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Application of a new methodological approach to overcome paediatric clinical trial challenges: GAPP study

PANSIERI CLAUDIA

EPTRI General Assembly and Scientific Meeting 13-15 March Bologna

GAPP

GAbapentin in Pediatric Pain

TOWARD NEW THERAPIES TO CHALLENGE CHRONIC PAIN IN CHILDREN

THERAPEUTIC NEED

Poor is the attention on the paediatric research among European initiatives even if the right to healthcare and safe medicine is recognised in many legal texts such as the EU Charter of Fundamental Rights and the Treaty on European Union. In addition, in 2015 the European Strategy Forum on Research Infrastructures (ESFRI) stated that **'children have been poorly served by research even though they have specific emotional and physical needs that must be met'.**

Lack of Paediatric Data
Off-Label Use
Lack of Age-Appropriate Formulation

Many factors contribute to defining the need of a therapy:

- Target disease
- Availability of other drugs, i.e., efficacy and/or safety profile, pharmaceutical form
- Target patient population, e.g., ages

Who defines the need?

Mostly the "need" is defined by the treating physicians, by the Regulators, or is defined according to available guidelines.

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PAEDIATRIC CHRONIC PAIN

Paediatric Need

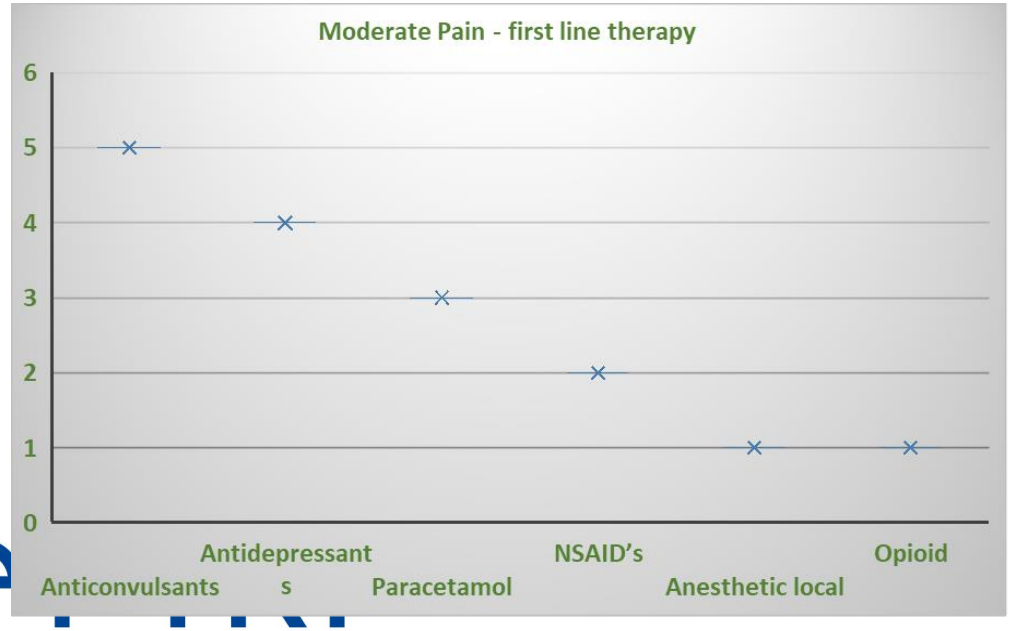
Chronic pain is an area of unmet needs in children with few available properly authorized medicines.

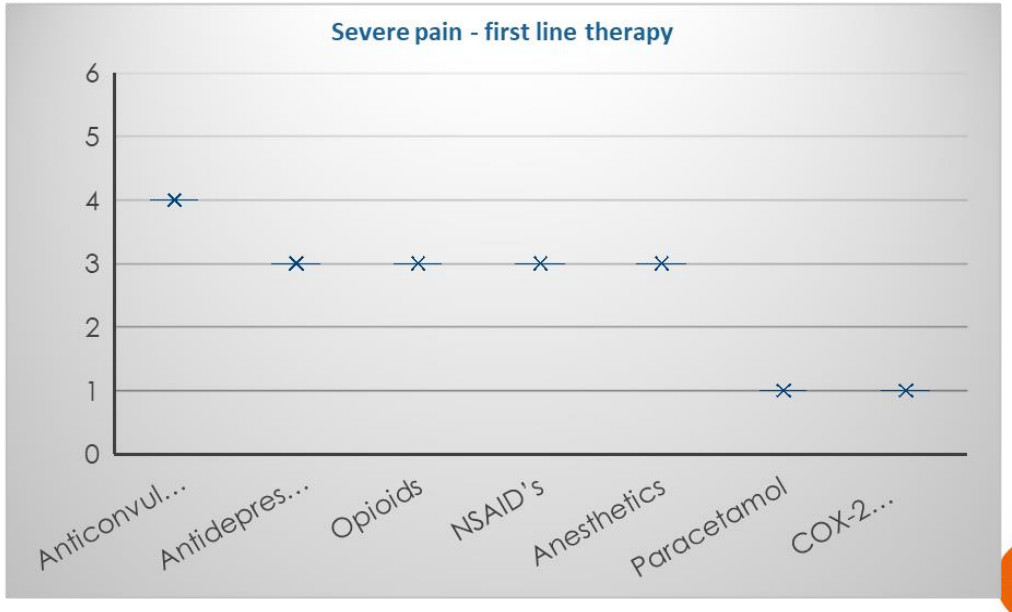
Off label uses

Unadapted pharm. formulations

High risk of ADRs & medical errors

No Standards of care & several treatment options:





EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

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GABAPENTIN IN PAEDIATRIC PAIN

Approved Indications in several European Member States

- **partial seizures**:
  - adjunctive therapy in adults and children aged 6 years and above (in some Countries from 3 years)
  - monotherapy in adults and adolescents aged 12 years and above.
- **peripheral neuropathic pain** (i.e. painful diabetic neuropathy and post-herpetic neuralgia) in adults

The indication for **neuropathic pain** is not approved in the **paediatric population**, but the existing therapeutic need has led to a large **off-label gabapentin use** in the treatment of many pain conditions.

The **lack of a suitable oral formulation** complicates the treatment in the younger patients also in the approved indication (epilepsy).

Gabapentin was included in the "**Revised priority list for studies into off-patent paediatric medicinal products currently used off-label**" (Doc. Ref. EMA/98717/2 012), intended to address unmet therapeutic needs in children. **According to the list, paediatric data on efficacy and safety are requested for the treatment of chronic pain with gabapentin.**

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GAPP PROJECT

AIM

To increase the availability of paediatric medicines by developing a full clinical strategy on gabapentin tested in chronic pain and making results available for a PUMA application.

Primary objective

Development of an age appropriate oral liquid formulation for the conduction of appropriately designed paediatric studies for a new paediatric indication (treatment of chronic pain of neuropathic origin)

Specific objectives

1. Juvenile animal toxicity study (pre-GABA) for the investigation of the potential effects of gabapentin on the central nervous system development.

2. Two controlled, parallel-arm efficacy-safety clinical trials in patients aged from 3 months to less than 18 years with moderate and severe pain (GABA-1 e GABA-2 protocol studies respectively).

3. Bridging study (GABA-3) to specifically address the paucity of data in children from 3 months to 3 years, integrating data of the GABA-1 and GABA-2 studies and designed to confirm the dose rationale for this specific population.

MAIN GOALS

1) PHARMACEUTICAL & PRECLINICAL DEVELOPMENT:

A **liquid formulation of Gabapentin (syrup - 75mg/ml)** was developed. Palatability in young children was specifically addressed in order to facilitate acceptability and compliance to a chronic treatment.

A toxicity study was conducted in **juvenile rats** administered with Gabapentin twice daily for 25 days. No observed Adverse Effect Level of at least 2000 mg/kg bw/day was derived.

2) CLINICAL STUDIES

GABA-1	**Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, efficacy and safety of gabapentin liquid formulation to tramadol in children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic or mixed pain (EudraCT: 2014-004851-30).**
GABA-2	**Randomized, double-blind, placebo controlled, multi-center superiority phase II study to evaluate the safety, pharmacokinetic, efficacy of gabapentin liquid formulation as add-on to morphine in children from 3 months to less than 18 years of age experiencing severe chronic neuropathic or mixed pain (EudraCT: 2014-004897-40)**

GAPP TERMINATION

In July 2017 the project officially terminated since its duration was only 4 years and no extension was obtained by the European Commission. Further funding would be needed to terminate the Paediatric Investigation Plan (EMEA-001310-PIP01-12).

GABA-1

Participating Countries (centres): Albania (1), France (4), Germany (1), Greece (1), Italy (2), The Netherlands (2); Poland (1); United Kingdom (1)

Pts enrolled and randomised : 2 from Germany. They completed all the visits and did not show any Serious Adverse Event. For the patient treated with gabapentin, the IMP showed a good efficacy-safety profile.

Status: early terminated in June 2019 due to insufficient recruitment

GABA-2

Participating Countries (centres): Albania (1), France (4), Germany (1), Italy (2), The Netherlands (2)

Pts enrolled and randomised: 0

Status: the GABA-2 study could not be started due to exhaustion of funding provided by the European Commission within the Seventh Framework Programme

GAPP TERMINATION - MAIN ISSUES

GABA-1 & GABA-2

The project implementation posed special difficulties due to the **small patient population** and the need to involve a large **number of recruiting centres**. The main issues encountered were related to the **inclusion/exclusion criteria**.
The main key barriers included:

- the **required wash-out period** that was considered not acceptable by many patients/parents,
- the choice of an **opioid** (Tramadol) as **active comparator** that still today cannot be considered as a recognised standard of care,
- the issue related to **the off-label access** to Gabapentin for the patients, that led to a reduction of interest in participating in the trial and thus significantly impacting recruitment potential.

In addition, the long and different **approval times** from Competent Authorities and Ethic Commitees caused a slowdown of the studies progress.

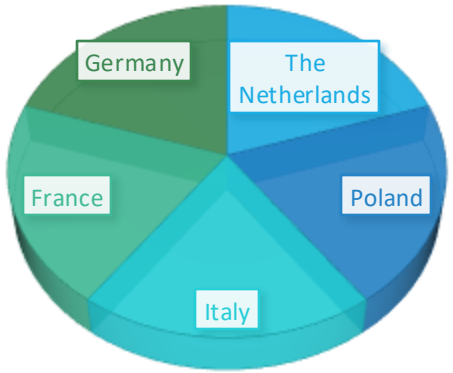
Gabapentin in Paediatric Chronic Pain
GAPP study

Title: To evaluate Efficacy, Pharmacokinetics, and Safety of Gabapentin in children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic, nociplastic or mixed pain: an Adaptive-design Prospective Cohort Study (GAPP Study).

Study population:

- Male or female aged 3 months to less than 18 years at screening.
- Subjects that meet the diagnostic criteria for moderate to severe chronic neuropathic, nociplastic, and mixed pain

Six Clinical Centers:



Sample size: 67 naïve and non naïve paediatric patients

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GAPP Study

Clinical Trial Feasibility

The goal of the study remains unchanged: **to evaluate the efficacy, pharmacokinetics, and safety of gabapentin in pediatric patients with chronic and mixed pain.**

However, the **new adaptive study design (and bayesian methodology) instead of a traditional superiority study** offers two **key benefits**:

- **Avoiding the Selection of a Comparator:** In a traditional superiority study, a direct comparison between gabapentin and another treatment (like a placebo or another active drug) is required to prove that gabapentin is more effective. The adaptive design helps to sidestep this issue by allowing the study to focus on the drug's effectiveness without necessarily comparing it against a fixed alternative. This flexibility means that decisions can be made during the study, such as modifying dosing, sample size or patient groups based on interim results.
- **Reducing the Sample Size:** The Bayesian methodology allows for more flexibility in statistical modeling, which can lead to a reduced number of patients needed for the study. This is because Bayesian methods use prior information (like data from previous studies or expert opinion) combined with current study data to draw conclusions, which can achieve sufficient statistical power with fewer participants.

GAPP study

Adaptive-design Prospective Cohort Study

Study design: *Adaptive-design Prospective Cohort Study*
This is an **adaptive, single arm** study that employed a **Bayesian trial design**.
The Bayesian trial design utilizes Bayes theory to generate probabilities based on prior observed data. Bayesian trial design analyses the data collected at regular time-points and terminates the enrolment when the target probability is achieved or when the target probability is deemed unobtainable with the resources available. This can reduce the number of subjects required when compared with non-adaptive frequentist models.

Adaptive approach

The central advantage of adaptive design is the ability to include prospectively planned opportunities for modifying study design elements and hypotheses based upon interim data analyses. After interim analysis, when the half-planned sample size is enrolled and the efficacy evaluation is available, considering the use of an adaptive trial design:

- study can be stopped for **futility**;
- **sample size** can be re-estimated to provide an adequate study power.

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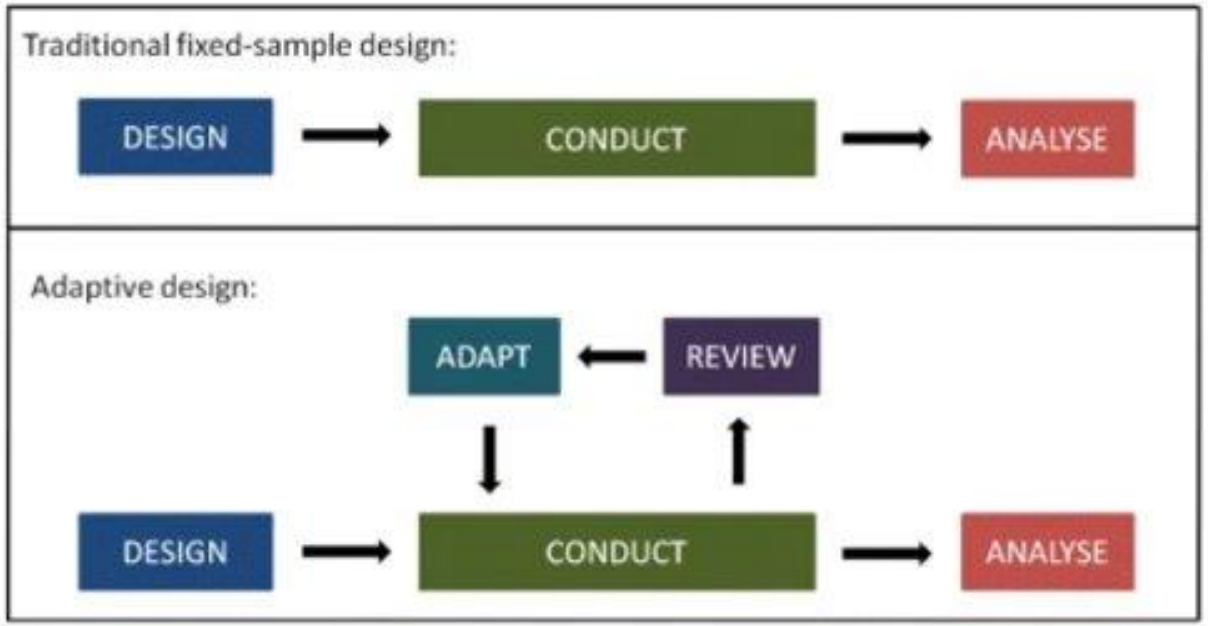
Innovative methodological approaches

Adaptive designs can make clinical trials more flexible by utilising results accumulating in the trial to modify the trial's course in accordance with pre-specified rules. Trials with an adaptive design are often more efficient, informative and ethical than trials with a traditional fixed design since they often make better use of resources such as time and might require fewer participants.



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Regulatory Acceptability

Innovative METHODOLOGICAL approaches

Innovative methodological approaches for study design such as the Adaptive Study and the Master Protocols (Umbrella and Basket), play a crucial role in pediatrics by ensuring the feasibility of the study and the validity of the results.

ADVANTAGES:

- ***Increase Efficiency*** *in testing novel therapies*
- ***Decrease the patient populations***
- *Easier patient* ***access****, higher* ***retention***
- *Ensure* ***feasibility*** *and* ***validity*** *of data*
- *Offer* ***flexibility*** *in trial design as data emerges allowing for adaptation of therapies, reduction of trial duration and patient burden*
  - ***Improvement*** *of Ethical Standards*
  - ***Patient-Centric*** *Approaches*
  - ***Safety*** *Monitoring*
- ***Optimization*** *of resource use*

LIMITATIONS:

- ***Conservatism and Resistance to Change*** *as new approaches can appear risky or insufficiently validated compared to traditional methods*
- ***Complexity in planning*** *and* ***management***
- ***Regulatory Concerns*** *regarding the interpretation and generalization of results*
- ***Specialized expertise*** *in advanced methodologies and statistical analysis contributes to* ***increased costs***
- ***Limited familiarity*** *and* ***lack of specialized training*** *among researchers and clinicians*

Although the fundaments of these innovative approaches have been already streamlined in comprehensive scientific and regulatory guidelines and accepted at the regulatory level long ago, their implementation in paediatric clinical research practice remains very limited

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