Each year, hundreds of millions of prescription medications are dispensed to pediatric patients. A significant proportion of prescriptions are used in an off-label manner, outside the specifications approved by the US Food and Drug Administration (FDA), rendering off-label prescribing a “public health issue for infants, children and adolescents,” as described by the Committee on Drugs for the American Academy of Pediatrics. The committee also explicitly states that off-label use “does not imply an improper, illegal, contraindicated or investigational use.”

Yet, when used in research, clinical practice, or even the lay media, the term off-label commonly carries a negative connotation. This interpretation probably reflects the sense of uncertainty in understanding the risk–benefit balance of a medication without FDA review and approval. However, prescribing according to the package insert does not necessarily translate to the safe and effective use of a medication. The clinical trial data required for FDA approval often represent highly select populations in controlled settings with limited follow-up. These data may not translate well to real-world use, hence the need for postmarketing surveillance and research. Conversely, lack of pediatric labeling for a medication does not necessarily indicate a lack of evidence. It may simply mean the pharmaceutical company has not submitted an application for FDA approval to add a new indication or population.

This apparent paradox gives us the opportunity to consider how we, the pediatric community of clinicians, researchers, and policymakers, think about the issue of off-label prescribing and how best to direct future efforts in medication research and policy. The Best Pharmaceuticals for Children Act prioritization process focuses on gathering expert opinion to inform research priorities related to therapeutic needs, with a primary goal of identifying drugs for pediatric clinical trials. We argue that such approaches should be complemented by a structured consideration of risks and benefits informed by increasingly available data from practice. Pediatric research on off-label prescribing often focuses on the dichotomy of on-label versus off-label prescribing rates, defined mainly by age limits and occasionally indication. Understanding the extent of off-label practice is important, but it represents only a single dimension of a complex issue. This information does not necessarily determine whether the way a medication is prescribed is safe and effective.

Beyond the Label: Steering the Focus Toward Safe and Effective Prescribing

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Table 1: Potential Practice, Research, and Policy Implications of Exemplar Medications Being Used Off-Label in the Pediatric Population Based on Degree of Use, Benefit–Risk Balance, and Uncertainty of the Evidence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Off-Label Use (Relative # of Prescriptions)</th>
<th>Benefits</th>
<th>Risks</th>
<th>Level of Certainty</th>
<th>Example Drug and Indications*</th>
<th>Potential Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>↑↑↑↑</td>
<td>↑</td>
<td>↓↓</td>
<td>↑</td>
<td>Azithromycin and acute otitis media</td>
<td>Generation of additional pediatric data may be necessary and sufficient.</td>
</tr>
<tr>
<td>B</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
<td>Antipsychotic and behavior outside of autism spectrum disorder in 2- to 5-y-olds</td>
<td>Policy changes directed toward risk mitigation may be necessary, decision support to clinicians around risks and generation of additional pediatric data.</td>
</tr>
<tr>
<td>C</td>
<td>↑↑↑↑</td>
<td>↓</td>
<td>↓↓</td>
<td>↑↑↑</td>
<td>Albuterol and bronchiolitis</td>
<td>Efforts to stimulate practice change through education, dissemination, or policy change.</td>
</tr>
<tr>
<td>D</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>Sertraline and pediatric major depressive disorder</td>
<td>Continue ongoing surveillance for new or long-term effects (beneficial and adverse). Prompt shared decision-making about risks and benefits.</td>
</tr>
<tr>
<td>E</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Sildenafil and pulmonary arterial hypertension</td>
<td>Closer monitoring of these select cases by clinicians and encouragement to collect data.</td>
</tr>
</tbody>
</table>

* The number and directionality of arrows are qualitative assessments by the authors and practicing clinicians from the Comparative Effectiveness Research Through Collaborative Electronic Reporting collaborative based on focused literature reviews and their combined clinical and research experience. The examples are provided for illustrative purposes alone, not as comprehensive reviews.

medication is being used warrants alarm, policy changes, or even additional research. A more nuanced and evidence-based evaluation would incorporate assessments not only of how the medication is being used in the real world (which patients, what indications, which dosing regimens, and to what extent) but also of the therapeutic benefits, the risks of adverse effects, and the uncertainty behind the risks and benefits, based on both existing data and expert input. Such an evaluation could better identify areas of greatest impact for prioritizing limited resources for future research and policy efforts.

Several drug examples highlight the utility of a multidimensional approach (Table 1). The first 4 medications listed in the table all have high off-label use, but the varying risk–benefit profiles and levels of uncertainty suggest distinct future implications. For some, generating additional pediatric data is warranted, whereas for others, policy change or additional education efforts to practitioners or the public might yield greater impact. In example E from Table 1, the frequency of off-label use is low, but that does not necessarily mean it can be ignored. The low certainty of the risk–benefit profile still mandates additional evidence generation to optimize safe and effective use. These examples illustrate how a 1-size-fits-all, on-versus off-label dichotomy is insufficient for addressing this complex phenomenon.

Fortunately, there are a growing number of data sources and advances in methods and technology to help us fill knowledge gaps for each dimension and even possibly affect prescribing practice at the clinician level. Although randomized controlled trials, the standard requirement for initial FDA approval, will always provide important drug information, they require substantial resource and time investments, often have limited generalizability, and require sufficient clinical equipoise. This latter requirement can be particularly difficult with many medications, because clinicians may have already established a pattern of use and be unwilling to subject their patients to randomization. Given these limitations, methodologically sound observational studies are increasingly recognized as valuable for examining medication use, effectiveness, and safety in the postmarketing period. Data sources for such pharmacoepidemiology studies are numerous, with certain strengths and limitations. Health care claim data provide large sample sizes, important for rare exposures or outcomes, but have limited clinical information. Clinical registries may provide more clinical data for the population of interest, but the quality of data is highly dependent on the process of data collection within the registry, and medication specifics may be absent, depending on the purpose of the registry.

To complement these data sources, there has been growing interest in leveraging the clinical information contained in electronic health records (EHRs), including medication regimens and health care utilization as well as other information, for research purposes. This interest has led to the establishment of EHR-based research systems that facilitate real-world evaluations of medication use, therapeutic benefits, and adverse events, including extremely rare ones. Pediatric-specific EHR networks, such as Comparative...
Effectiveness Research Through Collaborative Electronic Reporting, have the additional advantage of access to data from a large sample of pediatric patients (> 1.2 million).6,7 Because these networks are often practice based, they can also be used to obtain patient-reported data on effectiveness, adverse events, and preferences through innovative approaches such as the use of mobile health tools, including smartphone apps. These data, in combination, can then inform a more comprehensive risk–benefit assessment of medications by using 1 of numerous proposed methods.8 Ensuring sustainability and usefulness of such data systems requires ongoing financial and regulatory support and increased collaboration between clinicians, vendors, researchers, and policymakers.

Such information will be useful not only to researchers and policymakers but also to prescribing clinicians and their patients. However, ongoing efforts to develop new or improve existing methods of communicating pediatric drug information will be essential for ensuring the safe and effective use of medications in pediatric patients. Although the current efforts to improve the FDA monograph will improve the readability and interpretation of the label, practicing pediatricians and other clinicians caring for children (eg, family practitioners) use such FDA resources infrequently.9 To augment such resources, clinical decision support tools available to the practicing clinician at the point of care, a valuable resource for disseminating new or existing pediatric drug knowledge in the real world, may be an effective tool for risk mitigation efforts by the FDA or for prompting shared decision-making.

**CONCLUSIONS**

Despite significant progress, there remains a lack of pediatric data for a majority of medications, with considerable work to be done to ensure safe and effective use of medications.10 Taking an organized and more intentional approach to evaluation of medication use would allow better identification of high-priority medications and the gaps that must be filled, including evidence generation through clinical trials and observational studies, policy changes and educational efforts to guide practice change, and ongoing monitoring and promotion of safe and effective medication use. We encourage the pediatric community of clinicians, researchers, and policymakers to persist in collaborative efforts to advance the field through innovative methods and maintaining a broader vision for the future of pediatric medication use.

**ABBREVIATIONS**

EHR: electronic health record  
FDA: US Food and Drug Administration

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