ERDERA

European Rare Diseases Research Alliance

Making Europe a world-leader in rare diseases research and innovation

Pharmacovigilance and off-label use in pediatric settings

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Disclaimer

The views presented are solely my own and do not necessarily represent the views of the National Organization for Medicines (EOF) and/or the European Medicines Agency (EMA).

What pharmacovigilance is

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

The Importance of Pharmacovigilance, WHO 2002

Monitoring safety of medicines and taking actions if needed

Why do we need Pharmacovigilance?

01. There is more to learn from monitoring the safety of medicines once they are in use

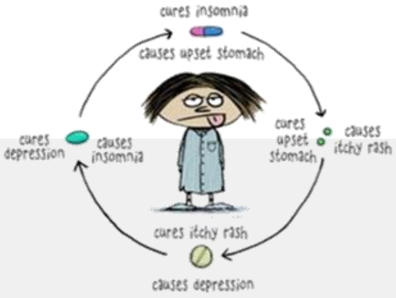
02. This allow us to take actions if necessary

What kind of side affects are associated to medicines?

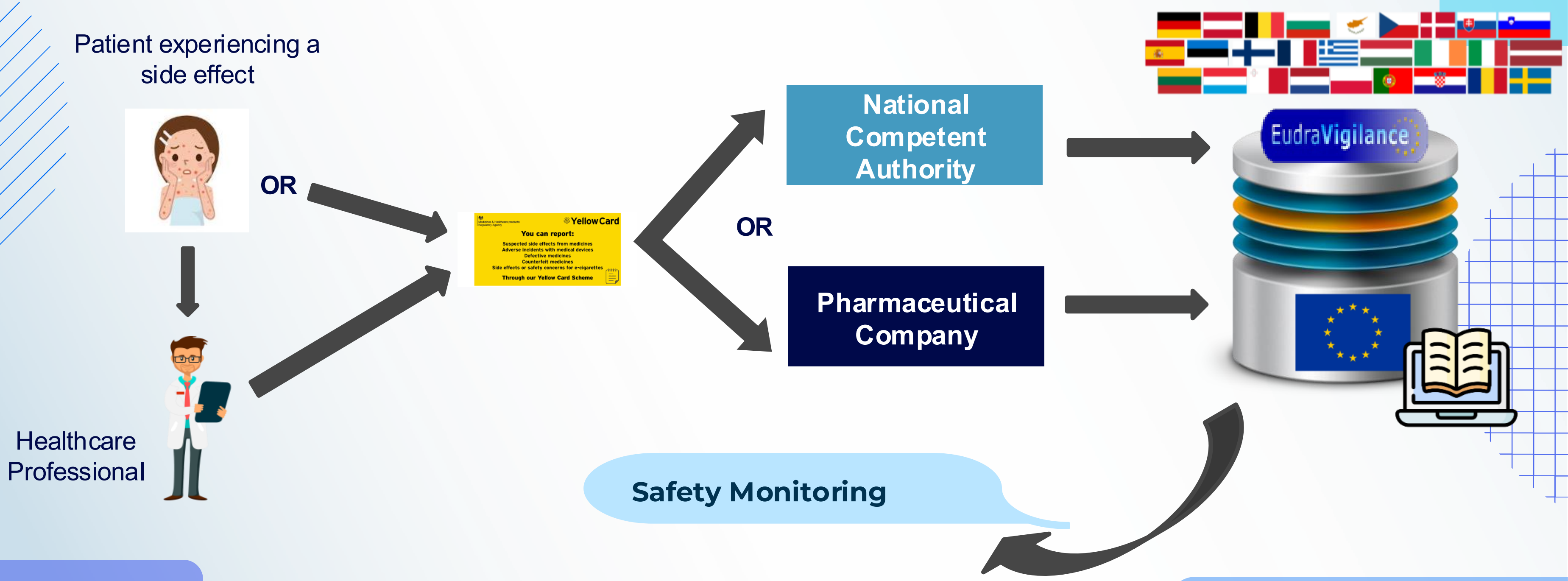
Side affects, also known as adverse reactions are unintended harm from a medicine and can range from the inconvenient to life-threatening

- Some adverse reactions are predictable
- Others, such as allergic reactions, are less predictable
- Side effects can occur as a result of prescribing or administration errors
- Some may occur in susceptible individuals

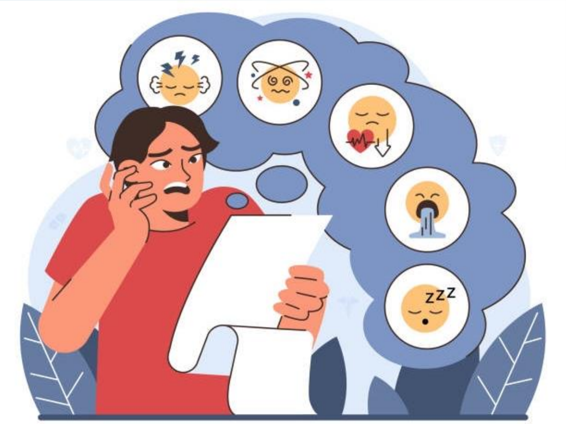
Or after prolonged use



How are side effects monitored?



What defines the value of the side effects?



Science
- New signal?

Regulation
- Need for amendment product information?
- Suspension/withdrawal from market?

Physician
- Can ADR be treated?
- Prevention of ADRs?

Patients
- Quality of life?
- Which risk will I accept?

Misconceptions about side effects' reporting

should only be reported if absolutely certain

All serious side effects are known by the time a product is marketed

No one will pay attention to my report

Reporting takes time

One single report can't make a difference

All side effects are important and should be reported!

Identify and treat side effects
Prevent their occurrence

Input from patients is crucial

What to report?

Suspected side effect

Any noxious or unintended effect occurred after the use of a product

Listed and not listed

All effects, serious and non serious, whether described in the PI or not

Lack of efficacy

unexpected failure of the intended effect

Medication errors

Unintended failure in treatment process that leads to/has the potential to lead to harm the patient

Off-Label use

Product used not in accordance with the terms of the marketing authorisation

Pregnancy exposure

Exposure in utero (maternal exposure during pregnancy and/or paternal exposure before conception)

Occupational exposure

Accidental exposure to a product (professional or not)

Patient role in key steps of Pharmacovigilance

- Collect information on the potential side effects
- Decide if new or changing side effects are observed
- Decide if action is needed to optimize the safe and effective use of the medicine
- Take action and communicate to users

Report suspected side effects

Consulted in expert meetings, written consultations, public hearing
PRAC representative

Review PI / communications

What an orphan drug is

According to the US Food and Drug Administration (FDA), an orphan drug is defined as one "intended for the treatment, prevention or diagnosis of a rare disease or condition, which is one that affects less than 200,000 persons in the US" (which equates to approximately 6 cases per 10,000 population) "or meets cost recovery provisions of the act".

In the European Union (EU), the European Medicines Agency (EMA) defines a drug as "orphan" if it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically and seriously debilitating condition affecting not more than 5 in 10,000 EU people.

Pilot on early dialogue with patient organisations (orphans)

(January 2021 – May 2022)

- ➢ Living with the condition and its daily impacts
- ➢ Current treatment options
- ➢ What are considered important improvements
- ➢ Level of acceptable risks
- ➢ Impact of side effects a
- ➢ Desired benefits for new treatment

- 37 products
- **41% of the cases**: patient information contributed to the development of the D80 AR
- **Patient information valuable and insightful**

Extension to other products
Contact Healthcare professionals

Adapted from: https://www.ema.europa.eu/en/documents/report/pilot-early-dialogue-patient-organisations-orphan-marketing-authorisation-applications-outcome-report_en.pdf

Patient Engagement during assessment

Scientific advice / ad hoc expert groups

Review of documents
(product information, safety communications)

Pharmacovigilance

What off label use is

Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration.
Both prescription drugs and over-the-counter drugs (OTCs) can be used in off-label ways, although most studies of off-label use focus on prescription drugs.

Legislation off label use- adverse reactions

Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as:

- ✓ a different indication in term of medical condition;
- ✓ a different group of patients;
- ✓ a different route or method of administration;
- ✓ a different posology.

1. The off-label use of a medicinal product results in patient's harm with occurrence of a suspected adverse reaction

2. The off-label use of a medicinal product does not result in patient's harm and occurrence of a suspected adverse reaction

Legislation off label use-adverse reactions

If collected in the frame of the routine pharmacovigilance activities, individual reports of off-label use with no suspected adverse reaction should not be submitted to the EudraVigilance database.

Off label use in orphan drugs in the paediatric population

Clinician prescribing of off-label medications is common due to a lack of pediatric-specific data regarding the dosing, efficacy and safety of medications regularly prescribed to children.

31 studies, with off-label prescription rates from 3.2 % to 95%. The local retrospective chart review included 1,323 prescriptions; 504 were off-label (38.1%) and 819 were approved.

Summary of Prescription Off-label Status by Drug (N=1323 prescriptions

	Off-label N (%)	Approved N (%)
Drug		
amikacin	1 (50.0)	1 (50.0)
atropine	4 (100)	-
cefepime	2 (66.7)	1(33.3)
ceftazidime	-	1 (100)
ciprofloxacin	120 (66.7)	60 (33.3)
clozapine	3 (100)	-
diazepam	43 (22.3)	150 (77.7)
haloperidol	6 (54.6)	5 (45.4)
heparin	95 (100)	-
hydromorphone	6 (100)	-
lidocaine	9 (4.3)	201 (95.7)
lurasidone	18 (85.7)	3 (14.3)
methylprednisolone	-	285 (100)
midazolam	2 (66.7)	1 (33.3)
nafcillin	1 (100)	-
piperacillin	4 (100)	-
timolol	28 (100)	-
tobramycin	31 (31.3)	68 (68.7)
valproic acid	13 (61.9)	8 (38.1)
vancomycin	1 (4.3)	22 (95.7)
warfarin	89 (89.9)	10 (10.1)
ziprasidone	28 (90.3)	3 (9.7)

https://pmc.ncbi.nlm.nih.gov/articles/PMC6677268/pdf/nihms-1038249.pdf

Off label use in orphan drugs and paediatric population

Off-label use of (orphan) medicinal products for (rare) diseases is quite common but not underpinned by clinical studies to confirm efficacy and safety. No risk-analyses by regulatory agencies are carried out.

Patient population
A final determining factor is the patient population. Children are subjected to off-label use more often than adults because not all medicinal products are registered for paediatric use.

"Yes, in neonatology intensive care, I think it will be up to 80 or 90 % off-label. Almost every leaflet states that the medicinal product can't be used in children." (AET07111C&N)

https://pmc.ncbi.nlm.nih.gov/articles/PMC5086036/

Examples of use of orphan drugs in paediatric population

Orphacol is a medicine containing cholic acid, a substance found in the bile, which is used to digest fats.

It is used to treat adults and children from one month of age who have a genetic abnormality that makes them unable to produce bile. Orphacol is used in patients who do not have enough of two specific liver enzymes (3?-hydroxy-?5-C27-steroid oxidoreductase or ?4-3-oxosteroid-5?-reductase). This makes their liver unable to produce enough of the main components of bile, called primary bile acids, such as cholic acid. When these primary bile acids are lacking, the body produces abnormal bile acids instead which can damage the liver, potentially leading to life-threatening liver failure.

Because the number of patients with inborn errors in primary bile acid synthesis is low, the condition is considered ‘rare’, and Orphacol was designated an ‘orphan medicine’ (a medicine used in rare diseases) on 18 December 2002.

Examples of use of orphan drugs in paediatric population

Ophthalmic diagnosis and novel management of infantile Refsum disease with combination docosahexaenoic acid and cholic acid

This case report describes a case of infantile Refsum disease (IRD) in a child with retinitis pigmentosa-like ocular findings, sensorineural hearing loss, and self-resolving hepatic disease, who developed novel findings of macular oedema refractory to carbonic anhydrase inhibitors and was managed with a phytanic acid-restricted diet and combination docosahexaenoic acid and cholic acid therapy, which helped to limit progression of the child's disease. The 5-year-old female patient with a clinical diagnosis of Usher syndrome was referred for initial retinal evaluation. The physical exam revealed the presence of epicanthal folds, upper lid ptosis, and bilateral single transverse palmar creases. The patient had approximately 15 degrees of residual left esotropia at presentation. Fundoscopic examination revealed bilateral "salt and pepper" changes, a hypopigmented patch in the macula of both eyes, and bilateral nummular patches of hyperpigmentation in the periphery. Given the involvement of both the central and peripheral retinas with atypical hypopigmented nummular patches, the absence of disc pallor or significant vascular attenuation, and the absence of typical bone spicules, the previous diagnosis of Usher syndrome was questioned.

Examples of use of orphan drugs in paediatric population

Ophthalmic diagnosis and novel management of infantile Refsum disease with combination docosahexaenoic acid and cholic acid

Measurement of serum very long chain fatty acids showed elevation of C26:0 and C22:0 puritanic acid and phytanic acid, suggestive of a possible peroxisomal biogenesis disorder. Genetic evaluation revealed that she was homozygous for a PEX1 mutation (c.2528 G>A, p. GLY843ASB) consistent with IRD. Following the diagnosis, the patient was started on a phytanic acid-restricted diet. At 6 years of age, the patient was noted to develop new bilateral cystoid macular oedema, a finding not previously reported in this syndrome. At the age of 9, the patient began therapy with 200 mg daily docosahexaenoic acid and 350 mg daily cholic acid (Cholbam). The patient's developmental delay improved on this treatment regimen, and the patient began excelling in schoolwork. Eight years after initial presentation, the patient's Snellen visual acuity was 20/100 in the right eye and 1/200 E in the left. The authors have concluded that the patient has benefited from the combined treatment of docosahexaenoic acid and cholic acid, which appeared to slow the progression of IRD. This is the first reported use of docosahexaenoic acid and cholic acid in combination for IRD.

Examples of use of orphan drugs in paediatric population

Ophthalmic diagnosis and novel management of infantile Refsum disease with combination docosahexaenoic acid and cholic acid

IRD is a medical condition within the Zellweger spectrum of peroxisome biogenesis disorders which is not included under the indication of Orphacol. The authors stated that to their knowledge this is the first reported use of docosahexaenoic acid and cholic acid in combination for IRD. Published literature reports that cholic acid has been previously used individually in patients with Zellweger spectrum disorders with controversial results. These drugs are aimed at increasing deficient polyunsaturated fatty acids in patients with Zellweger spectrum disorders and decreasing the concentrations of toxic bile acid intermediates. While some studies suggest a beneficial effect of docosahexaenoic acid supplementation in patients with Zellweger spectrum disorders, a randomized double-blind placebo-controlled trial showed no improvement of visual function and growth. Additional research is needed to evaluate the efficacy of cholic acid in IRD.

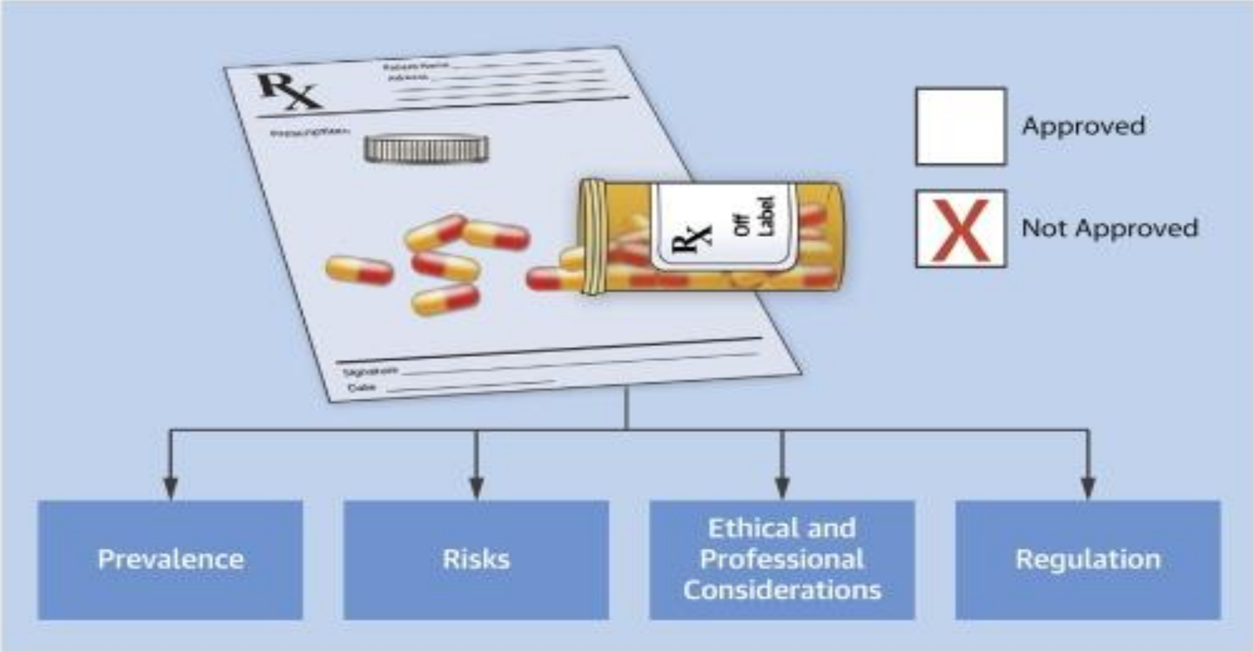
Conclusions

-In comparison to adults, there is limited data pertaining to the dosing, efficacy, and safety of medications in children. This relative lack of data can be attributed to many causes, including

- ✓ unfamiliarity with age-related developmental pharmacology in pediatric patients,
- ✓ ethical considerations with conducting pediatric research,
- ✓ a lack of financial incentive for the pharmaceutical industry.

-Patients need to be given a stronger voice in the use of drugs apart from their intended use, as certain diseases remain untreated.

CENTRAL ILLUSTRATION: Off-Label Drug Use: Prevalence, Ethical and Professional Considerations, and Regulation



Van Norman GA, J Am Coll Cardiol Basic Trans Science. 2023;8(2):224-233.

Rare diseases research and innovation section

Engagement with patients and consumers is a cornerstone of EMA's mission to protect public health and critical to fostering innovation informed by patients' needs and experiences.
Inclusion of patients' perspectives leads to better quality and outcomes of regulatory processes, supports transparency and increases trust.

Marko Korenjak, PCWP Co-Chair

Adapted from: https://www.ema.europa.eu/en/documents/report/stakeholder-engagement-report-2022-2023_en.pdf

ERD ERA

European **Rare Diseases** Research Alliance

Thank you!

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