13 and 14, 2021

Edress Darsey, PharmD, FPPA

Pediatric Clinical Director

Pediatric Center of Excellence

Global Product Development

Pfizer, Inc.

Current newborn/infant pain interventional trials on www.clinicatrials.gov

- Not yet recruiting; recruiting; active,not recruiting
- 22 trials
  - 18 studies were non-pharmacological interventions (touch/comfort glucose)
  - 4 pharmacological studies, all independent universities

Terms and Synonyms Searched:

Terms Synonyms	Search Results*	Entire Database**
pain neonates infants	--	0 studies
infants	22 studies	8,560 studies
babies	2 studies	466 studies
neonates	22 studies	6,106 studies
Newborn	14 studies	4,687 studies
Neonatal	8 studies	1,687 studies
pain	22 studies	22,148 studies
AChE	--	30 studies
Dolor	--	9 studies
Painful	--	615 studies

www.clinicatrials.gov

Trial Design Considerations for Acute Pain in Neonates and Infants: Industry Perspective: current situation

Pediatric Labeling Changes | FDA

(FDAAA BPCA/PREA Pediatric labeling)

Lack of studies/clinical data and labeling for analgesics in infants/neonates; most drugs used are off label; before BPCA/PREA

- As of June 2021:
  - 671 pediatric label changes due to BPCA/PREA
  - 9 label changes in 3 therapeutic categories - (Pain, Non-opioid; Pain, Opioid and Pain, Topical)
  - Included two products for ages birth – 2 years
    - Caldolor (ibuprofen injection) expanded label down to 6 months
    - Ofirmev (acetaminophen injection) – studied for treatment of pain and fever in patients birth – 2 years
      - Label did not expand use below 2 years of age for treatment of pain due to lack of efficacy shown in study of infants and neonates.

Pediatric Labeling Changes | FDA

Industry must start a neonatal/infant pain study:

so many questions; where do you start???

Trial Design Considerations for Acute Pain in Neonates and Infants:

Industry Perspective: challenges clinically/trial design

Trial Design Challenges

- Neonatal trials are often combined with infants and children
  - Study design must accommodate different age groups, premature neonate; neonate; infant; child; adolescent
  - ADME differences in this wide age span
- Placebo-controlled trials used in adults – ethical issues in children
- Differences in labeling and Standard of Care between regions (but only a few analgesics labeled for neonates – makes it difficult to design studies with SOC)
- Formulation, palatability and acceptability considerations – some take years to develop
- Limited blood volume for sampling – need to use microsampling techniques when possible

Trial Design Considerations for Acute Pain in Neonates and Infants:

Industry Perspective: challenges clinically/trial design

Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations - PubMed (nih.gov)

JPR_A_195788 1649..1664 (sharepoint.com)

Immediate rescue designs in pediatric analgesic trials: a systematic review and meta-analysis - PubMed (nih.gov)

Trial Design Considerations

- Over 40 different validated pain assessment tools for neonates and infants.
- What pain model do you use?
  - Not consistent across ages (neonate, heel lance/circumcision; Infant/toddler, tonsillectomy, herniorrhaphy)
- Sample size – must consider many pediatric populations may be difficult to enroll
  - Study design almost impossible to enroll if long term opioid use required
  - How can we minimize exposure?
- Endpoints
  - Immediate Rescue/opioid sparing
  - Time to first rescue
  - Assessment of pain
  - Adverse events

Trial Design Considerations for Acute Pain in Neonates and Infants:

Industry Perspective: operational challenges

Operational Challenges

- Parents generally not interested in enrolling infants/neonate in study
  - limited benefit to patient
  - chance of suffering additional pain
  - extra blood draws, already sick infant/neonate, other invasive procedures

- Pain studies in children (PI– anesthesiologist, hospitalist, gen peds, intensivist);
- Pain study in Neonates (PI– neonatologist)

- Number of eligible patients to fit study design are low

- Informed consent

- Opioids – opiod crisis, no interest in enrolling in these studies

Example of site identification and initiation for a pediatric opioid trial

- Just under 2000 potential investigators contacted (3 rounds) – in US
  - Feasibility started in 2013
  - 560 investigators declined
  - 2017 - 36 sites selected/ 20 sites had a Site Initiation Visit – 14 active sites

There are some answers of where to start:

Tools and References for Infant and Neonatal Trial Design

FDA Guidance Document for Neonatal studies

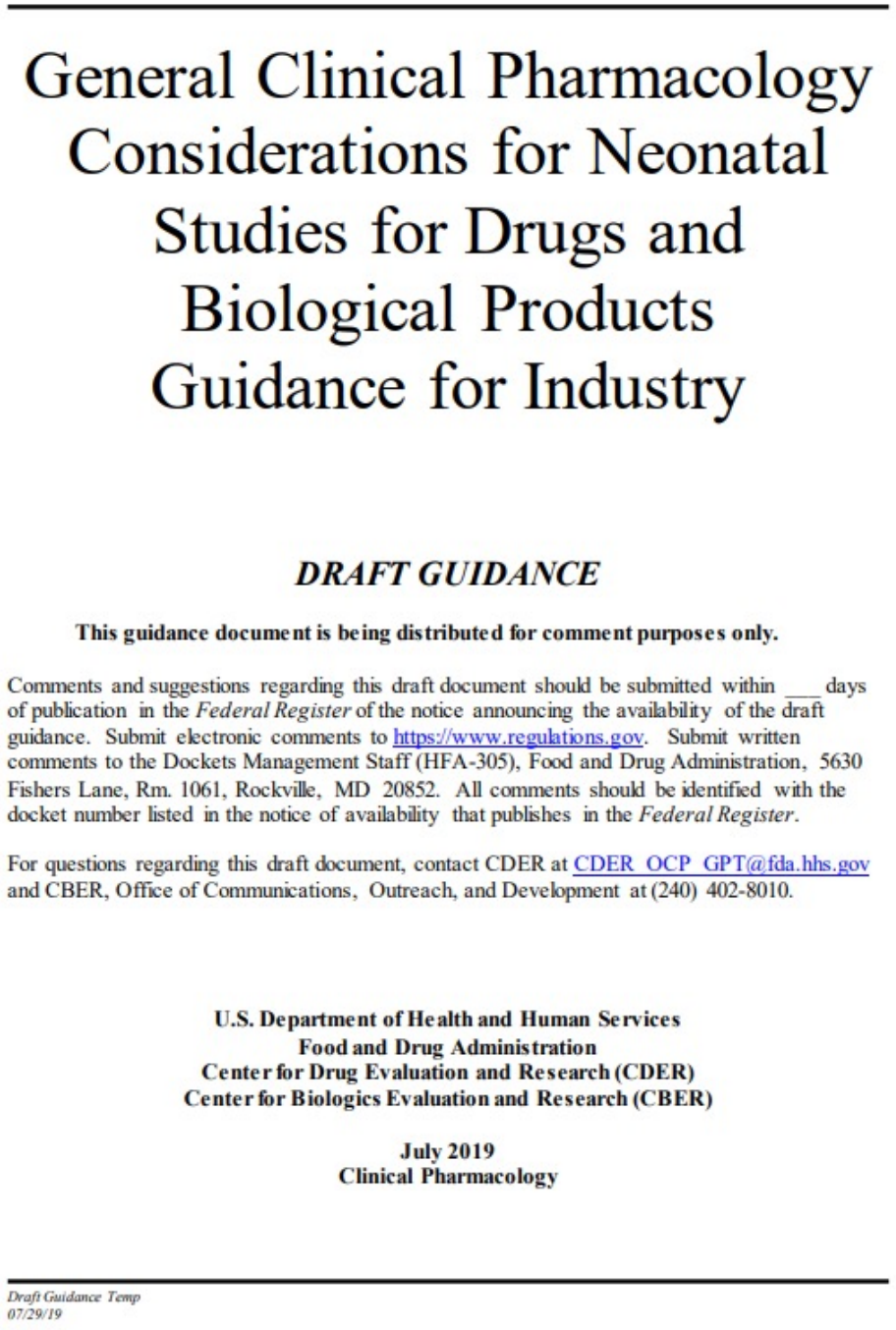
neonatal subgroup classifications

Pharmacokinetic, dynamics and genomics differences

Study design considerations – dose selection; formulation, sample size, blood vol limits;

Data analysis : modeling and simulation; pop pk; PBPK modeling

[General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry (fda.gov)]



General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact CDER at CDER_OCP_GPT@fda.hhs.gov and CBER, Office of Communications, Outreach, and Development at (240) 402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2019
Clinical Pharmacology

Draft Guidance Temp
07/29/19

Other regulatory guidance to support pediatric studies

- European Medicines Agency
  - Scientific guidelines: paediatrics | European Medicines Agency (europa.eu)

- ICH E11
  - GUIDELINE FOR GOOD CLINICAL PRACTICE (ich.org)

Guidance/Literature: neonatal and infant pain study design and considerations:

- FDA workshop – Dec 2009
- Publication Jan 2012
  - Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop - PubMed (nih.gov)
- This is a consensus developed during the workshop on pediatric analgesic clinical trial design
  - immediate-rescue designs using opioid-sparing, rather than pain scores, as a primary outcome measure

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

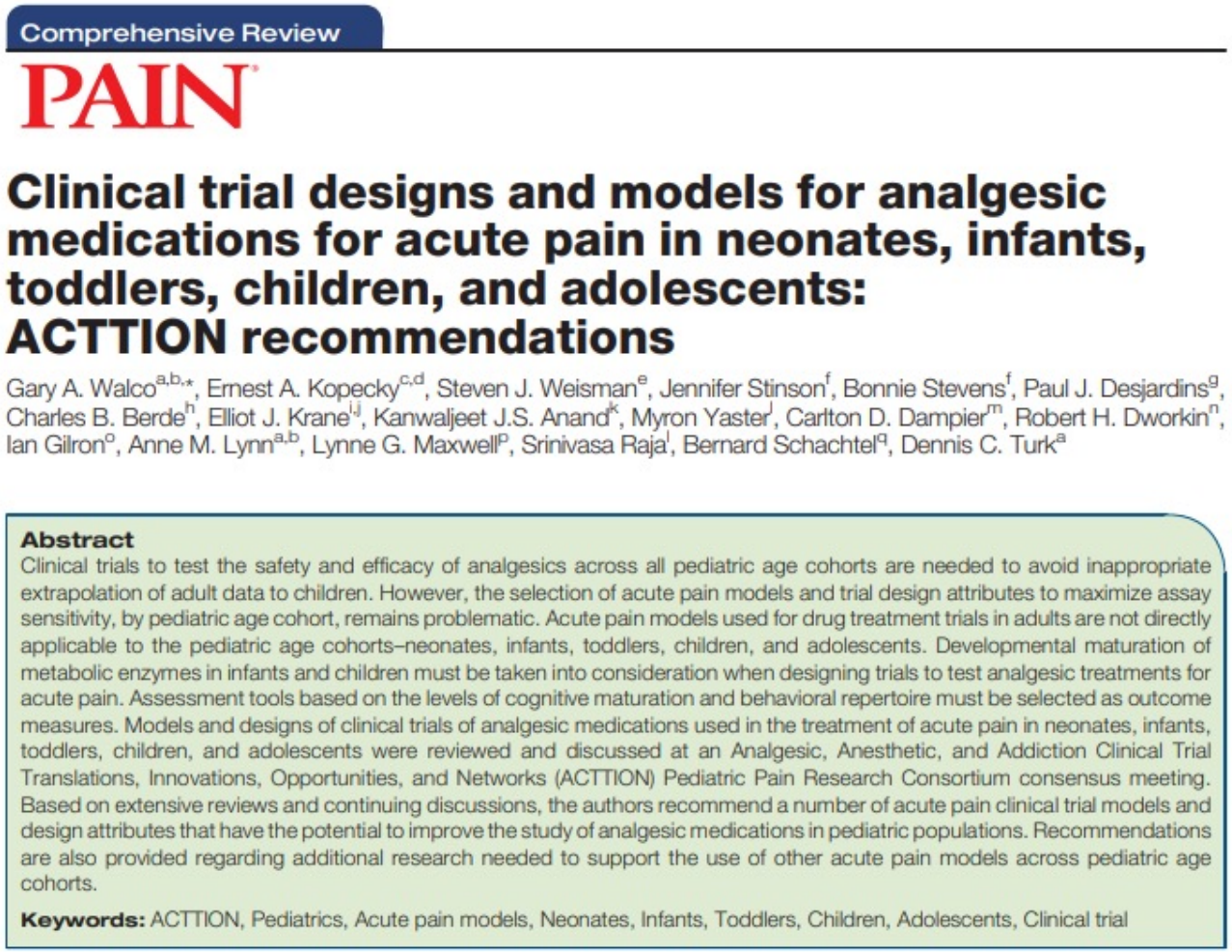
Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

Charles B. Berde, Gary A. Walco, Elliot J. Krane, K. J. S. Anand, Jacob V. Aranda, Kenneth D. Craig, Carlton D. Dampier, Julia C. Finkel, Martin Grabois, Celeste Johnston, John Lantos, Alyssa Lebel, Lynne G. Maxwell, Patrick McGrath, Timothy F. Oberlander, Laura E. Schanberg, Bonnie Stevens, Anna Taddio, Carl L. von Baeyer, Myron Yaster and William T. Zempsky

Pediatrics 2012;129;354
DOI: 10.1542/peds.2010-3591 originally published online January 16, 2012;

Guidance/Literature: neonatal and infant pain study design and considerations:

- Overview for considerations when designing protocol
- Pain Models
- Recommendation for trial design



Comprehensive Review

PAIN

Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations

Gary A. Walco[a,b,*], Ernest A. Kopecky[c,d], Steven J. Weisman[e], Jennifer Stinson[f], Bonnie Stevens[f], Paul J. Desjardins[g], Charles B. Berde[h], Elliot J. Krane[i,j], Kanwaljeet J.S. Anand[k], Myron Yaster[l], Carlton D. Dampier[m], Robert H. Dworkin[n], Ian Gilron[o], Anne M. Lynn[a,b], Lynne G. Maxwell[p], Srinivasa Raja[l], Bernard Schachtel[q], Dennis C. Turk[a]

Abstract

Clinical trials to test the safety and efficacy of analgesics across all pediatric age cohorts are needed to avoid inappropriate extrapolation of adult data to children. However, the selection of acute pain models and trial design attributes to maximize assay sensitivity, by pediatric age cohort, remains problematic. Acute pain models used for drug treatment trials in adults are not directly applicable to the pediatric age cohorts–neonates, infants, toddlers, children, and adolescents. Developmental maturation of metabolic enzymes in infants and children must be taken into consideration when designing trials to test analgesic treatments for acute pain. Assessment tools based on the levels of cognitive maturation and behavioral repertoire must be selected as outcome measures. Models and designs of clinical trials of analgesic medications used in the treatment of acute pain in neonates, infants, toddlers, children, and adolescents were reviewed and discussed at an Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) Pediatric Pain Research Consortium consensus meeting. Based on extensive reviews and continuing discussions, the authors recommend a number of acute pain clinical trial models and design attributes that have the potential to improve the study of analgesic medications in pediatric populations. Recommendations are also provided regarding additional research needed to support the use of other acute pain models across pediatric age cohorts.

Keywords: ACTTION, Pediatrics, Acute pain models, Neonates, Infants, Toddlers, Children, Adolescents, Clinical trial

[Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations - PubMed (nih.gov)]

Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

PERSPECTIVES

The challenge of developing pain medications for children: therapeutic needs and future perspectives

This article was published in the following Dove Press journal:
Journal of Pain Research

Mariëlle Eerdekens[1]
Christoph Beuter[1]
Claudia Lefeber[1]
John van den Anker[2,3]

[1]Grünenthal GmbH, Aachen, Germany; [2]Division of Paediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel, Switzerland; [3]Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA

Abstract: It is broadly accepted that children of all age groups including (preterm) neonates and young infants can perceive pain and that there is an absolute need to treat their pain safely and effectively. The approved treatment options for children, particularly (preterm) neonates and young infants, are very limited with only a few medications specifically labelled for this population. This article presents the challenges of developing pain medications for children. A short overview gives information on pain in children, including pain perception, prevalence of pain and the long-term consequences of leaving pain untreated in this vulnerable population. Current pain management practices are briefly discussed. The challenges of conducting pediatric clinical trials in general and trials involving analgesic medications in particular within the regulatory framework available to develop these medications for children are presented. Emphasis is given to the operational hurdles faced in conducting a pediatric clinical trial program. Some suggestions to overcome these hurdles are provided based on our experience during the pediatric trial program for the strong analgesic tapentadol used for the treatment of moderate to severe acute pain.

Keywords: pediatric patients, Pediatric Investigation Plan, pain relief, acute pain, tapentadol

https://pfizer.sharepoint.com/sites/PedCoEPresentations/Shared Documents/General/FDA Analgesic Clinical Trial Design Birth - 2 yr Oct 2021/Neonate Infant Pain Library/EerdekensStudyChallJPainRes2019.pdf

Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Outcomes of the Pediatric Development Plan of Tapentadol

This article was published in the following Dove Press journal:
Journal of Pain Research

Mariëlle Eerdekens
Tatjana Radic
Melanie Sohns
Feras Khalil
Beata Bulawa
Christian Elling

Grünenthal GmbH, Aachen, Germany

Abstract: The opioid analgesic tapentadol was the first pain medication to be developed for the treatment of pain in children under a formal process established by the regulatory authorities. This article summarizes the outcomes of the pediatric development program for tapentadol across the entire age range from birth (including neonates) to adolescents <18 years of age. In addition, the challenges experienced when designing and conducting the pediatric tapentadol clinical trials as well as the interactions with the regulatory authorities are discussed. As a first outcome, the oral solution of tapentadol was authorized in the EU in 2018 as a new treatment option in the hospital setting for moderate to severe acute pain in children from 2 to <18 years of age.

Keywords: pain, pediatric, regulations, tapentadol, review

Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Tapentadol for the Treatment of Moderate-to-Severe Acute Pain in Children Under the Age of Two Years

This article was published in the following Dove Press journal:
Journal of Pain Research

Ayman Eissa[1]
Eva Tarau[2]
Christoph Beuter[3]
Tatjana Radic[3]
Estelle Watson[3]
Melanie Sohns[3]
Claudia Lefeber[3]
Gregory B Hammer[4]

[1]Anaesthetic Department, Sheffield Children's Hospital, Western Bank, Sheffield, UK; [2]Grünenthal USA Inc., Overland Park, KS, USA; [3]Grünenthal GmbH, Aachen, Germany; [4]Department of Pediatrics and Anesthesiology, Perioperative and Pain Management, Stanford University School of Medicine, Stanford, CA, USA

Background: Pharmacokinetics (PK), efficacy, and safety of the opioid analgesic tapentadol in the treatment of moderate-to-severe acute pain have so far not been investigated in pediatric patients <2 years of age.

Patients and Methods: Two multicenter, open-label trials assessed the pharmacokinetic profile, safety, tolerability, and efficacy of single doses of tapentadol oral solution (OS; NCT02221674; n=19) or intravenous infusion (IV, EudraCT 2014-002259-24; n=38) in children from birth to <2 years of age. Of these, 8 preterm neonates were included in the IV trial. A third randomized, double-blind, placebo-controlled trial (NCT02081391) investigated the efficacy and safety of multiple tapentadol OS doses in patients from birth to <2 years (placebo n=4, tapentadol n=11) using an immediate rescue trial design. Patients in all three trials underwent surgery that, in the investigator's opinion, reliably produced moderate-to-severe pain requiring opioid treatment.

Results: Administration of single tapentadol doses resulted in tapentadol serum concentrations within the targeted range known to be safe and efficacious in adults and compared well to the range observed for children aged 2 to <18 years. Pain intensity already improved 15 min after administration. In the multiple dose trial, amounts of supplemental opioid analgesic medication within the first 24 h after start of trial medication were low (placebo 0.02 mg/kg, tapentadol 0.05 mg/kg). All patients stopped treatment with the trial medication because opioid analgesics were no longer required. Treatment-emergent adverse events occurred in 42.1% (tapentadol OS single dose), 28.9% (tapentadol IV), and 75% of placebo and 54.5% of tapentadol patients (tapentadol OS multiple doses), none of them serious.

Conclusion: Tapentadol showed a favorable PK and safety profile in children <2 years of age. Multiple tapentadol OS dosing is efficacious and generally well tolerated in children ≥2 years and might also be a useful treatment option for children <2 years in need of strong analgesics.

Keywords: infants, intravenous formulation, neonates, oral formulation, pain management, tapentadol

jpr-290487-outcomes-of-the-pediatric-development-plan-of-tapentadol.pdf

JPR_A_269530 229..248 (nih.gov)

From an industry standpoint, what would help infant and neonatal acute pain clinical trial success?

- Workshops like this to share new ideas and collaborate
- Collaborative working groups (industry, academia, regulatory, parents)
  - Sharing info
  - Patient/parent insights
- Additional opportunities for open dialog and feedback with the regulatory agencies, including the review division and pediatric division to accommodate challenges regarding neonatal pain study design