INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Off-Label Medication Use in Paediatric Patients: Prevalence, Safety Concerns and Rational Prescribing Practices – A Narrative Review

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ARTICLE INFO

Published: 12 Jun. 2026

Keywords:
Off-label prescribing, Pediatrics, Adverse drug reactions, Pediatric pharmacotherapy, Rational prescribing, Medication safety

DOI:
10.5281/zenodo.20648440

ABSTRACT

Off-label medication use refers to prescribing drugs outside the approved labeling regarding age, dose, indication, route, or frequency of administration. In pediatric practice, off-label prescribing is highly prevalent due to the limited availability of adequately tested and licensed medications for children. This narrative review aims to summarize the prevalence of off-label medication use in pediatric patients, evaluate associated safety concerns, and discuss rational prescribing practices to optimize therapeutic outcomes. Evidence from published literature demonstrates that off-label prescribing rates range widely from 3.2% to 95%, particularly in neonatal and intensive care settings. Although off-label use may provide essential therapeutic benefits, it is associated with increased risks of adverse drug reactions (ADRs), dosing errors, and insufficient evidence regarding efficacy and safety. Regulatory initiatives such as the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) have improved pediatric labeling; however, significant gaps remain. Rational prescribing practices, including evidence-based prescribing, clinical pharmacist involvement, pharmacovigilance and adherence to pediatric formularies are crucial for minimizing risks associated with off-label drug use. Further pediatric clinical trials and strengthened regulatory policies are necessary to improve medication safety in children.

INTRODUCTION

Off-label medication use refers to the prescription of medicines outside the approved product labeling for age group, indication, dosage, route of administration, or frequency. Off-label prescribing is legal and frequently practiced worldwide, especially in pediatric medicine where approved therapeutic alternatives are limited. (1) Children are often considered “therapeutic orphans” because many medications used in adults lack sufficient pediatric clinical trials to establish efficacy and safety. Ethical challenges, developmental pharmacokinetic variability, limited financial

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

incentives for pharmaceutical industries, and difficulties in conducting pediatric studies contribute to inadequate pediatric labeling. [2,3] Despite regulatory improvements over the past two decades, off-label prescribing remains highly prevalent in pediatric populations, particularly among neonates, critically ill children, and patients with rare diseases. [1,3,21]

This narrative review discusses the prevalence of off-label medication use in children, associated safety concerns, and strategies for rational prescribing practices.

1. METHODOLOGY

A narrative literature review was conducted using published articles retrieved from databases including PubMed, Google Scholar, and Scopus. Articles published between (2000 and 2025) related to off-label medication use in pediatric patients were reviewed. Keywords used included "off-label prescribing," "pediatric drug use," "adverse drug reactions," "unlicensed medicines," and "rational prescribing in children." A total of 25 relevant articles including systematic reviews, observational studies, policy statements, and narrative reviews were selected for analysis.

Search terms: Off-label prescribing, off-label drug use, pediatric phramcotherapy, children, neonates, adverse drug reaction (ADR), medication safety, rational prescribing.

Inclusion criteria:

- Studies involving pediatric patients (0–18 years).
- Articles related to off-label medication use, safety, or prescribing practices.
- Original research articles, reviews, and policy statements.
- Articles published in English between 2000 and 2025.
- Full-text articles available for review.

Exclusion criteria:

- Studies involving only adult populations.
- Articles unrelated to off-label medication use in children.
- Conference abstracts, editorials, letters, and duplicate publications.
- Articles with insufficient data or unavailable full text.
- Non-English publications.

2. Prevalence Of Off-Label Medication Use In Pediatrics

Off-label prescribing is substantially more common in children than adults due to the scarcity of pediatric-specific clinical evidence. Several studies have reported wide variability in prevalence depending on healthcare setting, patient population, and study methodology. [2,3,5] A systematic review by Allen et al. identified off-label prescribing rates ranging from 3.2% to 95% across pediatric healthcare settings. Neonatal intensive care units (NICUs) demonstrated the highest prevalence due to the lack of approved medications for premature infants. [2]

Similarly, Shuib *et al.* reviewed 47 observational studies and reported off-label prescription rates ranging from 7.4% to 99.5% in hospitalized pediatric patients. Studies conducted in tertiary care hospitals in India also revealed high rates of off-label medication use among pediatric inpatients. Antibiotics, anticonvulsants, respiratory drugs, and gastrointestinal medications were among the most commonly prescribed off-label medications. [3,6,9,13,15]

The prevalence is particularly elevated in: [10,11,12,13]

- Neonatal intensive care units (NICUs)
- Pediatric intensive care unit (PICUs)
- Oncology wards
- Pediatric palliative care settings

Common categories of off-label prescribing include [1,3,5]

- Use outside approved age range
- Unapproved indication
- Higher or lower dosage than labeled recommendations
- Alternative routes of administration

The lack of suitable pediatric formulation further contributes to medication manipulation and unlicensed use.

4 FACTORS CONTRIBUTING TO OFF-LABEL PRESCRIBING [1,3,14,18,21]

4.1 Limited Pediatric Clinical Trials

Children are underrepresented in clinical research due to ethical concerns, recruitment challenges, and developmental variability. Consequently, many medications approved for adults lack adequate pediatric evidence.

4.2 Developmental Pharmacokinetics

Drug absorption, distribution, metabolism and excretion differ significantly among neonates, infants, children and adolescents. Extrapolation of adult dosing may therefore be inappropriate and potentially harmful.

4.3 Lack of Commercial Incentives

Pharmaceutical companies may have limited financial motivation to conduct pediatric trials due to smaller market size and increased research costs.

4.3 Absence Of Pediatric Formulations

Many medications are unavailable in child-friendly dosage forms such as liquid formulations, leading to extemporaneous preparation and dosing inaccuracies.

5 SAFETY CONCERNS ASSOCIATED WITH OFF-LABEL MEDICATION USE [1,3,11,12,13,14,16,17,18]

5.1 ADVERSE DRUG REACTIONS (ADRs)

Several studies associated off-label prescribing with increased ADR incidence in pediatric patients. Immature organ systems and altered pharmacodynamics make children particularly vulnerable to medication toxicity.

Common ADRs associated with off-label use include:

- Sedation
- Respiratory depression
- Hepatotoxicity
- Renal impairment
- Cardiovascular complications

Psychotropic medications prescribed off-label in children require especially close monitoring due to risks of metabolic and neurological adverse effects.

5.2 DOSING ERRORS

Off-label dosing often relies on empirical calculations or extrapolation from adult studies, increasing the likelihood of underdosing or overdosing. Medication manipulation such as tablet splitting or dilution may further compromise dose accuracy.

5.3 LIMITED EVIDENCE OF EFFICACY

van der Zanden *et al*. demonstrated that only a minority of pediatric off-label prescriptions are supported by high-quality evidence such as randomized controlled trials or meta-analyses. Many pediatric off-label practices depend on expert consensus rather than robust clinical evidence, potentially compromising treatment outcomes.

5.4 PHARMACOVIGILANCE CHALLENGES

Detection of ADRs in children remains difficult because pediatric patients may be unable to clearly communicate symptoms. Underreporting of ADRs further limits safety surveillance.

6 ETHICAL AND REGULATORY CONSIDERATIONS [1,3,21,22]

Off-label prescribing in children raises important ethical concerns regarding informed consent, patient safety, and evidence-based care. The American Academy of Pediatrics acknowledges that off-label prescribing may be appropriate when supported by sound scientific evidence or expert clinical judgment.

Regulatory initiatives such as:

- Best Pharmaceuticals for Children Act (BPCA) [2002-2022]
- Pediatric Research Equity Act (PREA) [2017-2026]

These have significantly improved pediatric drug labeling and encouraged pediatric clinical research. However, many pediatric medications remain inadequately studied, especially in neonates and critically ill children. Healthcare providers must carefully balance in the potential benefits, available evidence and possible risks before initiating off-label therapy.

7 RATIONAL PRESCRIBING PRACTICES [1,2,5,18,19,20,23]

Rational prescribing is essential to minimize risks associated with off-label medication use.

7.1 EVIDENCE-BASED PRESCRIBING

Clinicians should prioritize medications supported by pediatric guidelines, systematic reviews, randomized controlled trials and pediatric formularies. The Dutch Pediatric Formulary has emerged as an important evidence-based resource for pediatric pharmacotherapy.

7.2 CLINICAL PHARMACIST INVOLVEMENT

Clinical pharmacists play a vital role in dose calculation, ADR monitoring, medication reconciliation and identification of drug interactions. Collaborative multidisciplinary care improves medication safety in pediatric settings.

7.3 PHARMACOVIGILANCE AND ADR REPORTING

Strengthening pediatric pharmacovigilance systems is necessary to identify previously unrecognized adverse effects and improve medication safety databases.

7.4 PARENT AND CAREGIVER EDUCATION

Caregivers should receive adequate counseling regarding medication administration, potential side effects, adherence and monitoring requirements. Therapeutic communication helps improve therapeutic outcomes and informed decision-making.

7.5 NEED FOR PEDIATRIC CLINICAL RESEARCH

Additional pediatric clinical trials are urgently needed to generate high-quality safety and efficacy data for commonly prescribed medications.

8 FUTURE PERSPECTIVES [1,3,5,19,20,21]

Future efforts should focus on expanding pediatric clinical trials, improving pediatric drug formulations, implementing artificial intelligence-assisted pharmacovigilance and harmonizing international pediatric prescribing guidelines. Global collaboration between regulatory authorities, healthcare professionals and pharmaceutical industries is essential to reduce unsafe off-label prescribing practices.

9 CONCLUSION [1,3,5,16,18,21,23]

Off-label medication use remains highly prevalent in pediatric healthcare due to limited pediatric-specific evidence and the lack of approved therapeutic alternatives for many conditions. Although off-label prescribing is often clinically necessary and may provide significant therapeutic benefits, it is associated with important safety concerns, including adverse drug reactions, dosing errors, and uncertainties regarding efficacy. Rational prescribing based on the best available evidence, active pharmacovigilance, and multidisciplinary collaboration involving physicians, pharmacists, and caregivers is essential to optimize medication safety and therapeutic outcomes in children. Further pediatric clinical research and strengthened regulatory initiatives are required to expand evidence-based pediatric labeling and promote safer use of medicines in the pediatric population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENT

The authors acknowledge institutional support.

FUNDING

No funding was received for this study.

REFERENCES

1. Petkova V, Georgieva D, Dimitrov M, Nikolova I. Off-label prescribing in pediatric population—literature review for 2012–2022. Pharmaceutics. 2023;15(12):2652.
2. Allen HC, Garbe MC, Lees J, Aziz N, Chaaban H, Miller JL, et al. Off-label medication use in children, more common than we think: a systematic review of the literature. J Okla State Med Assoc. 2018;111(8):776–83.
3. Balan S, Hassali MAA, Mak VSL. Two decades of off-label prescribing in children: a literature review. World J Pediatr. 2018;14(6):528–40.
4. Eguale T, Buckeridge DL, Verma A, Winslade NE, Benedetti A, Hanley JA. Association of off-label drug use and adverse drug events in an adult population. JAMA Intern Med. 2016;176(1):55–63.
5. Yuan X, Zhang Y, Li H, Wang J, Liu Y. Off-label and unapproved pediatric drug utilization: a meta-analysis. Exp Ther Med. 2024;28(4):1–12.
6. Saiyed MM, Ong PS, Chew L. Off-label medicine use in pediatric inpatients: a prospective observational study at a tertiary care hospital in India. Int J Pediatr. 2014;2014:415815.
7. Akici N, Kalaça S, Ugurlu MU, Toklu HZ, Iskender E, Oktay S. Prescribing habits of general practitioners in the treatment of childhood diseases. Eur J Clin Pharmacol. 2004;60(3):211–6.

8. AlAzmi A, Alenezi M, Alanzi T, Alhamdan H. Off-label drug use in pediatric outpatient care: a multicenter observational study. Hosp Pharm. 2021;56(6):657–64.
9. Dornelles AD, Pizzol TSD, Mengue SS. The unlicensed and off-label prescription of medications in a general pediatric ward: an observational study. Curr Pediatr Rev. 2019;15(2):95–102.
10. Luedtke KE, Buck ML. Evaluation of off-label prescribing at a children's rehabilitation center. J Pediatr Pharmacol Ther. 2015;20(4):296–301.
11. García-López I, Fuentes-Ríos JE, Manrique-Rodríguez S, Fernández-Llamazares CM. Off-label and unlicensed drugs in pediatric palliative care: a prospective observational study. J Pain Symptom Manage. 2020;60(5):923–31.
12. García-López I, Manrique-Rodríguez S, Fernández-Llamazares CM. Off-label and unlicensed drug use in a pediatric intensive care unit: a pilot study. An Pediatr (Barc). 2017;86(1):28–36.
13. 't Jong GW, Eland IA, Sturkenboom MCJM, van den Anker JN, Stricker BHC. Unlicensed and off-label prescription of drugs to children: population based cohort study. BMJ. 2002;324(7349):1313–4.
14. Ilma DL, Widayati A, Prabandari YS. Off-label pediatric drug use in Indonesia: a systematic review. J Holist Pharm. 2020;10(2):81–90.
15. Arbo A, Rossi F, Marchetti F. Off-label prescribing in Italian pediatric practice: insights from a nationwide survey. Eur J Pediatr. 2025;184(2):611–20.
16. Ramesh M, Pandit J, Parthasarathi G. Adverse events associated with labeled and off-labeled use of medications in children. Pediatr Res. 2011;70(4):1–6.
17. Saiyed MM, Lalwani T, Rana D. Is off-label use a risk factor for adverse drug reactions in pediatric patients? Int J Risk Saf Med. 2015;27(2):69–76.
18. van der Zanden TM, de Wildt SN, Allegaert K, Tibboel D, de Hoog M. Off-label, but on-evidence? A review of the level of evidence for pediatric pharmacotherapy. Br J Clin Pharmacol. 2022;88(11):4804–18.
19. Reps JM, Garibaldi JM, Aickelin U, Soria D, Gibson JE, Hubbard RB. Signalling paediatric side effects using an ensemble of simple study designs. arXiv [Preprint]. 2014. Available from: https://arxiv.org/abs/1409.0772
20. Gamalo M, Tiwari R, Bell J, Hall M. Extent of safety database in pediatric drug development: types of assessment, analytical precision, and pathway for extrapolation through on-target effects. Ther Innov Regul Sci. 2022;56(6):1048–57.
21. Frattarelli DAC, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, et al. Off-label use of drugs in children. Pediatrics. 2014;133(3):563–7.
22. Colombo M, Ricci F, Esposito S. Beyond the label: ethical and clinical implications of off-label drug use in pediatric emergency care. Ital J Pediatr. 2025;51(1):88.
23. Jagadeesan M, Suresh B, Kumar VS. Rational prescribing challenges in paediatrics: an evidence-based review. Res J Pharm Technol. 2020;13(11):5607–12.
24. Ekins-Daukes S, Helms PJ, Simpson CR, Taylor MW, McLay JS. Off-label prescribing to children: attitudes and experience of general practitioners. Br J Clin Pharmacol. 2005;60(2):145–9.
25. Jîtcă CM, Pantea Stoian A, Găman MA, Diaconu CC, Socea B. Off-label pediatric medication prescribing and dispensing: awareness and attitudes among community pharmacists. Pharmacy (Basel).

2024;12(5):145.

HOW TO CITE: J.S. Venkatesh, Manasa T., Ananda Krishnan , Anjum K., Anugraha Biju, Archa S., Off-Label Medication Use in Paediatric Patients: Prevalence, Safety Concerns and Rational Prescribing Practices – A Narrative Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 3055-3061. https://doi.org/10.5281/zenodo.20648440