Farmacovigilância em idade Pediátrica
Desafios sub-18

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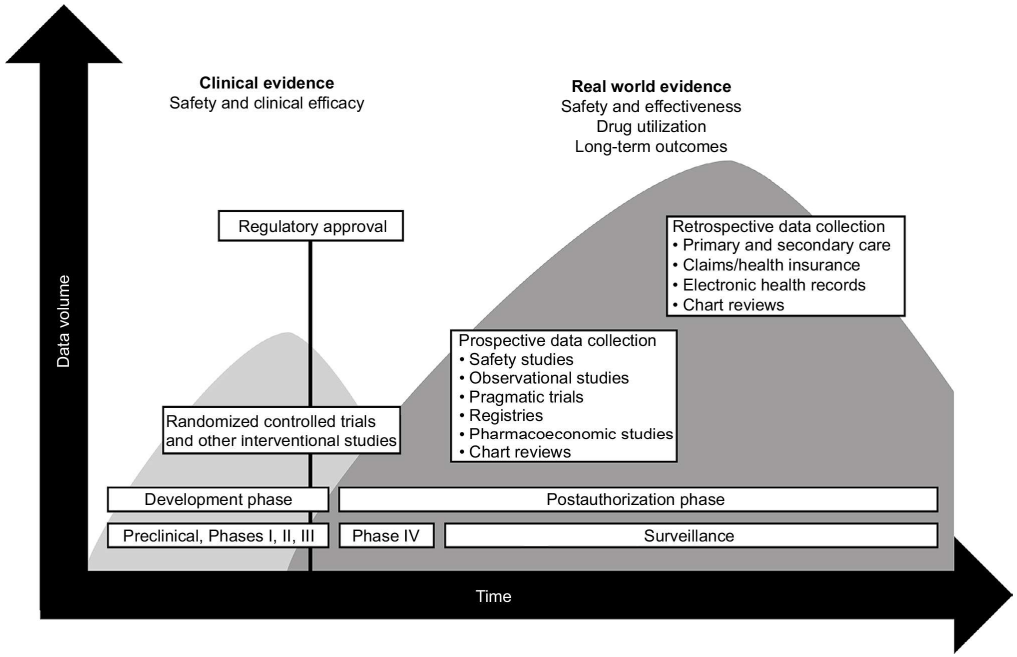
Challenges in pediatric drug therapy

- **Pediatric clinical pharmacology**
  - Maturation, ontogeny and development in PK/PD
- **Pediatric formulations**
- **Gaps in pediatric evidence**
- **Unlicensed and off-label drug use**
- **Ethics and methodology of pediatric research**
- **Rare and ultra-rare diseases**
- **Other medicinal products and devices/medtech**
- **Voices of children/young people and families**



Challenges in signal detection and assessment of short and long-term safety and benefit-risk throughout the drug lifecycle

Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. Journal of multidisciplinary healthcare. 2018 Jul 2:295-304.

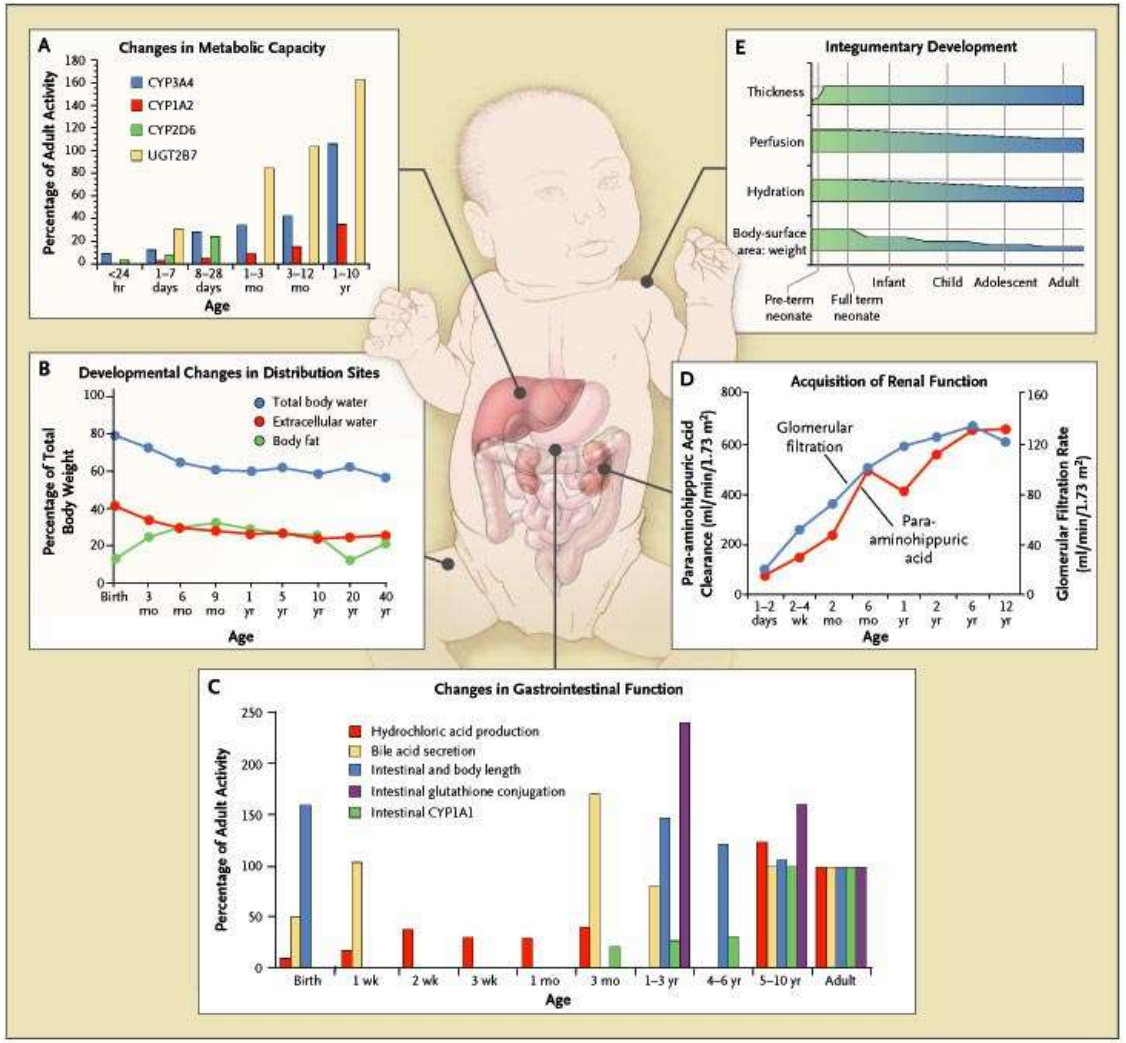
"NOT SMALL ADULTS"

Neonate → Adolescent

Pharmacokinetics:
- Absorption, distribution, excretion, metabolism
- Genetics

Pharmacodynamics:
- Receptor numbers and affinity- mode of action
- Disease progression/natural history
- Disease severity
- Co-morbidities
- Impact of growth and normal developmental processes
- Age-specific aspects of disease
- Differences in microbiome
- Genetics

Three Gymnasts the Same Chronological Age!



Kearns 2003
Barker 2018

A disturbing legacy

Chloramphenicol and grey baby syndrome

FATAL CIRCULATORY COLLAPSE IN PREMATURE INFANTS RECEIVING CHLORAMPHENICOL*

LAFAYETTE E. BURNS, M.D.,† JOAN E. HODGMAN, M.D.,‡ AND ALONZO B. CASS, M.D.§

LOS ANGELES, CALIFORNIA

A SURVEY was made of premature infants born twenty-four hours or longer after spontaneous rupture of the fetal membranes, because of a higher mortality in this group than in the premature infants whose membranes had ruptured at birth. Routinely, these infants had been placed on antibiotics shortly after birth because of assumed exposure to infection. The role of antibiotics in this higher mortality was questioned. A comparative study of these infants on different treatment schedules was conducted from March, 1958, to February, 1959. This paper is a report of that study.

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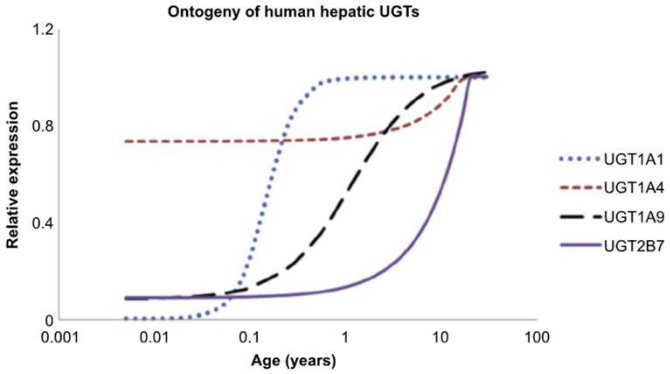
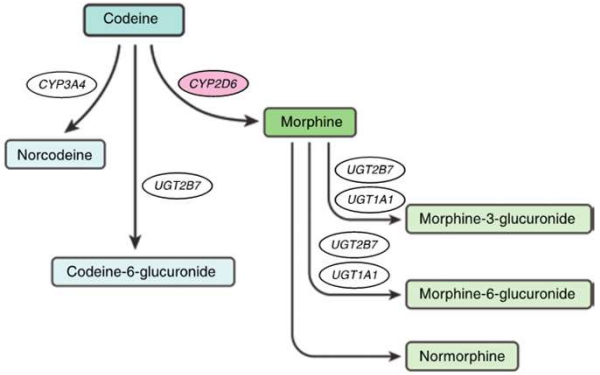
METHOD

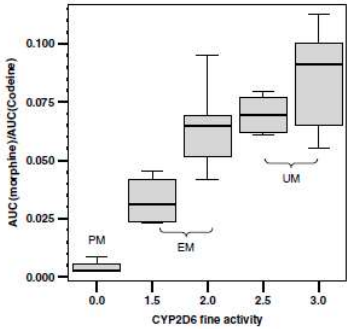
All premature infants delivered in the birth suites of the Los Angeles County Hospital after spontaneous rupture on the fetal membranes for twenty-four hours or more were assigned to one of four groups according to the time of admission to the premature center. Group 1 received no antibiotics. Group 2 received chloramphenicol,¶ 100 to 165 mg. per kilogram of body weight per day intramuscularly. Group 3 received procaine penicillin, 150,000 to 600,000 units per day, and streptomycin, 50 mg. per kilogram of body weight per day. Group 4 received all three antibiotics in the same dosage previously mentioned. Half of the daily dose of each antibiotic was given intramuscularly every twelve hours.

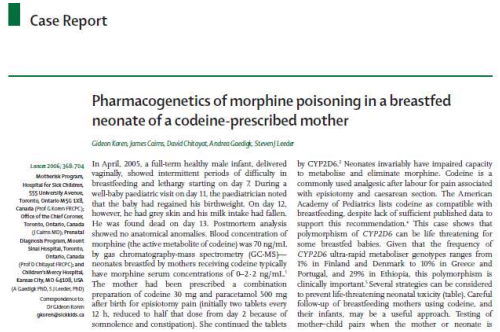
¶In the form of Chloromycetin Intramuscular, Parke, Davis and Company, Detroit, Michigan.



Codeine, ultra-metabolizers and neonatal poisoning







Case Report

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

Lancet 2006; 368: 704

Motherisk Program, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada (Prof G Koren FRCPC); Office of the Chief Coroner, Toronto, Ontario, Canada (J Cairns MD); Prenatal Diagnosis Program, Mount Sinai Hospital, Toronto, Ontario, Canada (Prof D Chitayat FRCPC); and Children's Mercy Hospital, Kansas City, MO 64108, USA (A Gaedigk PhD, S J Leeder, PhD)

Correspondence to: Dr Gideon Koren gkoren@sickkids.ca

In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2·2 ng/mL.[1] The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets by CYP2D6.[2] Neonates invariably have impaired capacity to metabolise and eliminate morphine. Codeine is a commonly used analgesic after labour for pain associated with episiotomy and caesarean section. The American Academy of Pediatrics lists codeine as compatible with breastfeeding, despite lack of sufficient published data to support this recommendation.[3] This case shows that polymorphism of *CYP2D6* can be life threatening for some breastfed babies. Given that the frequency of CYP2D6 ultra-rapid metabolizer genotypes ranges from 1% in Finland and Denmark to 10% in Greece and Portugal, and 29% in Ethiopia, this polymorphism is clinically important.[4] Several strategies can be considered to prevent life-threatening neonatal toxicity (table). Careful follow-up of breastfeeding mothers using codeine, and their infants, may be a useful approach. Testing of mother-child pairs when the mother or neonate is

Crews 2011, Krekels 2017

The risks of dosing and administering

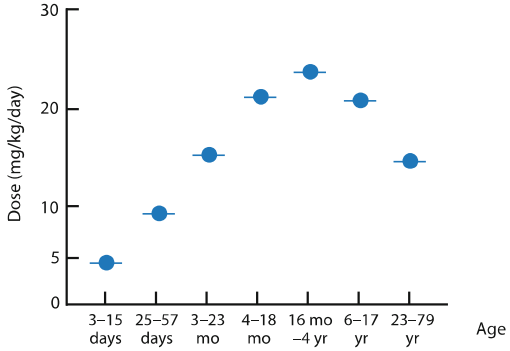
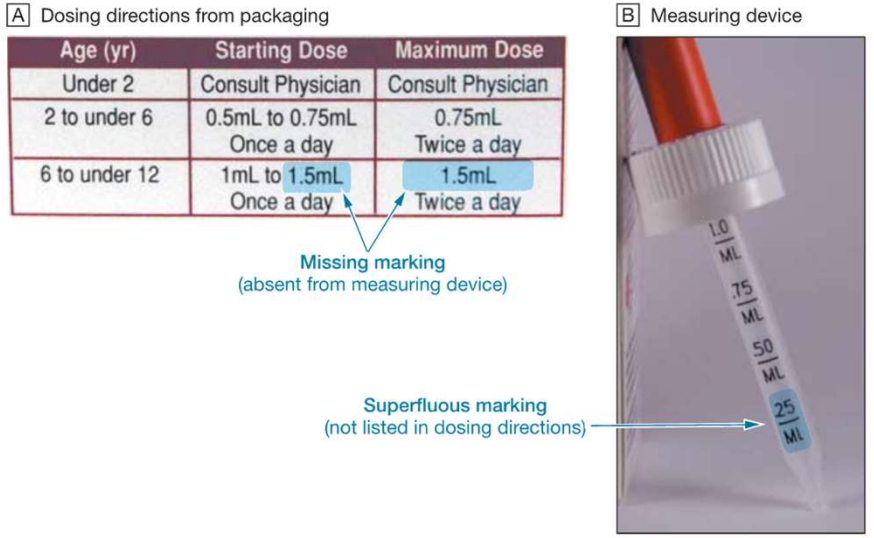


Table 1. Advantages and disadvantages of various methods of dose adjustment for children.

Method of dose adjustment	Advantages	Disadvantage
Age	Very easy to use in clinical practice	Inaccurate. Requires wide therapeutic index to be safe.
Body weight (BW)	Easy to apply in clinical practice	Nonlinear relationship between weight and dose. Also, for pre-clinical work: smaller species are generally more tolerant of drug treatment than larger species [13].
Body surface area (BSA)	More accurate than BW, particularly during infancy and childhood [14]	Over-predicts clearance in neonates [14]. Harder to use in routine clinical practice.
Allometric scaling	Superior to BW and BSA for scaling some PK parameters such as plasma clearance, volume of distribution and elimination half-life [15]	Complex calculation, difficult to apply to clinical practice.

Table 1 Reference doses (mg/kg) compared to intravenous formulations to illustrate the need for sequential dilutions in neonates

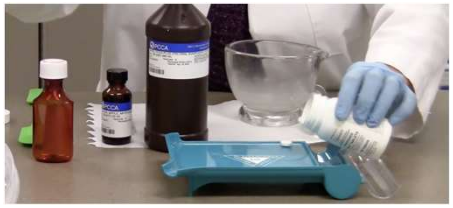
Active agent	Available concentration	Reference doses	Preterm, 1.5 kg	Term, 3 kg
Amikacin, adult vial	500 mg/2 mL	15-20 mg/kg	130 mg, 0.12 mL	50 mg, 0.2 mL
Amikacin, pediatric vial	100 mg/2 mL	15-20 mg/kg	30 mg, 0.6 mL	50 mg, 1.0 mL
Enoxaparin	40 mg/0.4 mL	1 mg/kg	11.5 mg, 0.015 mL	13 mg, 0.03 mL
Erythromycin	1000 mg/20 mL	5-10 mg/kg	12 mg, 0.24 mL	25 mg, 0.5 mL
Fentany[l]	100 μg/2 mL	1-3 μg/kg	13 μg, 0.06 mL	16 μg, 0.12 mL
Insulin	300 U/3 mL	0.1-1 U/kg per hour	10.3 U, 0.03 mL	10.6 U, 0.06 mL
Midazolam	15 mg/3 mL	0.1 mg/kg	10.15 mg, 0.03 mL	10.3 mg, 0.06 mL
Paracetamol	500 mg/50 mL	10 mg/kg	15 mg, 1.5 mL	30 mg, 3 mL
Phenobarbital	200 mg/1 mL	5 mg/kg	17.5 mg, 0.0375 mL	115 mg, 0.075 mL
Propofol	200 mg/20 mL	1-3 mg/kg	2 mg, 0.2 mL	4.5 mg, 0.45 mL
Ranitidine	50 mg/2 mL	0.5-1 mg/kg	11.5 mg, 0.06 mL	13 mg, 0.12 mL



Yin HS, Wolf MS, Dreyer BP, Sanders LM, Parker RM. Evaluation of consistency in dosing directions and measuring devices for pediatric nonprescription liquid medications. Jama. 2010 Dec 15;304(23):2595-602. Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Archives of disease in childhood. 2013 Sep 1;98(9):737-44.

The long road to pediatric formulations

- **The critical role and caveats of extemporaneous preparations**
  - From common (eg prednisolone) to life-saving (eg benzoate)
  - Palatability et al
- **Not so inert: excipients and safety**



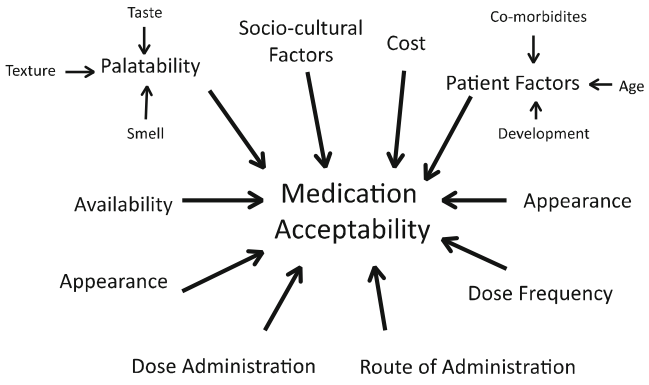
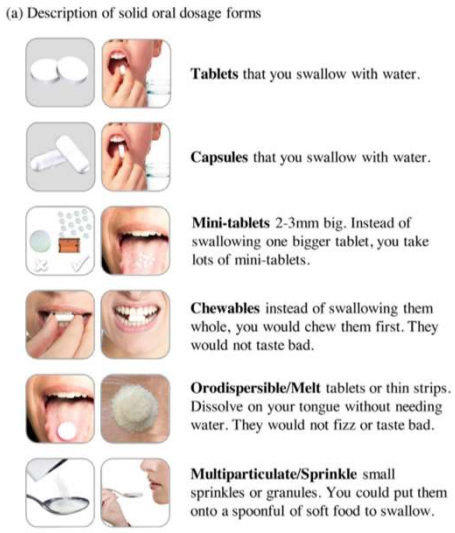


TABLE 2 Examples of Excipients With Elevated Toxicity and Safety Risks for (Preterm and Term) Newborns and Infants <6 Months of Age[7,8,53–60]

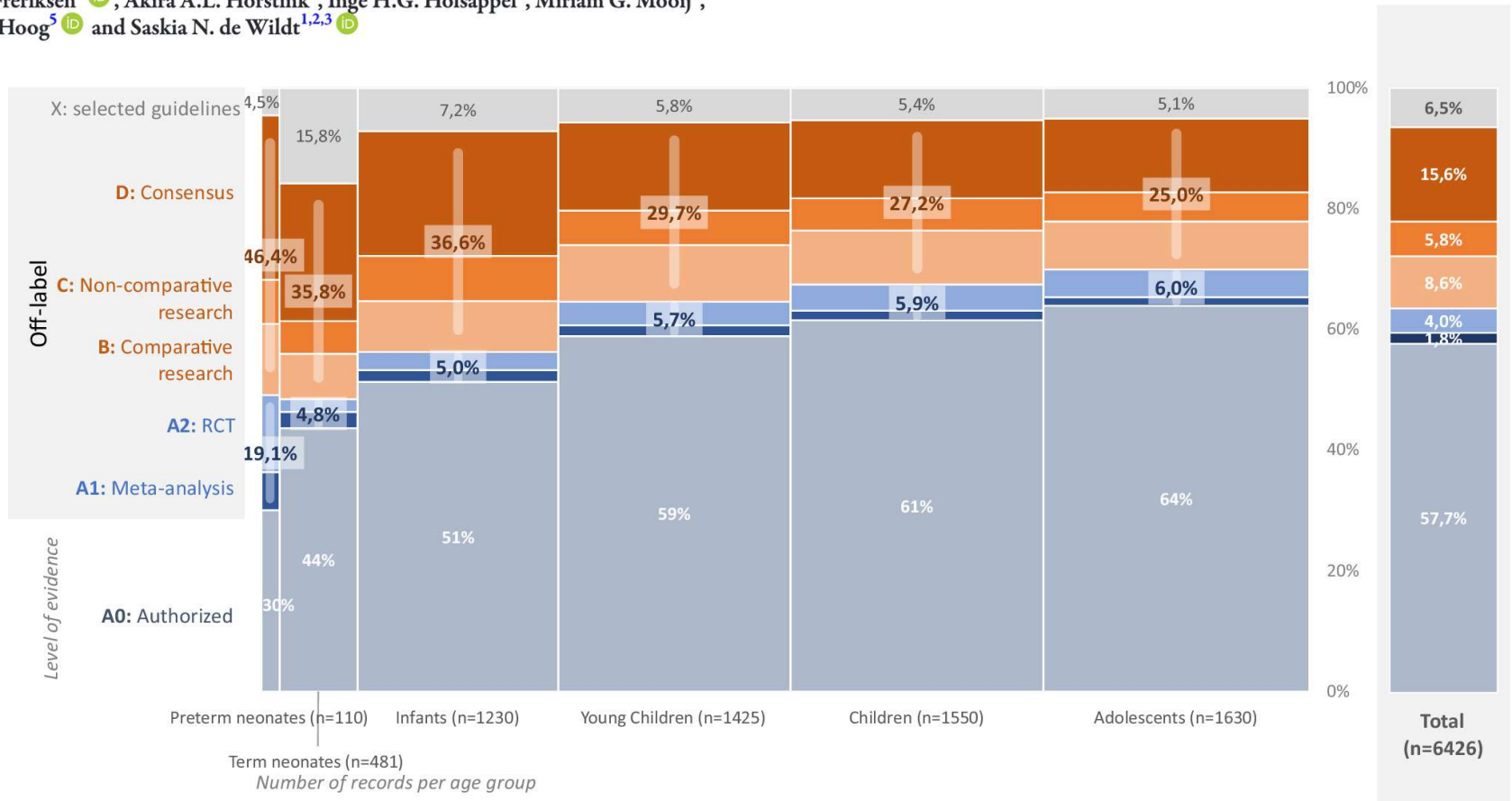
Excipient	Adverse Reaction
Benzyl alcohol[7,8,53,54]	Neurotoxicity, metabolic acidosis
Ethanol[55]	Neurotoxicity, cardiovascular problems
Propylene glycol[54,56–59]	Neurotoxicity, seizures, hyperosmolarity
Polysorbate 20 and 80[60]	Liver and kidney failure



Rieder M. Size and taste matters: recent progress in the development of age-appropriate medicines for children. Pharmaceutical Medicine. 2018 Feb;32(1):21-30.
Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014 Aug;134(2):361-72.

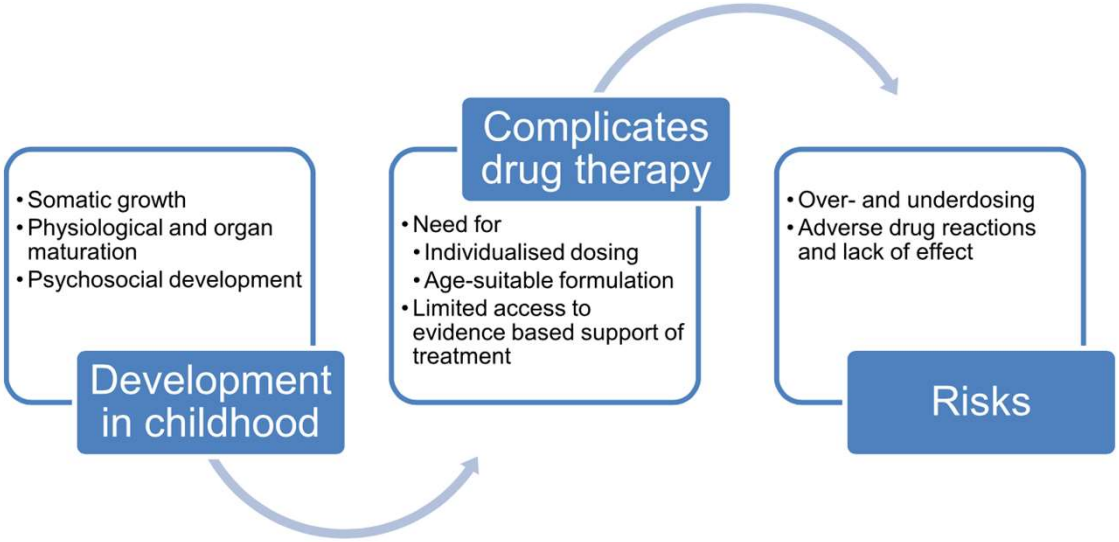
Off-Label, but on-Evidence? A Review of the Level of Evidence for Pediatric Pharmacotherapy

Tjitske M. van der Zanden[1,2,3,*,†], Nori J.L. Smeets[1,2,†], Marika de Hoop-Sommen[1,3,4], Michiel F.T. Schwerzel[1], Hui Jun Huang[1], Lieke J.C. Barten[1], Joyce E.M. van der Heijden[1], Jolien J.M. Freriksen[1], Akira A.L. Horstink[1], Inge H.G. Holsappel[4], Miriam G. Mooij[5], Matthijs de Hoog[5] and Saskia N. de Wildt[1,2,3]



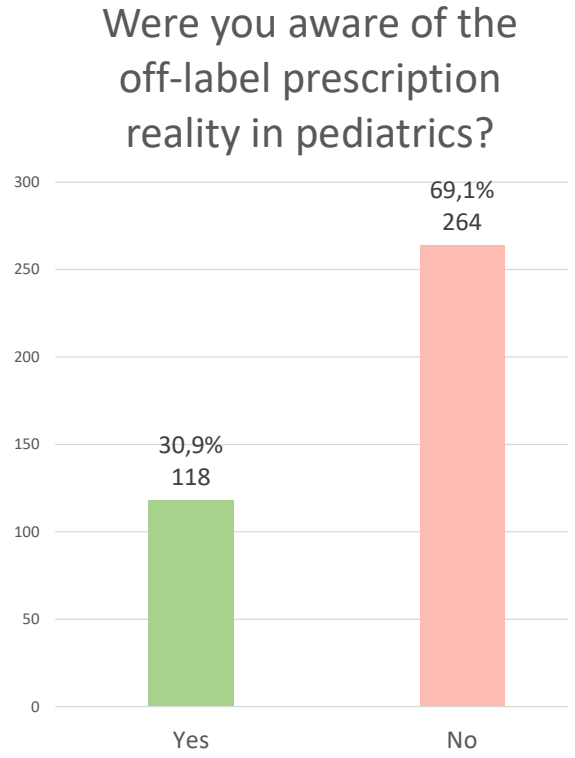
van der Zanden TM, Smeets NJ, de Hoop-Sommen M, Schwerzel MF, Huang HJ, Barten LJ, van der Heijden JE, Freriksen JJ, Horstink AA, Holsappel IH, Mooij MG. Off-label, but on-evidence? A review of the level of evidence for pediatric pharmacotherapy. Clinical Pharmacology & Therapeutics. 2022 Sep 7.

Off-label, perception and drug safety



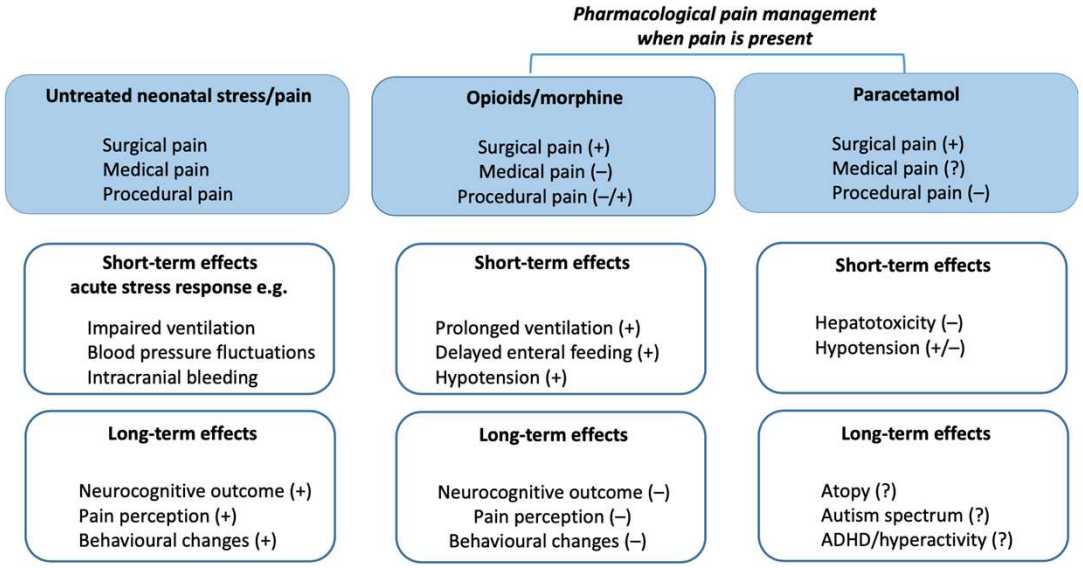
No ex ante evaluation of risks and benefits
Uncertainty of dosing and contraindications
Less effective pharmacovigilance system

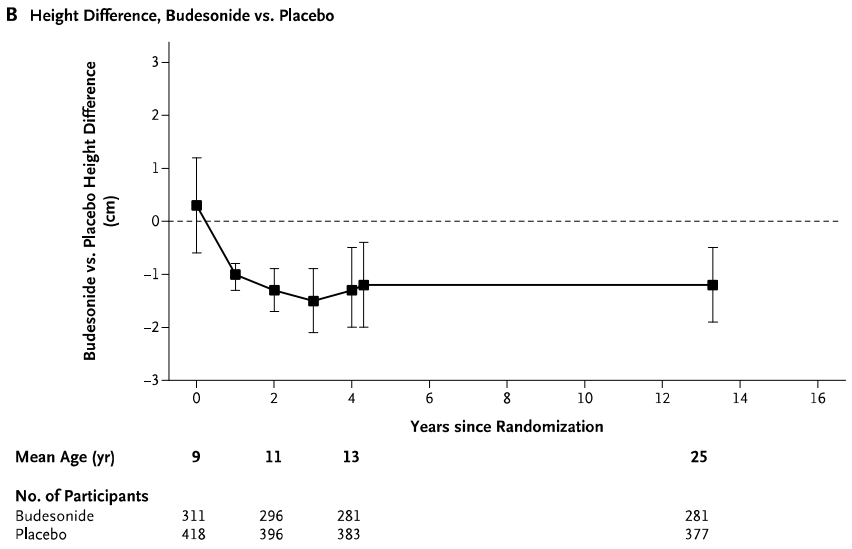
POPPI Project



Lisman 2019

Beyond today: long-term perspective on harms





Smits, 2007

Methodological limitations in pediatric trials

Open access Original article

BMJ Paediatrics Open

Reporting of data monitoring committees and adverse events in paediatric trials: a descriptive analysis

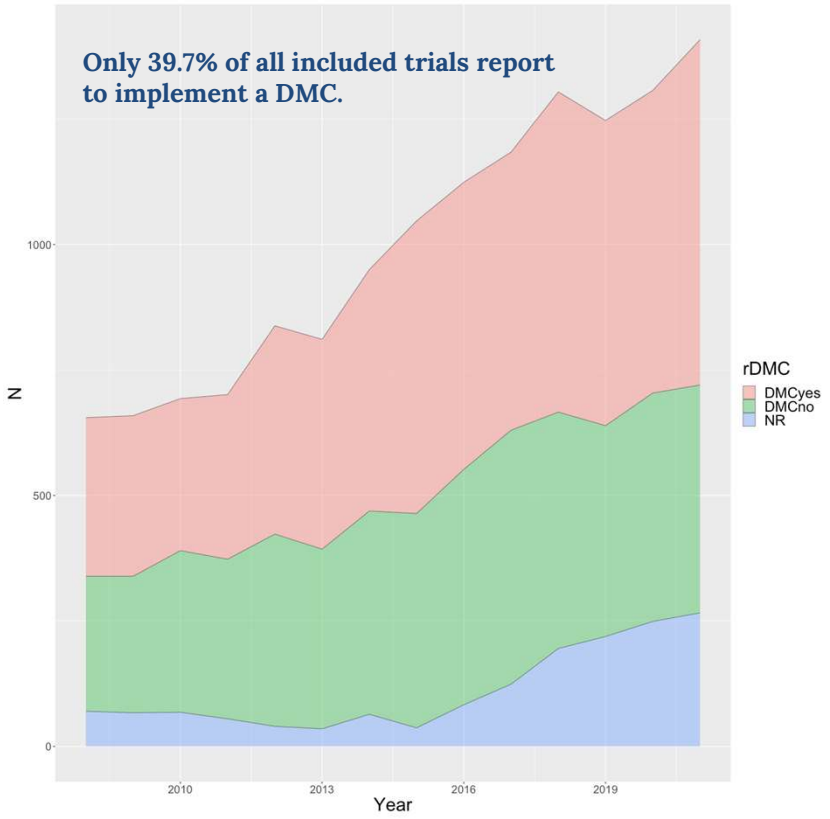
Allison Gates,[1] Patrina Caldwell,[2,3] Sarah Curtis,[4] Leonila Dans,[5] Ricardo M Fernandes,[6] Lisa Hartling,[1] Lauren E Kelly,[7,8] Ben Vandermeer,[1] Katrina Williams,[9] Kerry Woolfall,[10] Michele P Dyson[1]

What this study hopes to add?

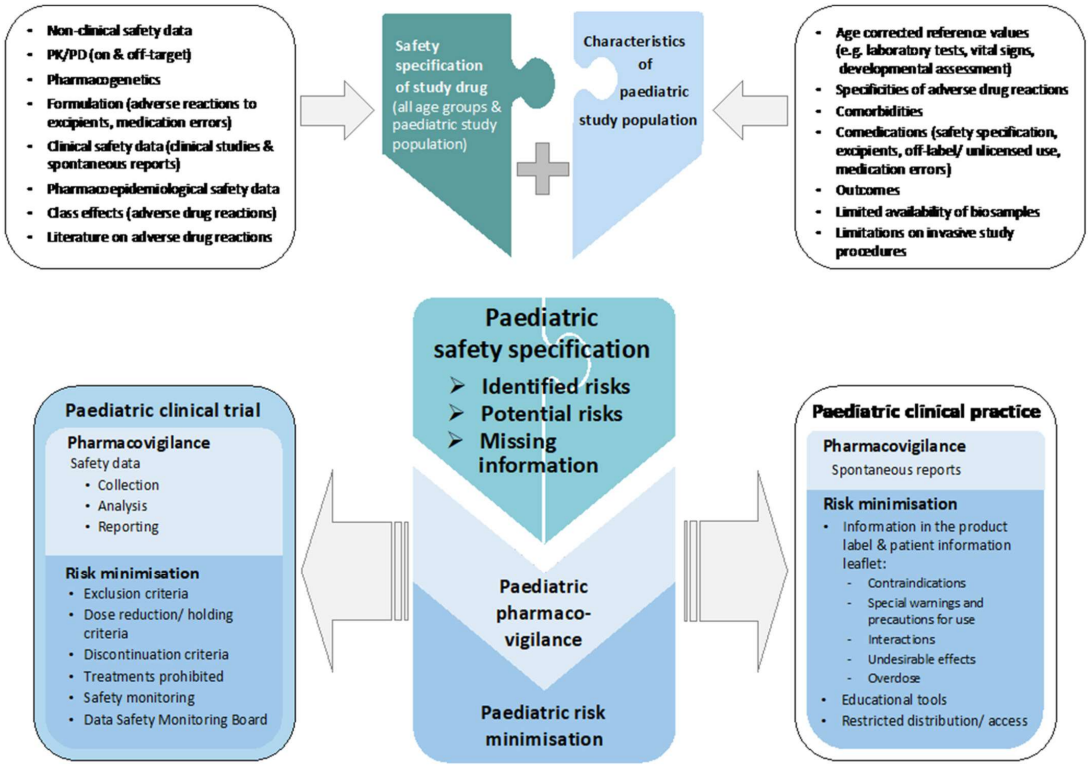
- In a randomly selected sample of 300 paediatric trials published in 2012, 18% reported a data monitoring committee.
- Fifty-two per cent of trials did not report any adverse events data.
- Only 32% of drug trials reported a data monitoring committee; 18% and 19% did not report on adverse events or harm-related endpoints, respectively.

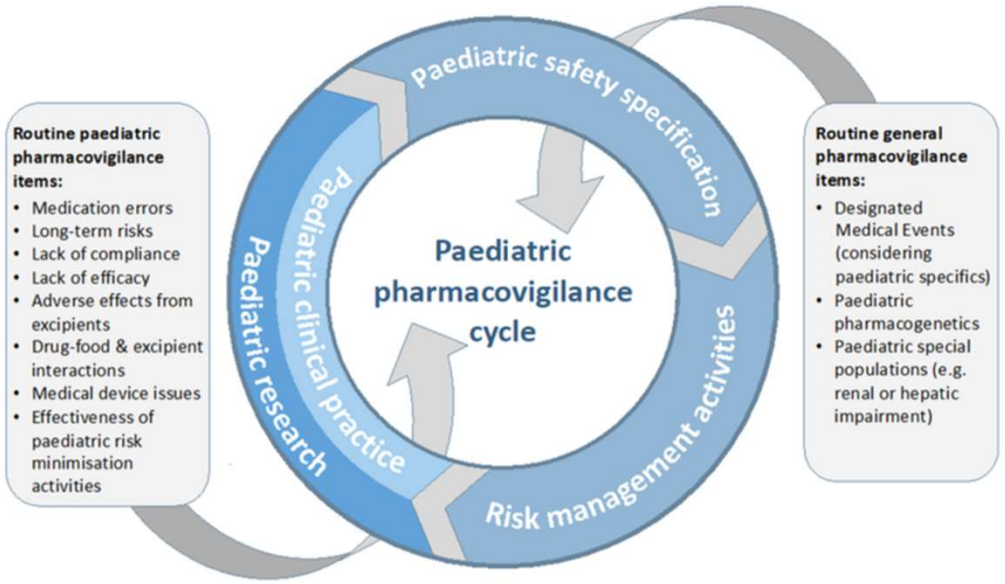
Data Monitoring Committees in Pediatrics

A review of randomized controlled trials registered in ClinicalTrials.gov



Moving forward in pediatric PV





Aurich B, Apele-Freimane D, Banaschewski T, Chouchana L, Day S, Kaguelidou F, Kelly LE, Kindblom JM, Neubert A, Wong IC. c4c: Paediatric pharmacovigilance: Methodological considerations in research and development of medicines for children–A c4c expert group white paper. British journal of clinical pharmacology. 2022 Dec;88(12):4997-5016.

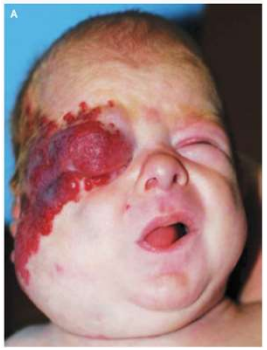
Different needs, different treatment options…


FEBRE NA CRIANÇA / ADOLESCENTE

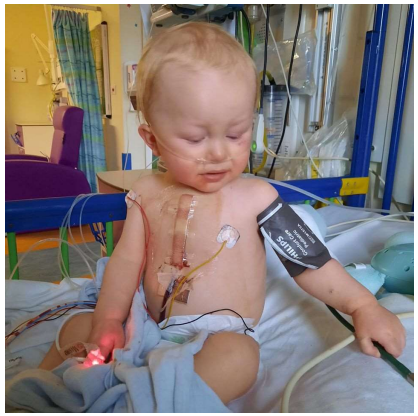
Folheto informativo para pais e cuidadores

antipyretic regimens…


RSV anti-virals and vaccines…


propranolol…


nusinersen, onasemnogene abeparvovec, risdiplam…

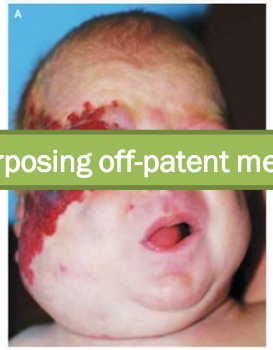

sacubitril/valsartan…

…different archetypes and pathways of pediatric drug development

Post-approval evidence

antipyretic regimens…

RSV anti-virals and vaccines…



Re-purposing off-patent medicines

propranolol…

De novo pediatric medicines

nusinersen, onasemnogene abeparvovec, risdiplam…

Pediatric development on the backbone of adult innovation

sacubitril/valsartan…

Extrapolation of Efficacy:

Disease/response "similarity" is a continuum

Different	Dissimilar	Similar	Same
No overlap between adult and pediatric condition	Some degree of overlap with significant differences between adult and pediatric condition	Large degree of overlap with some differences between adult and pediatric condition	Significant overlap; no known significant differences between adult and pediatric condition

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

Pediatric RCT(s)

Pharmacodynamic markers, Bayesian methodologies, etc.

Exposure matching

Planning, set-up & conduct of a Paediatric Development Program

A multifaceted challenge…

Defining the medical need	Right indication and population	Preparing and agreeing a Paediatric Development Plan	Small patient populations – competing developments
Use/acceptance of innovative study designs	Insufficient trial infrastructure	Divergent view of Ethic Committees	Contradictory local regulations
Diverse standard of care across Europe	Impact on daily lives of patients and families	Dose, route of administration, application device	Acceptance of Paediatric research in society

CONECT4CHILDREN

COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

Why PPP

The **paediatric clinical trial infrastructure in the EU is fragmented and not sufficiently developed**.
A broad **multidisciplinary public-private collaboration is required to meet the challenges** and to be transformative and to **collectively address children's needs for better medicines**.

Impact

Improved paediatric development plans and study designs
More efficient implementation and conduct of Paediatric clinical trials
Improved data quality, better trial feasibility and faster enrollment

Status & Value

Expert advice and patient/parent involvement
Access to over 300 Clinical and methodological paediatric experts
Inclusion of YPAGs, patients and parent groups in advice meetings; Single contracting structure, coordination of Expert Advice

Single Point of Contact
Access to local networks in 21 European countries and over 250 clinical sites
Aligned processes across the entire network increase efficiency and quality

c4c Training Academy
Providing standardized training to all study sites and site personal, Master courses on Pediatric Drug Development

Paediatric Data Dictionary & CDISC TAUG
1st Pediatric Data Dictionary established to allow standardization of data collection across Paediatric studies

Working together on safety in pediatric trials

Received: 14 October 2022 | Revised: 5 January 2023 | Accepted: 13 January 2023

DOI: 10.1111/bcp.15669

REVIEW ARTICLE

Implementation of a centralized pharmacovigilance system in academic pan-European clinical trials: Experience from EU-Response and conect4children consortia

Vida Terzić[1,2] | Léa Levoyer[1,2] | Mélanie Figarella[1,2] | Elisabetta Bigagli[3,4] | Noémie Mercier[1,2] | Lucie De Gastines[1,2] | Séverine Gibowski[1,2] | Marius Trøseid[5] | Jacques Demotes[6] | Inge Christoffer Olsen[7] | Maya Hites[8] | Florence Ader[9] | José Ramón Arribas Lopez[10] | France Mentré[11] | Hélène Espérou[12] | Dominique Costagliola[13] | John-Arne Røttingen[14] | Julien Poissy[15] | Jean-Christophe Rozé[16] | Adilia Warris[17] | Jackie O'Leary[18] | Ricardo M. Fernandes[19] | Lambert Assoumou[13] | Regis Hankard[20] | Mark A. Turner[21,22] | Yazdan Yazdanpanah[1,2,23] | Alpha Diallo[1,2] | EU-Response safety group | c4c safety group

ORIGINAL RESEARCH

Standardizing Paediatric Clinical Data: The Development of the conect4children (c4c) Cross Cutting Paediatric Data Dictionary

Anando Sen*, Victoria Hedley*, John Owen†, Ronald Cornet‡, Dipak Kalra§, Corinna Engel‖, Avril Palmeri*, Joanne Lee*, Jeane Christophe Roze¶, Joseph Standing**, Adilia Warris††, Claudia Pansieri‡‡, Rebecca Leary*, Mark Turner§§ and Volker Straub*

Introduction: Standardization of data items collected in paediatric clinical trials is an important but challenging issue. The CDISC data standards are well understood by the pharmaceutical industry but lack the implementation of some paediatric-specific concepts. When a paediatric concept is absent within CDISC standards, pharmaceutical companies and research institutions take multiple approaches in the collection of paediatric data, leading to different implementations of standards and potentially limited utility for reuse. **Objective:** To overcome these challenges, the conect4children consortium has developed a cross-cutting paediatric data dictionary (CCPDD).

TABLE 3 Paediatric Case Reports Form design: Points to consider for safety data collection

Item	Points to consider
Age	• Different practices may exist for how age is documented in neonates and premature infants • Ensuring age is correctly documented and in a harmonised manner across study sites will facilitate the calculation of growth percentiles/*z*-scores and using age corrected references ranges for test results for efficacy and safety
Weight and height and percentile or *z*-score	• Depending on the study population and the duration of the study, weight and height may be measured repeatedly • Weight, height and/or age may be used to calculate the dose of the study drug and any co-medications • Both measures are plotted on growth charts which may be population-specific (e.g., for premature infants or children with certain conditions such as Down's syndrome)
Alert values for laboratory and vital signs	• Alert values should be appropriate for the age group • Some reference values change as the child develops and may therefore need to be adapted during the trial; in neonates these changes can occur within days
Adverse events	• Coding dictionaries may not include sufficient granularity to code paediatric conditions correctly • Consider addressing any potential coding issues in a trial-specific coding guidance/standard operating procedure • Consider seeking paediatric pharmacovigilance expert advice
Co-medication	• Co-medications should be captured with sufficient detail including the brand name of the product, because excipients may vary depending on the brand • Additional information in the CRF should include whether these were extemporaneous preparations and the exact dose (e.g., mg/kg/dose) frequency and duration of administration • Medication errors and device issues for co-medications should be captured as they may be confounding factors for AEs
Medical history	Antenatal (including in utero exposure and perinatal complications) and family history and the socio-cultural context should be captured where these may be risk factors or confounders for treatment related risks and overall outcome in children
Developmental assessment	• Should be completed at least at base-line and, depending on the duration of the study, at the time of routine appointments for developmental assessments, trial completion and at the end of follow-up • For multinational/multisite studies, one single method should be used where possible, ensuring that the tools can be used in different cultural contexts

CRF, Case Report From; AE, adverse event.

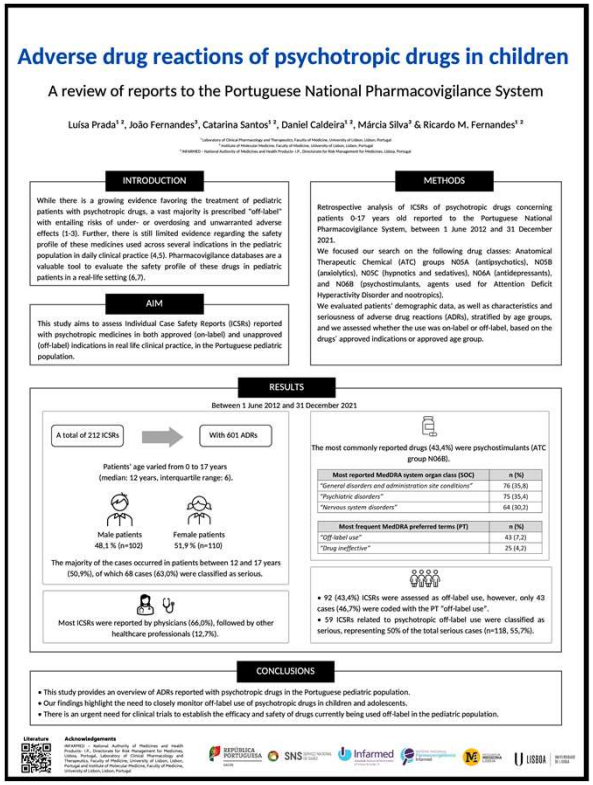
Post-approval: a continuous challenge

Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Adverse drug reactions in adolescents: A review of reporting to a National Pharmacovigilance System

Eva Rebelo Gomes, Inês Ribeiro- Vaz, Cristina Costa Santos & Maria Teresa Herdeiro



Adverse drug reactions of psychotropic drugs in children

A review of reports to the Portuguese National Pharmacovigilance System

Luísa Prada[1,2], João Fernandes[3], Catarina Santos[1,2], Daniel Caldeira[1,2], Márcia Silva[2] & Ricardo M. Fernandes[1,2]

INTRODUCTION

While there is a growing evidence favoring the treatment of pediatric patients with psychotropic drugs, a vast majority is prescribed "off-label" with entailing risks of under- or overdosing and unwarranted adverse effects [1-3]. Further, there is still limited evidence regarding the safety profile of these medicines used across several indications in the pediatric population in daily clinical practice [4,5]. Pharmacovigilance databases are a valuable tool to evaluate the safety profile of these drugs in pediatric patients in a real-life setting [6,7].

AIM

This study aims to assess Individual Case Safety Reports (ICSRs) reported with psychotropic medicines in both approved (on-label) and unapproved (off-label) indications in real life clinical practice, in the Portuguese pediatric population.

METHODS

Retrospective analysis of ICSRs of psychotropic drugs concerning patients 0-17 years old reported to the Portuguese National Pharmacovigilance System, between 1 June 2012 and 31 December 2021.

We focused our search on the following drug classes: Anatomical Therapeutic Chemical (ATC) groups N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics and sedatives), N06A (antidepressants), and N06B (psychostimulants, agents used for Attention Deficit Hyperactivity Disorder and nootropics).

We evaluated patients' demographic data, as well as characteristics and seriousness of adverse drug reactions (ADRs), stratified by age groups, and we assessed whether the use was on-label or off-label, based on the drugs' approved indications or approved age group.

RESULTS

Between 1 June 2012 and 31 December 2021

A total of 212 ICSRs → With 601 ADRs

Patients' age varied from 0 to 17 years (median: 12 years, interquartile range: 6).

Male patients 48,1 % (n=102) | Female patients 51,9 % (n=110)

The majority of the cases occurred in patients between 12 and 17 years (50,9%), of which 68 cases (63,0%) were classified as serious.

Most ICSRs were reported by physicians (66,0%), followed by other healthcare professionals (12,7%).

The most commonly reported drugs (43,4%) were psychostimulants (ATC group N06B).

Most reported MedDRA system organ class (SOC)	n (%)
"General disorders and administration site conditions"	76 (35,8)
"Psychiatric disorders"	75 (35,4)
"Nervous system disorders"	64 (30,2)

Most frequent MedDRA preferred terms (PT)	n (%)
"Off-label use"	43 (7,2)
"Drug ineffective"	25 (4,2)

- 92 (43,4%) ICSRs were assessed as off-label use, however, only 43 cases (46,7%) were coded with the PT "off-label use".
- 59 ICSRs related to psychotropic off-label use were classified as serious, representing 50% of the total serious cases (n=118, 55,7%).

CONCLUSIONS

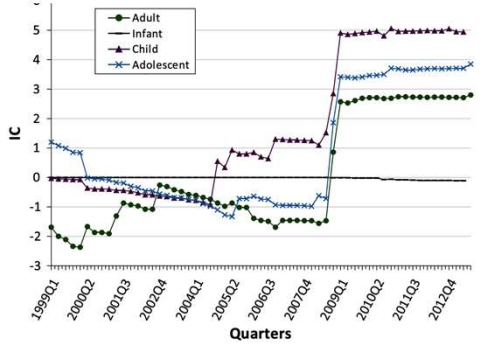
- This study provides an overview of ADRs reported with psychotropic drugs in the Portuguese pediatric population.
- Our findings highlight the need to closely monitor off-label use of psychotropic drugs in children and adolescents.
- There is an urgent need for clinical trials to establish the efficacy and safety of drugs currently being used off-label in the pediatric population.

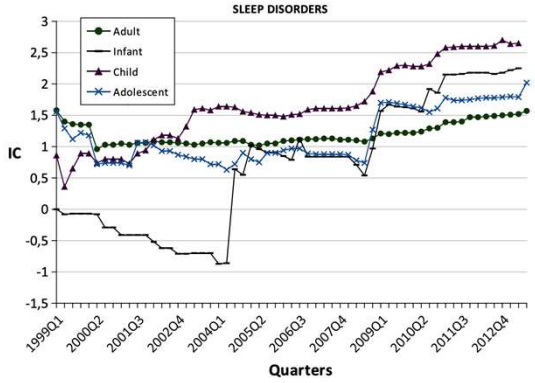
Drug Saf (2016) 39:69–78
DOI 10.1007/s40264-015-0360-2

ORIGINAL RESEARCH ARTICLE

Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase®

Ana Aldea Perona[1] · Mar García-Sáiz[1] · Emilio Sanz Álvarez[2]





Katkade 2017

Pediatric pharmacoepidemiology to the rescue?

- **Rare events, rare diseases**
- **Exposures, outcomes**
- **Sources of data/information and databases**
- **Advanced methods**

Drugs - Real World Outcomes (2020) 7:97–107
https://doi.org/10.1007/s40801-020-00182-y

SYSTEMATIC REVIEW

Real-World Evidence to Assess Medication Safety or Effectiveness in Children: Systematic Review

Tamar Lasky[1,2] · Bruce Carleton[3] · Daniel B. Horton[4,5,6] · Lauren E. Kelly[7,8] · Dimitri Bennett[9,10] · Angela S. Czaja[11] · Dina Gifkins[12] · Osemeke U. Osokogu[13] · Ann W. McMahon[14]

Big Data in the Assessment of Pediatric Medication Safety

Ann W. McMahon, MD, MS, FISPE,[a] William O. Cooper, MD, MPH,[b] Jeffrey S. Brown, PhD,[c] Bruce Carleton, PharmD,[f] Finale Doshi-Velez, PhD,[e] Isaac Kohane, MD, PhD,[c] Jennifer L. Goldman, MD,[g] Mark A. Hoffman, PhD,[h] Rishikesan Kamaleswaran, PhD,[i] Michiyo Sakiyama, MD,[j,k] Shohko Sekine, MS,[k] Miriam C.J.M. Sturkenboom, PhD,[l] Mark A. Turner, MBChB, PhD,[m] Robert M. Califf, MD, MACC[n]

PEDIATRIC PH

Pharmacoepidemiology in pediatrics: Needs, challenges and future directions for research

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Supplement Article

Identifying the "Blip on the Radar Screen": Leveraging Big Data in Defining Drug Safety and Efficacy in Pediatric Practice

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© 2018, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.1141

Michael L. Christensen, PharmD[1] and Robert L. Davis, MD, MPH[2]

Improving the quality of pediatric drug prescribing: toolkits and formularies

Validation par consensus d'un outil d'identification de prescriptions inappropriées en pédiatrie (POPI)

Consensus validation of a tool to identify inappropriate prescribing in pediatrics (POPI)

S. Prot-Labarthe[a,*,b,c], T. Weil[a], N.P.K. Nguyen[a], A. Berthe-Aucejo[a], F. Angoulvant[d], R. Boulkedid[e], C. Alberti[b,e], O. Bourdon[a,c,f,g]

RESEARCH ARTICLE

Development of the Liverpool Adverse Drug Reaction Avoidability Assessment Tool

Louise E. Bracken[1]*, Anthony J. Nunn[2], Jamie J. Kirkham[3], Matthew Peak[1,4], Janine Arnott[1,5], Rosalind L. Smyth[6], Munir Pirmohamed[7], Mark A. Turner[1,2,8]

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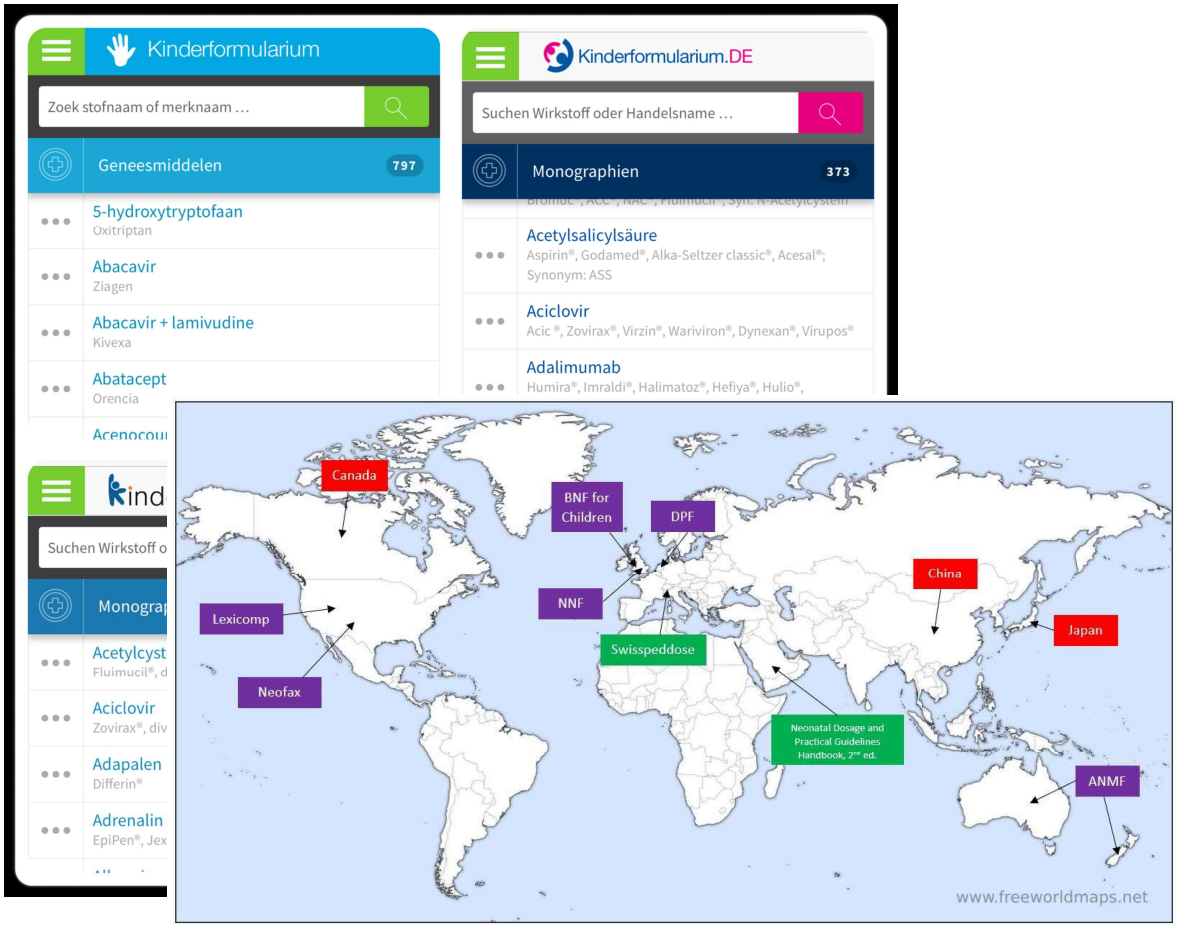

Ongoing challenges: medical devices perceived as medicines

REVIEW OF MEDICAL DEVICES FOR PEDIATRIC COUGH

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INTRODUCTION AND OBJECTIVES

Cough is the most common acute symptom in childhood. Complex natural substances found in medical devices (MD) are a new category of cough remedies. MD have distinct requirements for registration and evaluation from drugs and other medicinal products, but there is an ill-defined frontier between these products.

We aimed to identify and characterize MD and MD components with an explicit pediatric indication on cough currently marketed in Portugal, and their evidence base.

METHODS

Phase I

- Google search using the terms "*cough*" + "*medical devices*" (November 2020 - December 2020);
- Screening of on-line pharmacies and drugstores;
- Screening of National Association of Pharmacies catalog;
- Screening of INFARMED's MDs online database (December 2020 - January 2021).

Data collection

Phase II

- Identify the most common MD components;
- Search → Database MEDLINE (PubMed), and grey literature were searched through March 2021.
- Inclusion criteria: Randomised clinical trials; Controlled clinical trials; Pediatric population (0- <18 years old); Comparing herbal component with at least one other group (no treatment, placebo or usual therapy) for the treatment of cough.

RESULTS

MDs for Pediatric Cough included

26 MDs for cough in pediatric ages

Risk class:
- Class IIa (14)
- Class I (8)
- Not specified (3)

Efficacy and Safety
- Only 2 MDs mentioned clinical data to support their efficacy and safety

23 MDs with **information leaflet**

Age Limits:
- All displayed an inferior age limit
- Not all displayed a superior age limit

Total Components found	85
Most frequently mentioned components (Number of MDs mentioning the components)	
Honey (8)	
Althea extract (11)	
Plantago major extract (11)	

Controlled studies identified for the most frequently mentioned components

Honey	• 9 Studies Randomized Controlled Trials (RCTs) • 1.268 children and adolescents •4 RCTs included Placebo control
Althea	• No controlled studies were found
Plantago major	• No controlled studies were found

Honey was **more effective** than placebo in relieving nocturnal and diurnal cough and improving clinical scores

CONCLUSIONS

- MDs evaluated rely on very **limited clinical information**.
- Information included in MDs leaflets studied are **deficient**.
- There is lack of evidence on MDs safety.
- Plant-based components have **not been sufficiently studied**.
- **Urgent need to perform rigorous studies** to confirm the traditional experience of natural products used to relieve cough.

References

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Abuelgasim, Hibatullah, Charlotte Albury, and Joseph Lee. "Effectiveness of honey for symptomatic relief in upper respiratory tract infections: a systematic review and meta-analysis." BMJ Evidence-Based Medicine 26.2 (2021): 57-64.

Oduwole, Olabisi, et al. "Honey for acute cough in children." Cochrane Database of Systematic Reviews 4 (2018).

Involving children and youth

Key points

- Patient and Public involvement (PPI) in health research refers to research carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them
- Involving young people in health research leads to better recruitment, dissemination and quality.
- Children and young people benefit from getting involved in health research.
- Children have a right to express their views in respect of research that affects them.

Key points

- Involving children and young people is not the same as involving adults and requires different considerations
- Children and young people have a right to be involved in research that affects them
- Children and young people and the research conducted benefits from effective involvement
- Think clearly about exactly why you want to involve children and young people

Key points

- A Young Persons Advisory Group (YPAG) is a group composed of children and young people actively involved in research.
- YPAG members should change from research subjects (participants of research) into partners with researchers (designing the research)

Drug Saf (2015) 38:921–930
DOI 10.1007/s40264-015-0333-5

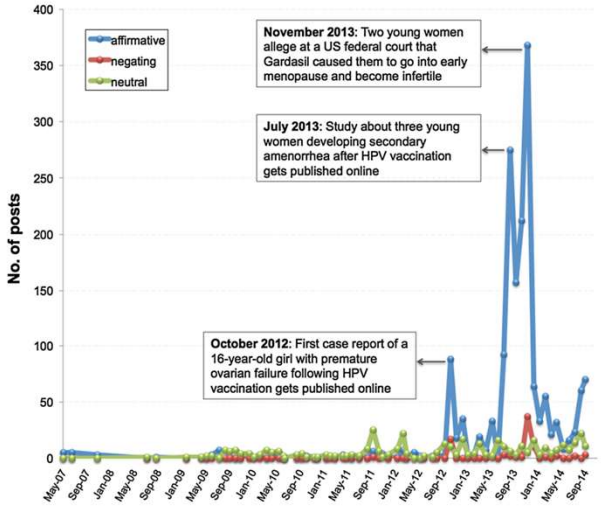
CrossMark

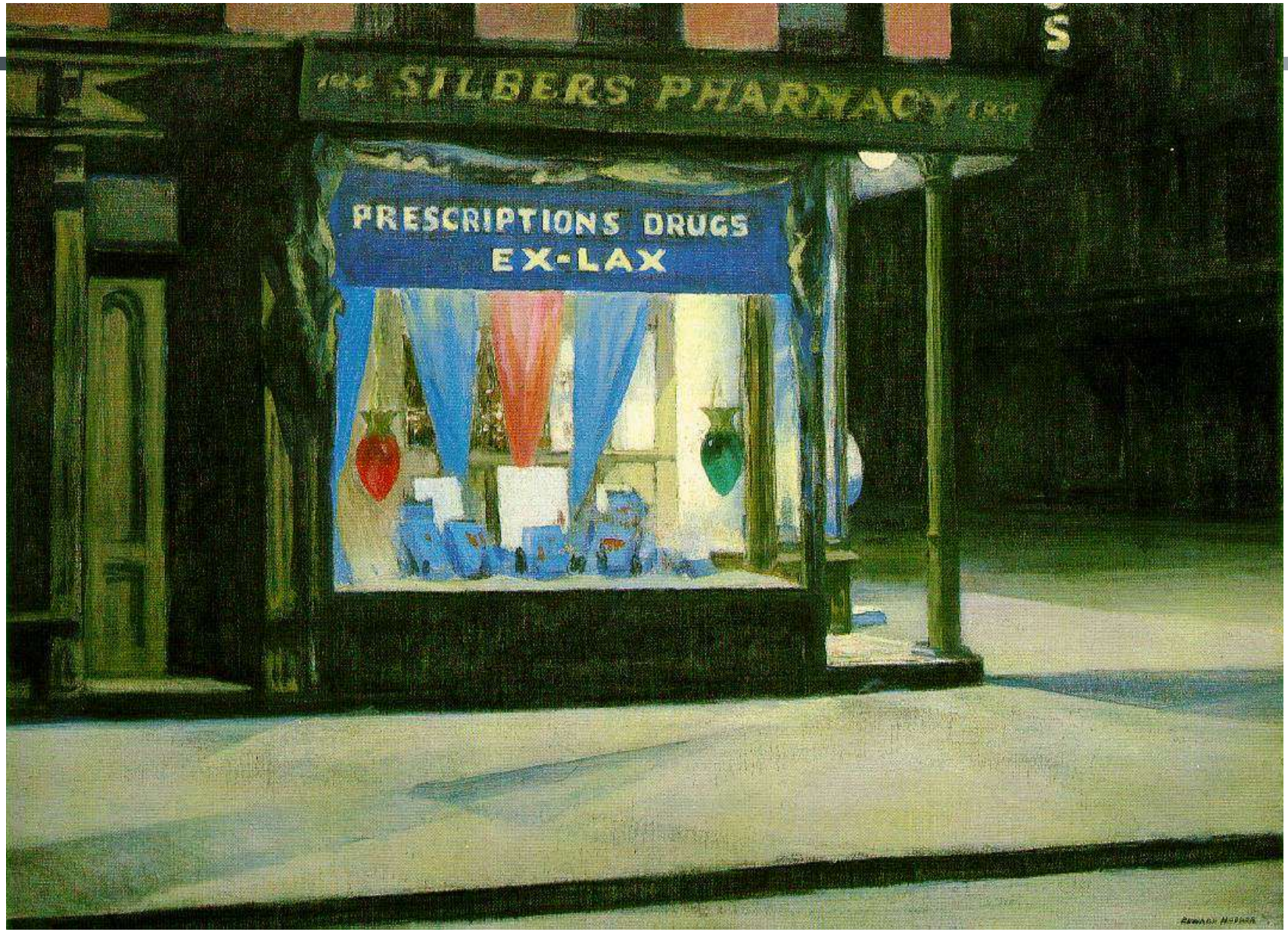
ORIGINAL RESEARCH ARTICLE

Evaluating Social Media Networks in Medicines Safety Surveillance: Two Case Studies

Preciosa M. Coloma[1] · Benedikt Becker[1] · Miriam C. J. M. Sturkenboom[1] · Erik M. van Mulligen[1] · Jan A. Kors[1]

Fig. 2 Trend of assertions of HPV vaccine/infertility-related posts over time. *HPV* human papilloma virus

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