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Assessing Drug Safety in Children — The Role of Real-World Data

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Over the past 20 years, several legislative initiatives in the United States have resulted in hundreds of clinical trials assessing the treatment effects of various drugs in children.¹ Since 1998, a total of 712 drug labels have been updated with information from randomized trials about drug use, efficacy, and safety in children. Among the most influential of the relevant laws were the 2002 Best Pharmaceuticals for Children Act and the 2003 Pediatric Research Equity Act, both of which require the Food and Drug Administration (FDA) to review case reports of adverse events associated with the use of medical products studied in children.

This review process, conducted by members of the FDA Pediatric Advisory Committee, has contributed substantially to our knowledge of medical product safety in children. But exclusive reliance on this approach doesn't allow the agency to gather data on the full range of safety issues that may arise when children use medical products (defined as drugs, biologics, or medical devices). By their nature, case reports are often unable to clearly link adverse effects with a particular product or quantify relatively small yet clinically relevant treatment-related effects. These limitations are especially relevant for adverse effects that occur months or years after treatment and those related to growth and development. Traditional clinical trials can provide more answers on the long-term effects of medical products but in this context can be unethical, impractical, or expensive.

There are important challenges specific to assessing drug safety in children. Long-term followup is needed to observe effects over multiple developmental stages. Drugs may contribute to decreased growth rates during or after exposure, and exposure to medications in utero may cause delayed effects. Children take medications less often than adults, and measurement of rare events requires large databases. Finally, treating rare diseases is an important part of pediatric care.

A wide range of study designs can be used to assess drug safety in both adult and pediatric populations. Increasingly, studies can incorporate data obtained in the course of clinical care, or real-world data, to generate real-world evidence. Sources of real-world data include electronic health records, claims and billing data, product- and disease-based registries, and mobile and wearable devices.

There are substantial gaps in evidence regarding the safety of many drugs in children. Real-world data could help to fill these gaps in several ways. First, such data can provide greater insight into the long-term effects of in utero exposure to medicines on growing children. For example, one observational study used chart reviews and clinical assessments to demonstrate that exposure to valproate in utero was associated with decreased IQ at 6 years of age, whereas exposure to carbamazepine, lamotrigine, or phenytoin was not.²

Similarly, real-world data can inform our understanding of the long-term effects of exposure to medicines early in children's development. For example, infants in the neonatal intensive care unit (NICU) are often treated with multiple medications and other interventions, some of which may be continued for months or years. Long-term follow-up reports on children cared for in the NICU show that as young adults, they may have abnormal neurodevelopmental outcomes. But such assessments are often confounded by the effects of other medical interventions or underlying disease pathophysiology, so attributing an outcome to a specific drug or other intervention is difficult. Incorporating collection of real-world data into thoughtful study designs — which may include randomization and comparator groups — could help investigators move the field toward more definitive answers.

Real-world data can also be useful for assessing the safety of medications used to treat chronic conditions. As the number of children with certain chronic diseases has increased, more children are being exposed to a range of drugs over a long period, but outcomes associated with long-term use are difficult to study in traditional clinical trials.³ Childhood prescriptions for asthma medications increased by 14% in the United States between 2002 and 2010, for example, and long-term use of these drugs may result in decreased growth rates.⁴ Carefully designed studies using both real-world data and clinical assessments can be more efficient for identifying long-latency outcomes in children with chronic diseases.

In addition, because most children are generally healthy, many drugs are used relatively infrequently in the pediatric population. Drug-associated adverse events that are rare in adults might be even rarer — and thus more difficult to detect — in children. Collecting data on large numbers of children is necessary for studying certain safety issues, and several data sources may be required, as is often the case in using real-world data. Moreover, short-term clinical trials have generally been used to assess the safety of drugs used for short periods in children. Sources of real-world data that include long-term follow-up could offer an effective way to assess longer-term safety. Determining long-latency effects using such data poses challenges, however, since children, like adults, frequently move from one health insurance plan to another, making longitudinal follow-up difficult. Using additional or alternative sources of real-world data can help overcome this limitation. For example, the Swedish Cancer Registry was able to track cancer outcomes over a 50-year period in patients who had been treated for inflammatory bowel disease in childhood.⁵

Finally, rare diseases manifesting during childhood, some of which may affect fewer than 100 people worldwide, generally can't be studied using large medical record-based databases. Disease-based registries that include clinical details are needed to assess treatment and disease-based outcomes, including adverse effects associated with drugs.

Use of real-world data for the study of drug safety is not new; administrative claims data linking dispensed prescriptions to medical diagnoses have been used for several decades to quantify the risks associated with various medicines. Those studies have generally — but not exclusively — focused on adults. For real-world data to extend our knowledge of drug safety in children, a range of data sources and study designs will be needed. Depending on the specific question being addressed, these sources will have to be designed to capture the types of longitudinal data that are unique to children, such as in utero exposure to medicines; weight-based dosing of medicines; measures of growth, development, and nutritional status; and performance in school. Investigators will also need access to information on medical diagnoses, medication usage, other medical interventions, and socioeconomic measures. Widely used data sources that are currently available, such as administrative claims databases and electronic health records, don't uniformly contain this range of information.

Several approaches have been used successfully to study the safety of various medications in children, such as linking maternal and child health records, developing disease- or drug-based registries that include detailed information specific to that disease or treatment, and combining multiple databases to study rare outcomes. Beyond these approaches, long-term follow-up can be facilitated by linking an individual child's health records from multiple care settings and health insurance systems. Linking medical record data to other data sources, such as registries, can improve the efficiency of these efforts. Such approaches can be useful for both observational studies and randomized clinical trials.

As with other initiatives that use evidence generated from personal data, these methods raise questions about personal privacy and data sharing, especially given the tensions that may arise between the public health goals of these efforts and the need to combine detailed child-level data, often from disparate sources, to achieve them. Open and ongoing discussion among all stakeholders could inform an approach that respects patient privacy and individual autonomy, promotes collaboration among competitors, and ensures scientific integrity.

As efforts to advance the use of real-world data to generate real-world evidence move forward — ultimately with the aim of providing useful, relevant, and actionable information about the safety and safe use of drugs — it is imperative that investigators not treat the use of medication in children as an afterthought.

References

1. Avant D, Wharton GT, Murphy D. Characteristics and changes of pediatric therapeutic trials under the Best Pharmaceuticals for Children Act. *J Pediatr*. 2018; 192:8–12. [PubMed: 29029810]
2. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013; 12:244–52. [PubMed: 23352199]
3. Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug utilization in US children, 2002–2010. *Pediatrics*. 2012; 130:23–31. [PubMed: 22711728]
4. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012; 367:904–12. [PubMed: 22938716]
5. Olén O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964–2014. *BMJ*. 2017; 358:j3951. [PubMed: 28931512]