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Best Pharmaceuticals for Children: How Far Have We Come?

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Introduction

Pharmaceutical policy initiatives, such as the Best Pharmaceuticals for Children Act, have made significant strides in improving pediatrics-focused therapeutics. At the same time, there is still a relative paucity of clinical pharmacology data in regard to the pediatric population. Here, we review past and current legislative efforts in the United States, highlight current limitations, and suggest future practice and policy initiatives to optimize pediatric drug therapy.

Background

In response to mounting concerns regarding the safety and efficacy of medications used in pediatric populations, the Best Pharmaceuticals for Children Act (BPCA) was enacted in 2002.[1] The purpose of the BPCA was to promote clinical trials of pharmaceuticals in children that would generate safety and efficacy data. The ultimate goal was pediatric-use approval for more pharmaceuticals and expansion of current drug labeling.[1,2] Additional legislation, in the form of the Pediatric Research Equity Act (PREA), passed in 2003.[3] The BPCA and PREA were reauthorized in 2007 and made permanent in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA).[1–4] Since its inception, the BPCA has stimulated pediatrics-focused clinical pharmacology research and led to hundreds of drug labeling revisions.[5] Despite these major strides, there remains a paucity of data regarding the safe and effective use of medication in pediatric populations. Here, we highlight the existing challenges in optimizing pediatric drug therapy and offer potential solutions.

Current Challenges in Pediatrics-Focused Drug Research

One of the major challenges in pediatric drug research is the conduct of clinical trials in children. It has been established that the pharmacokinetics and pharmacodynamics of drugs often differ between children and adults. Children are also in a dynamic state of growth and development and drug response and toxicity may differ significantly within pediatric age groups.[2] At the same time, there are ethical and practical concerns when studying pharmaceuticals in pediatric populations, such as the complexities of obtaining consent or analyzing small-volume blood samples. As such, the majority of pharmaceuticals are prescribed to children in an "off label" manner.[2,5]

Before the late 1990s, there was little incentive for pharmaceutical manufacturers to conduct clinical trials in pediatric populations. In 1997, the Food and Drug Administration Modernization Act offered manufacturers an additional six months of market exclusivity for conducting pediatrics-focused studies.[2,6] Depending upon sales, an exclusivity extension could translate into an additional $500 million in revenue for each drug pursued.[6] This financial incentive has stimulated pediatrics-focused clinical trials and led to an increase in drug approvals for pediatric use. On the other hand, manufacturers may perform trials of medications with limited utility in pediatric populations to reap the benefits of the longer exclusivity for adult sales. In addition, trials involving children often occur late in the life cycle of a drug, after it has been on the market many years. Most pediatrics-focused trials are performed using medications that have an adult indication; few trials are performed to test novel therapies for pediatrics-specific diseases. As such, these trials have limited benefits for children, which was not the intention of the legislation.[6]

Another major area of focus is to ensure appropriate pharmaceutical labeling. Even when a particular medication has pediatrics-specific data available in the labeling, it does not always provide clear guidance for the prescriber. It is often unclear what ages the drug is formally approved for and in many instances the specific age range is not listed in the indications section of the package insert. Approved pediatrics-specific dosing information, if available, is listed in another section of the label. Finally, the results of pediatrics-focused studies that have been performed may be listed in yet another section, under special populations.

The BPCA has done a great deal to stimulate labeling revisions for pediatrics use, yet there is often a significant lag time between when data becomes available and formal labeling revisions take place.[7] Years may elapse between when a specific toxicity is noted and the drug label is amended. In addition, many pharmaceuticals undergo postmarketing revisions regarding appropriate dosing (most often these are dose reductions due to safety concerns). Another shortcoming is that many drug references (for example, the Physicians' Desk Reference [www.pdr.net]) are based on information found in the package insert, which may be outdated.

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This is further complicated by the fact that providers generally do not consult multiple references when routinely prescribing medication.[7]

In addition to safety concerns, efficacy is an important factor when prescribing pharmaceuticals for pediatric populations.[2] Even though there has been an increase in the number of pediatric pharmaceutical trials performed, there is still a relative paucity of efficacy data in this population. It has been demonstrated that the results of negative clinical trials are generally less likely to be published.[5,6] Even if the results of a negative trial are published, there may be a substantial lag time until this information is disseminated to providers. As a result, pediatric patients may be continuously exposed to a medication from which they may not derive any therapeutic benefit. At the same time, patients, their families, and the health care system will continue to pay for medications that may not be effective. This is further compounded by the potential for adverse effects associated with unnecessary medication use.

Potential Solutions

During the past 2 decades, there have been major advances in pediatric clinical pharmacology, yet there is still much work to be done. Legislative efforts must continue to be supported by providers, industry, the Food and Drug Administration, and patient advocacy groups. Major progress was made in this area when, in 2012, FDASIA permanently reauthorized the BPCA and PREA. In addition, FDASIA strengthened Food and Drug Administration authority pertaining to pediatric clinical trials and promotes studies in underserved populations, specifically neonates.[4] Future legislation should expand on current efforts and address shortcomings, such as focusing on pediatric-specific diseases that may not have adult counterparts and unbiased reporting of clinical trial data. At this time, the true influence of FDASIA has yet to be determined and stakeholders must be vigilant in continuously evaluating current efforts and promoting future legislative change.

The pharmaceutical labeling format for pediatrics should be re-evaluated. The age groups a medication is formally approved for should be explicitly stated in package inserts. Data from pediatrics-focused studies should be clearly outlined and experience from pediatrics-specific studies should be clearly differentiated in the label from what is formally approved. Consideration should be given to consolidating pediatric clinical pharmacology data into 1 specific section of the package insert, so that providers do not have to go to multiple sections to find data. Making drug labeling clearer can promote safer prescribing practices.

Another major area to focus on is dissemination of information. With regard to toxicity data, providers and parents should be encouraged to report adverse drug events to the MedWatch program, which will facilitate labeling revisions. Current information technology platforms can facilitate the reporting process. Because formal labeling changes may take a significant amount of time, efforts should be made to provide updates when an adverse event is reported. Information can be disseminated through a variety of methods, including journals, continuing medical education programs, and Internet-based updates. In addition, these venues may also be used to disseminate the findings of pediatrics-focused studies, even if they are negative. There have also been efforts to require manufacturers to report their findings to peer-reviewed journals, which will limit the prescribing of medication that has not demonstrated efficacy in pediatric populations.

Conclusions

There has been a notable increase in pediatrics-focused pharmacology data in response to legislation; however, additional policy and practice steps need to be taken to ensure the safe and effective use of medications in pediatric populations.

References

[1] US Food and Drug Administration. Regulatory Information. Best Pharmaceuticals for Children Act. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/ucm148011.htm. Accessed March 27, 2013.
[2] National Institutes of Health. Best Pharmaceuticals for Children Act. http://bpca.nichd.nih.gov/. Accessed March 27, 2013.
[3] US Food and Drug Administration. Pediatric Research Equity Act. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf. Accessed March 27, 2013.
[4] US Food and Drug Administration. Regulatory Information: Pediatric Provisions in the Food and Drug Safety and Innovation Act. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm311038.htm. Accessed April 4, 2013.
[5] Institute of Medicine of the National Academies. Addressing the barriers to pediatric drug development: Workshop summary. http://www.ncbi.nlm.nih.gov/books/NBK3994/pdf/TOC.pdf. Accessed March 27, 2013.
[6] Benjamin Jr DK, Smith PB, Murphy MD, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA.* 2006;296:1266–1273.
[7] Mazer-Amirshahi M, Sokol G, van den Anker J, Cantilena L. A review of pharmaceutical labeling for overdose treatment and toxicity data. *Pharmacoepidemiol Drug Saf.* 2013;22:319–323.