Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS
Pharmacy

Off-Label use of Medications in Pediatrics: Problem or Miracle Solution?

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DOI: 10.36347/sajp.2023.v12i12.004 | **Received:** 08.11.2023 | **Accepted:** 13.12.2023 | **Published:** 16.12.2023

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Letter to the Editor

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Medication prescription in pediatrics constitutes a real problem. This is absolutely correct: given that pharmaceutical regulations control the way in which medicines are marketed, and not the way in which they are prescribed, once a medicine is authorized, it is the prescribers who evaluate it. the benefit/risk ratio and decide whether this medicine should be prescribed. Hence in our daily practice we often find ourselves forced to use medications off-label [1].

Regulatory approval is a lengthy and costly process. As a result, it is obvious that we cannot test all medications for each possible indication. Which means that, for better or for worse, “off-label” even if it is not completely legitimate, has become a regular practice, particularly in pediatrics because the drugs authorized in pediatrics represent a much larger fraction. small compared to adult forms [2].

The reasons for increasing off-label include the delay in the development of pharmaceutical dosage forms suitable for pediatric use accompanied by the lack of information on the adverse effects incurred resulting from the relatively low number of clinical trials in the world. And precisely, the high development costs and low expected returns of new drugs intended for children generally do not encourage the pharmaceutical industry to invest in this area [3].

The question that follows is where does this need for “pediatric” drugs come from?

First, always remember that the characteristics of children, in terms of physiology and development, differ from those of adults, and these also differ in the age range from newborn to adolescence. This obviously influences pharmacokinetics (PK), pharmacodynamics (PD) and therefore implicitly the action and response to a drug. And history has taught us that this is true for the desired action and for ISIS. I would like to note here that the lack of sufficient studies on pharmacokinetics in children complicates dosage adjustments, particularly in obese children. Therefore, Understanding the physiological differences at different stages of development helps in designing drug formulations and dosing regimens [4].

The formulation of new drugs constitutes a major challenge for the pharmaceutical industry. The complexity comes from the fact that precise dosing is needed for different age groups. The oral route of administration remains the most preferred given its convenience and stability. The main obstacles to improving compliance remain: firstly, acceptance of taste: is it feasible? Is it expensive?!! It's an obstacle! And secondly, find excipients adapted to the age group to avoid any subsequent risk of toxicity. All these factors further complicate the manufacturing process [5].

Concerning regulatory and ethical measures for off-label prescriptions in pediatrics, we cite in particular the results of a recent collaborative position statement, where the European Academy of Pediatrics and the European Society of Perinatal and Pediatric Developmental Pharmacology had recommended considering the off-label prescribing for children as rational and clinically appropriate, provided that the benefits outweigh the risks. However, there is a lack of precision on how to assess the benefits and risks of off-label use [6].

Similarly, in 2014, the American Academy of Pediatrics issued a statement informing pediatricians that "Off-label use is not improper or investigational if based on sound scientific evidence, expert medical judgment, or literature published" [7].

This leads to the conclusion that for such evidence to be available, doctors and manufacturers should be incentivized to collect and publish used off-label data. This would help to stimulate the process of off-label use.

An important ethical question arises: status of the healthcare professional responsible for informing parents when a child is prescribed an off-label medication?

Occasionally, doctors do not provide this information, while on the other hand, the pharmacist is obliged to provide it [8].

Two possibilities follow [9]:

(1) the parents are stressed and refuse to give their child a medication whose effectiveness and safety have not been established and
(2) parents return to the doctor in search of another alternative medication. Therefore, in our opinion, to avoid complications, it is the doctor's obligation (attested by informed consent), later confirmed by the pharmacist.

We reviewed literature published from 2012 to 2022 to provide an up-to-date summary of the extent of off-label use in pediatric patients. The proportion of off-label prescriptions in our survey varied from 3.3% (in Italy) to 94% (in Ireland for patients in neonatal intensive care units) [10, 11].

Many studies have shown that patients treated out of hospital are less likely to receive off-label prescriptions. In a hospital setting, the patient's illness and condition are of paramount importance. Oshikoya *et al.*, reported a low rate of off-label prescribing in the chronic treatment of epilepsy and asthma, while in the most vulnerable group of neonatal intensive care unit patients the percentage skyrocketed to 94%. The severity of the disease and the need for intensive care may explain the considerable number of prescriptions per patient [12].

The prevalence of off-label prescribing also varies significantly by drug class: use was highest among anti-infectives (such as amikacin, gentamicin, vancomycin, cefepime and cefazolin), CNS drugs (carbamazepine+++), of the digestive tract, pulmonology (especially inhaled corticosteroids), and cardiovascular medications. While the lowest off-label use was noted in treatment with antidiabetics [13, 14].

Ultimately, in our opinion, off-label use should be accepted as an already established practice, but assuming that it is based on evidence-based medicine.

Obtaining parental consent, then closely monitoring the child, taking necessary measures to address possible AEs and ensuring appropriate documentation while submitting the report to the CAPM are the main recommendations of our review to our pediatric colleagues.

REFERENCES

1. Aronson, J. K., & Ferner, R. E. (2017). Unlicensed and off-label uses of medicines: Definitions and clarification of terminology. *Br. J. Clin. Pharmacol*, *83*, 2615–2625.
2. Allen, H. C., Garbe, M. C., Lees, J., Aziz, N., Chaaban, H., Miller, J. L., Johnson, P., & DeLeon, S. (2018). Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. *J. Okla. State Med. Assoc*, *111*, 776–783.
3. Khan, D., Kirby, D., Bryson, S., Shah, M., & Mohammed, A. R. (2022). Paediatric specific dosage forms: Patient and formulation considerations. *Int. J. Pharm.*, *616*, 121501.
4. Klassen, T. P., Hartling, L., Craig, J. C., & Offringa, M. (2008). Children Are Not Just Small Adults: The Urgent Need for High-Quality Trial Evidence in Children. *PLOS Med.*, *5*, e172.
5. Van Riet-Nales, D. A., Kozarewicz, P., Aylward, B., de Vries, R., Egberts, T. C. G., Rademaker, C. M. A., & Schobben, A. F. A. M. (2017). Paediatric Drug Development and Formulation Design—A European Perspective. *AAPS Pharmscitech*, *18*, 241–249.
6. Schrier, L., Hadjipanayis, A., Stiris, T., Ross-Russell, R. I., Valiulis, A., Turner, M. A., ... & van den Anker, J. (2020). Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. *European journal of pediatrics*, *179*, 839-847.
7. Neville, K. A., Frattarelli, D. A., Galinkin, J. L., Green, T. P., Johnson, T. D., Paul, I. M., Anker, J. N. V. D., & American Academy of Pediatrics Committee on Drugs. (2014). Off-Label Use of Drugs in Children. *Pediatric*, *133*, 563–567.
8. Balan, S., Hassali, M. A., & Mak, V. S. L. (2015). Awareness, knowledge and views of off-label prescribing in children: A systematic review. *Br. J. Clin. Pharmacol.*, *80*, 1269–1280.
9. Tsujii, N., Saito, T., Izumoto, Y., Usami, M., Okada, T., Negoro, H., & Iida, J. (2016). Experiences with Patient Refusal of Off-Label Prescribing of Psychotropic Medications to Children and Adolescents in Japan. *J. Child Adolesc. Psychopharmacol*, *26*, 642–645.

10. Carnovale, C., Conti, V., Perrone, V., Antoniazzi, S., Pozzi, M., Merlino, L., Venegoni, M., Clementi, E., & Radice, S. (2013). Paediatric drug use with focus on off-label prescriptions in Lombardy and implications for therapeutic approaches. *Eur. J. Pediatr.*, *172*, 1679–1685.
11. Kieran, E. A., O'Callaghan, N., & O'Donnell, C. (2014). Unlicensed and off-label drug use in an Irish neonatal intensive care unit: A prospective cohort study. *Acta Paediatr, 103*, e139–e142.
12. Oshikoya, K. A., Oreagba, I. A., Godman, B., Fadare, J., Orubu, S., Massele, A., & Senbanjo, I. O. (2017). Off-label prescribing for children with chronic diseases in Nigeria; findings and implications. *Expert Opin. Drug Saf, 16*, 981–988.
13. Oshikoya, K. A., Oreagba, I. A., Godman, B., Fadare, J., Orubu, S., Massele, A., & Senbanjo, I. O. (2017). Off-label prescribing for children with chronic diseases in Nigeria; findings and implications. *Expert Opin. Drug Saf., 16*, 981–988.
14. Czarniak, P., Bint, L., Favié, L., Parsons, R., Hughes, J., & Sunderland, B. (2015). Clinical Setting Influences Off-Label and Unlicensed Prescribing in a Paediatric Teaching Hospital. *PLoS ONE, 10*, e0120630.