No population left behind: Improving paediatric drug safety using informatics and systems biology

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Adverse drug effects (ADEs) in children are common and may result in disability and death. The current paediatric drug safety landscape, including clinical trials, is limited as it rarely includes children and relies on extrapolation from adults. Children are not small adults but go through an evolutionarily conserved and physiologically dynamic process of growth and maturation. Novel quantitative approaches, integrating observations from clinical trials and drug safety databases with dynamic mechanisms, can be used to systematically identify ADEs unique to childhood. In this perspective, we discuss three critical research directions using systems biology methodologies and novel informatics to improve paediatric drug safety, namely child versus adult drug safety profiles, age-dependent drug toxicities and genetic susceptibility of ADEs across childhood. We argue that a data-driven framework that leverages observational data, biomedical knowledge and systems biology modelling will reveal previously unknown mechanisms of pediatric adverse drug events and lead to improved paediatric drug safety.

KEYWORDS
adverse drug reactions, informatics, pediatric drug safety, pharmacodynamics, pharmacovigilance, systems biology

1 CHILDREN AND ADVERSE DRUG EFFECTS

Millions of children are prescribed medication every year1,2 and adverse effects are common.3 A meta-analysis showed the prevalence of adverse drug effects (ADEs) in paediatric patients is as high as 16.8% and that 0.4–10.3% of hospitalizations are due to ADEs.4 Drugs associated to adverse effects are from various drug classes, with anti-epileptic, anti-neoplastic and antibiotic drugs being the most frequent culprits.5,6 Notably, the observed effects can be severe and 87% were found to be preventable.7 Adverse drug effects negatively impact the quality of life of children8 and chronic treatments can lead to late-onset or long-term ADEs.9 Few therapeutic studies have investigated long-term effects of drug exposures, making it difficult to anticipate the consequences of drug therapy during childhood.10 Traditional methods for establishing drug safety, including preclinical studies, clinical trials, and post-marketing surveillance, are failing the paediatric population.

In preclinical studies, in silico screening for developmental toxicity does not consider growth and maturation of children from infancy through adolescence.11,12 Additionally, juvenile animals in safety pharmacology studies have limited similarity in function and morphology to humans13 leading to poor detection of toxicities during child development.14 Clinical trials rarely include paediatric patients even if the drug is widely prescribed in this population (Figure 1). Moreover, paediatric clinical trials suffer from low completion rates, issues establishing generalizable study designs, lack of accepted and validated paediatric endpoints, scarce participants and inflated placebo effects, and inability to detect long-term ADEs.15–18 Post-marketing and epidemiological studies of ADEs in children are exploratory and descriptive in nature,19,20 and have limited clinical translation due to insufficient statistical control of bias and confounding.21 The current...
drug safety pipeline treats children as small adults which has led to a lack of understanding how to safely treat this vulnerable population. Improving drug safety in the paediatric population must follow from understanding paediatric biology and how drug actions and effects are altered during growth and development.

2 | PAEDIATRIC BIOLOGY AND PAEDIATRIC DRUG SAFETY

Unlike adults, children undergo dynamic biological and physical processes from accelerated growth and maturation. Children undergo an evolutionarily conserved process of genomic imprinting, hormonal regulation and adaptive phenotype trajectories across the stages of development. The obvious physical changes as children grow older are reflections of rapid and dynamic organ development, tissue differentiation and functional development across childhood. For example, the immune system dynamically develops where immune cells and immunoglobulins vary in number and concentration across many years, ultimately converging to adult levels. The human brain is constantly changing, from increasing and decreasing white and gray matter through adolescence, and adaptive expression of receptors and neurotransmitters from early life through adolescence. One of the most fascinating and possibly influential processes in human biology stems from our endocrine system, and in childhood different hormones coordinated by the developing brain regulate tissue differentiation, cell proliferation and receptor expression during the different stages of development. Advances in large-scale genomic technologies, as well as international collaborations such as the Pediatric Cell Atlas, allow researchers to probe and illuminate the molecular landscapes that are a reflection of this developmental period. A multi-omics perspective of the first week of life showed distinct molecular networks and pathways, such as increasing interleukin signalling and complement cascade, characterizing a stable developmental trajectory since birth. Stevens et al. highlighted the developing molecular landscape across childhood, showing clusters of genetic programmes towards each phase of growth, including dynamics of signalling pathways across growth phases such as NOTCH, TFGB and VEGF signalling. Moreover, concerted gene regulatory programmes are conserved across species, which is exemplified by distinct developmental trajectories in parallel with stages of child development from the mouse liver transcriptome. Distinct and evolutionarily conserved biological mechanisms during the period of growth and development distinguish children from adults.

Paediatric drug safety must follow from an understanding of how pharmacology is altered during growth and development. Prenatally, perinatally and postnatally, the response and effect of drug treatment coincides with the dynamic molecular patterns underlying physiological and structural development in children. For example, linear and nonlinear dynamics of cytochrome P450 and other metabolic enzymes influence drug disposition such as antipyrine, fentanyl, phenytoin, and many other drugs. Across child developmental stages, growth and maturation processes such as growth rates of immune and neural cell types may alter drug pharmacodynamics as well, resulting in hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, antiepileptic drugs such as phenobarbital, and drugs like warfarin and cyclosporin. The hypothalamus-pituitary-adrenal (HPA) axis, which secretes growth hormone and sex steroids, accelerates during puberty and may affect drug response and be affected by drug therapy. This is an example where drug toxicity may depend on growth and maturation processes during developmental stages as well as from previous developmental stages, such as during early
life.\textsuperscript{61–63} Another less characterized but observed phenomenon is how dynamic growth processes interact with pharmacogenes during childhood.\textsuperscript{68} Adverse drug effects manifest from disrupting gene variation, leading to hearing loss,\textsuperscript{69} and altered gene expression profiles, leading to teratogenicity,\textsuperscript{70} but genetic susceptibility to ADEs across childhood is largely unexplored. These and other effects during childhood, such as drug interactions,\textsuperscript{71} emphasize the basis for and importance of uncovering pharmacodynamic determinants of ADEs in the paediatric population.

\section{Systems Biology and Informatics Approaches to Improve Paediatric Drug Safety}

Paediatric drug safety consistently considers children as small adults without incorporating the unique biology of children.\textsuperscript{72–74} We highlight three key research directions that build upon foundational paediatric research and discuss novel approaches for improving paediatric drug safety (Figure 2).

\subsection{Child versus adult drug safety profiles}

A known but still unsolved problem is detection of ADEs in children and their comparison to adults.\textsuperscript{75} Population stratification is a popular approach to identify ADEs within the paediatric population and was used to discover the arrhythmogenic effects of short-acting beta-agonists from electronic health records.\textsuperscript{76} In other applications, paediatric populations are compared directly to adult populations, as was used to identify renal toxicity associated with enalapril in EudraVigilance.\textsuperscript{77} Recent work has started to refine these comparisons by comparing across developmental stages.\textsuperscript{78,79} The use of these detection methods, which are efficient and essential for identifying drug–adverse event associations (see reviews on disproportionality measures and data mining\textsuperscript{80,81}), are still burdened by potential confounding due to disease status, growth considerations at drug prescription and other extraneous factors. Methodologies must be nuanced enough to distinguish differences in adverse effects from differences in prescribing and reporting patterns. Moreover, fair and accurate comparisons of children to adults will potentially uncover effects of paediatric-specific mechanisms. Real-world data, like those found in electronic health record databases, gather clinical data on large populations of patients as a byproduct of the practice of medicine. As a result of their size, these resources can be used to identify less frequent but still clinically important adverse drug effects in children.\textsuperscript{82,83} Additionally, analysis of real-world data can prioritize plausible ADEs from thousands of data-mined hypotheses, helping to identify the needles in the adverse event haystack.\textsuperscript{84,85} As automated and computational methods become more commonplace, however, high-quality reference sets are required. Methodologies can be compared and evaluated against a common reference set, such as the one created by the GRiP consortium.\textsuperscript{86} Our lab developed a machine-

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\caption{Three unsolved and critical research directions to enhance paediatric drug safety. Novel informatics and systems biology approaches are needed to tackle both signal identification and mechanistic evaluation of adverse drug effects in children. Observational databases are critical for systematic analyses but inherent bias and confounding requires correction for producing sound detection results. Mechanistic databases, such as Drugbank or Chembl, evaluate adverse drug effects using biomedical and chemical knowledge to predict drug toxicities. Developed methodologies require adequate internal and external validation to ensure method robustness and generalizable results.}
\end{figure}
readable version of these data that is publicly available to the research community. Detection of adverse drug effects during childhood through comparison to adults requires novel statistical approaches for sound population comparison and corroboration within real-world data and a paediatric-specific reference set.

3.2 Drug toxicity profile across childhood

Paediatric drug safety can be evaluated in the pre-marketing phases by focusing on adverse drug reactions that may result from growth and maturation processes during childhood. Systems biology methods offer a way to extrapolate from the biology of developmental processes to the clinical effects they may modulate in paediatric drug treatment. These methods can integrate observational with mechanistic data, such as drug pharmacology in Drugbank and drug properties in Chemblo, to study how mechanisms of development may lead to drug toxicity. For example, researchers have linked observed ADEs to mechanisms, such as drug targets associated with heart failure, target inhibition associated with renal disorders, and drug structures associated with QT prolongation. However, the biological mechanisms characterizing ADEs during childhood require novel approaches that go beyond the guilt-by-association hypothesis and incorporate temporal and dynamic changes of biological networks. Time-series-based machine learning approaches can learn drug properties for predicting adverse reactions across childhood, similar to Matlock et al., who developed a time-embedding algorithm to predict CYP enzyme activity across childhood. Quantifying the age-dependence of toxicities across childhood would improve translation of effects during growth and maturation into developmental stage-specific clinical trials and clinical contexts. Approaches for validation are critical when developing these methodologies, including both internal validation for ensuring the method is accurate and external validation for assessing generalizability to other drugs, adverse effects and clinical settings. Once validated, drug toxicity hypotheses would be powerful for further investigation of metabolic, gene and clinical markers for incorporation into pharmacoepidemiology and juvenile animal studies. Systems biology and machine learning approaches can integrate observations and mechanisms to predict potential drug toxicity across childhood.

3.3 Genetic susceptibility of paediatric adverse drug events

The genetic basis of adverse reactions from drug exposure remains largely unknown. Genome wide association studies (GWAS) are established approaches that associate genetic polymorphisms with adverse drug reactions, such as anthracycline-induced cardiotoxicity in children. GWAS are limited, however, to understanding genetic contributors with single, often common phenotypes and lack the biological context that might be necessary to understand drug-induced phenotypes. There is an opportunity to use systems biology to provide the biological context needed to understand GWAS results of drug-induced phenotypes. For example, building long QT syndrome genetic networks showed enrichment of known gene variants from GWAS likely to affect the QT interval and the modular assembly of drug safety subnetworks (MADSS) algorithm significantly improved detection of adverse drug reactions by incorporating protein–protein interactions into adverse event neighbourhoods. In children, the growth and developmental processes during childhood interact with genetic factors and compound direct associations with adverse drug reactions. Notwithstanding, our research group developed a methodology founded on hypothesized population-specific mechanisms addressing statistical bias and confounding that uncovered thousands of ADEs, many with a potential basis in genetics, showing increased safety risks in women. Novel methodologies in paediatric drug safety are tasked to unravel both genetic mechanisms and their dependencies across child development to uncover paediatric-specific genetically-induced adverse drug effects.

4 CONCLUSION

Integrating knowledge of paediatric-specific biology into systems biology approaches can incorporate mechanistic insights and improve paediatric drug safety. These approaches become more powerful when used together within an overarching drug safety framework. In fact, recent studies are showing how frameworks bridging pharmacoepidemiology and pharmacodynamics link biological explanations with detected ADEs. This approach has been used to understand serotonin syndrome reporting and G protein-coupled receptor-mediated acetaminophen-induced movement disorders. However, more is needed for teasing apart correlation from causation, validating results within external and reference datasets, and tailoring analyses towards understanding biological mechanisms in the paediatric population. In previous work, we have demonstrated a data-driven methodology that incorporates large-scale detection, clinical evaluation and experimental validation of ADEs that has uncovered unforeseen drug–drug interactions such as paroxetine with pravastatin increasing blood glucose levels and lansoprazole with ceftriaxone prolonging the QT interval. While this framework has been applied for discovering novel drug–drug interactions in adults, it demonstrates novel informatics coupled with orthogonal evaluation and validation strategies can identify unknown drug pharmacology and adverse effects. A similar approach that is adapted to account for human growth and development may be a systematic and efficient strategy to identify, evaluate and validate ADEs in the paediatric population.

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COMPETING INTERESTS
The authors have no conflict of interests to declare.

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REFERENCES
1. 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(1):23-31. https://doi.org/10.1542/peds.2011-2879
2. Witt WP, Weiss AJ, Elixhauser A. Overview of hospital stays for children in the United States, 2012. HCUP Statistical Brief #187. 2014. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb187-Hospital-Stays-Children-2012.jsp
3. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/outpatients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001;52(1):77-83. https://doi.org/10.1046/j.0007-1188.2001.01407.x
4. Smyth RMD, Gargon E, Kirkham J, et al. Adverse drug reactions in children—a systematic review. PLoS ONE. 2012;7(3):e24061.
5. Sturkenboom MCJM, Neubert A, Cantarutti L, et al. Drug use in children: cohort study in three European countries. BMJ. 2008;337:a2245.
6. de Bie S, Ferrajolo C, Straus SMJM, et al. Pediatric drug safety surveillance in FDA-AERS: a description of adverse events from GRiP Project. PLoS ONE. 2015;10(6):e0130399. https://doi.org/10.1371/journal.pone.0130399
7. Priyadharsini R, Adithan C, Sahoo F, Surendiran A, Sreenivasan S. A study of adverse drug reactions in pediatric patients. J Pharmacol Pharmacother. 2011;2(4):277-280.
8. Arslan FT, Basbakkal Z, Kantar M. Quality of life and chemotherapy-related symptoms of Turkish cancer children undergoing chemotherapy. Asian Pac J Cancer Prev. 2013;14(3):1761-1768.
9. Kelly HW, Stemberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. J Pharmacol Exp Ther. 2012;347(3):904-912.
10. Coates M, Spanos M, Parmar P, Chandrasekhar T, Sikich L. A review of methods for monitoring adverse events in paediatric pharmacology clinical trials. Drug Saf. 2018;41(5):465-471. https://doi.org/10.1007/s40264-017-0633-z
11. Lavado GJ, Gadaleta D, Toma C, et al. Zebrafish AC50 modelling: (Q) SAR models to predict developmental toxicity in zebrafish embryo. Ecotoxicol Environ Saf. 2020;202:110936. https://doi.org/10.1016/j.ecoenv.2020.110936
12. Cendoya X, Quevedo C, Ipiñazar M, Planes FJ. Computational approach for collection and prediction of molecular initiating events in developmental toxicity. Reprod Toxicol. 2020;94:55-64. https://doi.org/10.1016/j.reprotox.2020.03.010
13. Hew KW, Keller KA. Postnatal anatomical and functional development of the heart: a species comparison. Birth Defects Res Part B: Dev Reprod Toxicol. 2003;68(4):309-320.
14. Baldrick P. Juvenile animal testing in drug development—is it useful? Regul Toxicol Pharmacol. 2010;57(2-3):291-299. https://doi.org/10.1016/j.yrtph.2010.03.009
15. Wharton GT, Murphy MD, Avant D, et al. Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. Pediatrics. 2014;134(2):e512-e518. https://doi.org/10.1542/peds.2013-2987
16. Momper JD, Mulugeta Y, Burckart GJ. Failed pediatric drug development trials. Clin Pharmacol Ther. 2015;98(3):245-251.
17. Ceci A, Giannuzzi V, Bonifazi D, Felisi M, Bonifazi F, Ruggieri L. Clinical trials in paediatrics—Regulatory and methodological aspects. In: Vallisuta O, Olimat S, eds. Drug Discovery and Development: From Molecules to Medicine. Rijeka, Croatia: InTech Open; 2015:271-298.
18. Hwang TJ, Orenstein L, Kesselheim AS, Bourgeois FT. Completion rate and reporting of mandatory pediatric postmarketing studies under the US Pediatric Research Equity Act. JAMA Pediatr. 2019;173(1):68-74.
19. Star K, Norén GN, Nordin K, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf. 2011;34(5):415-428. https://doi.org/10.2165/11587540-000000000-00000
20. World Health Organization. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva: WHO; 2002:1–52. Available from: http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf
21. Castro-Pastrana LI, Carleton BC. Improving pediatric drug safety: need for more efficient clinical translation of pharmacovigilance knowledge. J Popul Ther Clin Pharmacol. 2011;18(2):e76-e88. https://doi.org/10.1038/jctbm.2012.176
22. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357-369. https://doi.org/10.1111/bcp.12305
23. Jong Gt. Pediatric formulations. In: Bar-Shalom D, Rose K, eds. Pediatric Formulations: A Roadmap. AAPS Advances in the Pharmaceutical Sciences Series. Vol. 11. New York, NY: Springer; 2014.
24. Crespi B. The evolutionary biology of child health. Proc R Soc B Biol Sci. 2011;278(1711):1441-1449.
25. Blanco E, Pérez-Andrés M, Arriba-Méndez S, et al. Age-associated changes and effects of aging. J Allergy Clin Immunol. 2018;141(6):2208-2219.
26. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proceedings Biol Sci. 2015;282(1821):20143085.
27. Trück J, van der Burg M. Development of adaptive immune cells and receptor repertoires from infancy to adulthood. Curr Opin Syst Biol. 2020;24:105398. https://doi.org/10.1016/j.jocs.2020.08.008
28. Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 2011;31(30):10937-10947.
29. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A. 2004;101(21):8174-8179.
30. Peter RH. Synaptic density in human frontal cortex—Developmental changes and effects of aging. Brain Res. 1979;163(2):195-205.
31. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci Biobehav Rev. 2003;27(1-2):3-18.
32. Fillman SG, Duncan CE, Webster MJ, Elashoff M, Weickert CS. Developmental co-regulation of the β and γ GABAA receptor subunits with distinct α subunits in the human dorsolateral prefrontal cortex. Int J Dev Neurosci. 2010;28(6):513-519.
33. Andersen SL, Thompson AT, Rustein M, Hostetter JC, Teicher MH. Dopamine receptor pruning in prefrontal cortex during the perinatal period in rats. Synapse. 2000;37(2):167-169.
34. Csaba G. Receptor ontogeny and hormonal imprinting. Experientia. 1986;42:750-759. https://doi.org/10.1007/BF01941521
35. Csaba G. The biological basis and clinical significance of hormonal imprinting, an epigenetic process. Clin Epigenetics. 2011;2:187-196. https://doi.org/10.1007/s13148-011-0024-8
36. Taylor DM, Aronow BJ, Tan K, et al. The Pediatric Cell Atlas: defining the growth phase of human development at single-cell resolution. Dev Cell. 2019;49:10-29.
37. Chen J, Blackwell TW, Fermin D, et al. Evolutionary-conserved gene expression response profiles across mammalian tissues. OMICS. 2007;11(1):96-115.

38. Finkielstain GP, Forcinito P, Lui JCK, et al. An extensive genetic program occurring during postnatal growth in multiple tissues. Endocrinology. 2009;150(4):1791-1800.

39. Lee AH, Shannon CP, Amenyogbe N, et al. Dynamic molecular changes during the first week of human life follow a robust developmental trajectory. Nat Commun. 2019;10(1):1-14.

40. Stevens A, Hanson D, Whatmore A, Destenaves B, Chatelain P, Clayton P. Human growth is associated with distinct patterns of gene expression in evolutionarily conserved networks. BMC Genomics. 2013;14(1):547-562.

41. Gunewardenas SS, Yoo B, Peng L, et al. Deciphering the developmental dynamics of the mouse liver transcriptome. PloS ONE. 2015;10(10):e0141220. https://doi.org/10.1371/journal.pone.0141220

42. Kearns GL, Abdel-Rahman SM, Alandar SW, Blowey DL, Leeder JS, Kaufman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157-1167. https://doi.org/10.1056/NEJMra0305092

43. Hines RN. Ontogeny of human hepatic cytochromes P450. J Biochem Mol Toxicol. 2007;21(4):169-175.

44. Bhatt DK, Mehrata A, Gaedigk A, et al. Age- and genotype-dependent variability in the protein abundance and activity of six major uridine diphosphate-glucuronosyltransferases in human liver. Clin Pharmacol Ther. 2018;105(1):131-141.

45. Moolij MG, Schwarz U, De Koning BAE, et al. Ontogeny of human hepatic and intestinal transporter gene expression during childhood: age matters. Drug Metab Dispos. 2014;42(8):1268-1274.

46. Lam J, Baello S, Iqbal M, et al. The ontogeny of P-glycoprotein in the developing human brain: implications for the disposition and effect of drugs in the brain. Br J Clin Pharmacol. 2014;78(4):417-421. https://doi.org/10.1111/bcp.12850

47. Koukouriaki SB, Simpson P, Yeung CK, Rettie AE, Hines RN. Human hepatic flavin-containing monoxygenases 1 (FMO1) and 3 (FMO3) developmental expression. Pediatr Res. 2002;51(2):236-243.

48. Engel G, Hofmann U, Heidemann H, Cosme J, Eichelbaum M. Antipyrine as a probe for human oxidative drug metabolism: human hepatic flavin-containing monooxygenases 1 (FMO1) and 3 (FMO3) developmental expression. Pediatr Res. 2002;51(2):236-243.

49. Katz R, Kelly W. Pharmacokinetics of continuous infusions of fentanyl in critically ill children. Crit Care. 1993;21(7):995-1000.

50. Miura H, Minagawa K. Michaelis-Menten pharmacokinetics of diphenylhydantoin and application in the pediatric age patient. J Biochem Mol Toxicol. 1999;13(1):547-562. https://doi.org/10.1002/(SICI)1099-0716(199908)13:1<547::AID-JBMT3>3.0.CO;2-M

51. Ginsburg G, Hattis D, Sonawane B, et al. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci. 2002;66(2):185-200.

52. Waldman R, Whitaker-Worth D, Grant-Kels JM. Cutaneous adverse drug reactions: kids are not just little people. Clin Dermatol. 2017;35(6):566-582. https://doi.org/10.1016/j.clindermatol.2017.08.007

53. Nanau RM, Neuman MG. Ibuprofen-induced hypersensitivity syndrome. Trans Res. 2010;155(6):275-293.

54. Budevskar SB, Muranjan MN, Gogtay NJ, Kantharia V, Kshirsagar NA. Anticonvulsant hypersensitivity syndrome: lymphocyte toxicity assay for the confirmation of diagnosis and risk assessment. Ann Pharmacother. 2004;38(10):1648-1650.

55. Takahashi H, Ishikawa S, Nomoto S, et al. Developmental changes in pharmacokinetics and pharmacodynamics of warfarin enantiomers in Japanese children. Clin Pharmacol Ther. 2000;68(5):541-555. https://doi.org/10.1067/mcp.2000.110977

56. Marshall J, Kearns G. Developmental pharmacodynamics of cyclosporine. Clin Pharmacol Ther. 1999;66(1):66-75. https://doi.org/10.1016/S0009-9236(99)70055-X

57. Kennedy MJ. Hormonal regulation of hepatic drug-metabolizing enzyme activity during adolescence. Clin Pharmacol Ther. 2008;84(6):662-673. https://doi.org/10.1038/clpt.2008.202

58. Kawakami Y, Fuji S, Ishikawa G, Sekiguchi A, Nakai A. Takase M. Valproate-induced polycystic ovary syndrome in a girl with epilepsy: a case study. J Nippon Med Sch. 2018;85(5):287-290.

59. Caprio S. Insulin: the other anabolic hormone of puberty. Acta Paediatr Suppl. 1999;88(433):84-87. https://doi.org/10.1111/j.1651-2271.1999.tb14410.x

60. De Leonibus C, Attanasi M, Roze Z, et al. Influence of inhaled corticosteroids on pubertal growth and final height in asthmatic children. Pediatr Allergy Immunol. 2016;27(5):499-506.

61. Csaba G, Kovács P, Pällinger É. Prolonged impact of five imprinters on the serotonin content of white blood cells and mast cells of weaning rats: outstanding effect of benzyopyrene and chlorpheniramine. Cell Biol Int. 2004;28(3):217-222.

62. Waterland RA. Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. Am J Clin Nutr. 1999;69(2):179-197.

63. Barker DJ. The developmental origins of chronic adult disease. Acta Paediatr Suppl. 2004;93(446):26-33.

64. Solleveld MM, Schraante A, Puts NAJ, Reneman L, Lucassen PJ. Age-dependent, lasting effects of methylphenidate on the GABAergic system of ADHD patients. Neurolmage Clin. 2017;15:812-818. https://doi.org/10.1016/j.neucli.2017.06.003

65. Visentin S, Grumolato F, Nardelli GB, Di Camillo B, Grisan E, Cosmi E. Early origins of adult disease: low birth weight and vascular remodeling. Atherosclerosis. 2014;237(2):391-399. https://doi.org/10.1016/j.atherosclerosis.2014.09.027

66. McMahon AW, Dal Pan G. Assessing drug safety in children—the role of real-world data. N Engl J Med. 2018;378(23):2155-2157. https://doi.org/10.1056/NEJMfp1803292

67. Hsu SP, Wang D-Y, Min M-Y, Fu Y-S. Long-term challenge of methylphenidate changes the neuronal population and membrane property of dopaminergic neuron in rats. Neurochem Int. 2019;122:187-195.

68. Leeder JS, Kearns GL. Interpreting pharmacogenetic data in the developing neonate: the challenge of hitting a moving target. Clin Pharmacol Ther. 2012;92(4):434-436. https://doi.org/10.1038/clpt.2012.46

69. Ross CJ, Katzow-Eckert H, Dubé MP, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet. 2009;41(12):1345-1349.

70. Collins MD, Mao GE. Teratology of retinoids. J Nippon Med Sch. 2018;85(5):670-673.

71. Akbar M, Berry-Bibee E, Blithe DL, et al. FDA public meeting report on “Drug interactions with hormonal contraceptives: public health and drug development implications”. J Clin Pharmacol. 2018;58(12):1655-1665. https://doi.org/10.1002/jcph.1285

72. Stephenson T. How children’s responses to drugs differ from adults. Br J Clin Pharmacol. 2005;59(6):670-673.

73. Klassen TP, Hartling L, Craig J, Offringa M. Children are not just small adults: the urgent need for high-quality trial evidence in children. PLoS Med. 2008;5(8):e1223-1237.

74. Gentili M, Pozzi M, Peeters G, Radice S, Carnovale C. Review of the methods to obtain paediatric drug safety information: spontaneous reporting and healthcare databases, active surveillance programmes, systematic reviews and meta-analyses. Curr Clin Pharmacol. 2018;13(1):28-39.

75. Czaja AS, Ross ME, Liu W, et al. Electronic health record (EHR) based postmarketing surveillance of adverse events associated with...
pediatric off-label medication use: a case study of short-acting beta-2 agonists and arrhythmias. Pharmacoepidemiol Drug Saf. 2018; 27(7):815-822. https://doi.org/10.1002/psd.4562

77. Blake KV, Saint-Raymond A, Zaccaria C, Domergue F, Pelle B, Slattery J. Enhanced paediatric pharmacovigilance at the European Medicines Agency: a novel query applied to adverse drug reaction reports. Pediatr Drugs. 2016;18(1):55-63.

78. Osokogu OU, Dodd C, Pacuraruiu A, Kaguelidou F, Weibel D, Sturkenboom M CJM. Drug safety monitoring in children: performance of signal detection algorithms and impact of age stratification. Drug Saf. 2016;39(9):873-881. https://doi.org/10.1007/s40264-016-0433-x

79. Giangreco N, Tatonetti N, Giangreco N, Tatonetti N. Using precision pharmacovigilance to detect developmentally-regulated adverse drug reactions: a case study with antiepileptic drugs. F1000Research. 2018;11:7-7.

80. Duggirala HJ, Tonning JM, Smith E, et al. Use of data mining at the Food and Drug Administration. J Am Med Inform Assoc. 2016;23(2):428-434.

81. Dodd C, Osokogu O, Fregonese F, et al. Report on methods of safety signal generation in paediatrics from pharmacovigilance databases. 2014. http://www.grip-network.org/uploads/assets/WP2/GRIP-D2.7-Report_on_methods_of_safety_signal_generation_in_paediatrics_from_pharmacovigilance_databases.pdf

82. Wei R, Jia L-L, Yu Y-C, et al. Pediatric drug safety signal detection of non-chemotherapy drug-induced neutropenia and agranulocytosis using electronic healthcare records. Expert Opin Drug Saf. 2019; 18(5):433-441. https://doi.org/10.1080/14740338.2019.1604682

83. Ollivier NF, Sabouhanian A, Gallie BL. Single-center retrospective study of the effectiveness and toxicity of the oral iron chelating drugs deferrirone and deferasirox. PLoS ONE. 2019;14(2):e0211942. https://doi.org/10.1371/journal.pone.0211942

84. Tatonetti NP. The next generation of drug safety science: coupling detection, corroboration, and validation to discover novel drug effects and drug-drug interactions. Clin Pharmacol Ther. 2018; 103(2):177-179. https://doi.org/10.1002/cpt.949

85. Lorberbaum T, Sampson KJ, Woosley RL, Hripcsak G, Tatonetti N. An integrative data science pipeline to identify novel drug interactions that prolong the QT interval. Drug Saf. 2016;39(5):433-441.

86. Osokogu OU, Fregonese F, Ferrajolo C, et al. Pediatric drug safety signal detection: a new drug-event reference set for performance testing of data-mining methods and systems. Drug Saf. 2015;38(2):207-217. https://doi.org/10.1007/s40264-015-0265-y

87. Giangreco N. GRIP_pediatric_ADE-reference_set. 2020. https://github.com/ngiangre/GRIP_pediatric_ADE-reference_set. Accessed October 21, 2020.

88. Wishart DS, Knox C, Guo AC, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006;34:668-672.

89. Mendez D, Gaulton A, Bento AP, et al. ChEMBL: towards direct deposition of bioassay data. Nucleic Acids Res. 2019;47(D1):D930-D940.

90. Lesko LJ, Zheng S, Schmidt S. Systems approaches in risk assessment. Clin Pharmacol Ther. 2013;93(5):413-424.

91. Chen X, Wang Y, Wang P, et al. Systematic analysis of the associations between adverse drug reactions and pathways. Biomed Res Int. 2015;2015:1-12.

92. Ietswaart R, Arat S, Chen AX, et al. Machine learning guided association of adverse drug reactions with in vitro target-based pharmacology. EBioMedicine. 2020;57:102837.

93. Scheibler J, Jenkins JL, Sukuru SC, et al. Mapping adverse drug reactions in chemical space. J Med Chem. 2009;52(9):3103-3107.

94. Weinstein ZB, Bender A, Cokal M. Prediction of synergistic drug combinations. Curr Opin Syst Biol. 2017;4:24-28.

95. Matlock MK, Tambe A, Elliott-Higgins J, Hines RN, Miller GP, Swamidass SJ. A time-embedding network models the ontogeny of 23 hepatic drug metabolizing enzymes. Chem Res Toxicol. 2019;32(8):1707-1721. https://doi.org/10.1021/acs.chemrestox.9b00223

96. Kohler I, Hankemeier T, van der Graaf P, Knibbe C, van Hasselt J. Integrating clinical metabolomics-based biomarker discovery and clinical pharmacology to enable precision medicine. Eur J Pharm Sci. 2017;109:S15-S21. https://doi.org/10.1016/j.ejps.2017.05.018

97. Soldatos T, Taglang G, Jackson D. In silico profiling of clinical phenotypes for human targets using adverse event data. High Throughput. 2018;7(4):37-49. Available from: http://www.mdpi.com/2571-5135/7/4/37

98. Rieder MJ, Carleton B. Pharmacogenomics and adverse drug reactions in children. Front Genet. 2014;5:78-89.

99. Visscher H, Ross CJ, Rassekh SR, et al. Pharmacogenomic prediction of anticholinergic-induced cardiotoxicity in children. J Clin Oncol. 2012;30(13):1422-1428.

100. Liu W. Pharmacogenomics-guided approaches to avoiding adverse drug reactions. Clin Pharmacol Biopharm. 2012;01(3):1-5.

101. Crowley JJ, Sullivan PF, McLeod HL. Pharmacogenomic GWAS: lessons learned thus far. Pharmacogenomics. 2009;10(2):161-163.

102. Berger SS, Ma A, Ivanyar R, Ma’ayan A. Systems pharmacology of arrhythmias. Pharmacology. 2010;3(118):1-30.

103. Lorberbaum T, Nasir M, Keiser M, Vilar S, Hripcsak G, Tatonetti N. Systems pharmacology augments drug safety surveillance. Clin Pharmacol Ther. 2015;97(2):151-158. https://doi.org/10.1002/cpt.2

104. Leeder JS. Developmental and pediatric pharmacogenomics. Pharmacogenomics. 2003;4(3):331-341. https://doi.org/10.1517/phgs.4.3.331.22693

105. Becker ML, Leeder JS. Identifying genomic and developmental causes of adverse drug reactions in children. Pharmacogenomics. 2010;11:1591-1602.

106. Chandak P, Tatonetti N. AwareDX: using machine learning to identify drugs posing increased risk of adverse reactions to women. Patterns. 2020;1(7):100108. https://doi.org/10.1016/j.j.parther.2020.100108

107. Gatti M. Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. Eur J Clin Pharmacol. 2020;1-7. https://doi.org/10.1007/s00228-020-02990-1

108. Nguyen TTH, Pariente A, Montastruc J-L, et al. An original pharmacoepidemiological-pharmacodynamic method: application to antipsychotic-induced movement disorders. Br J Clin Pharmacol. 2017;83(3):612-622. https://doi.org/10.1111/bcp.13145

109. Tatonetti NP, Denny JC, Murphy SN, et al. Detecting drug interactions from adverse-event reports: interaction between paroxetine and pravastatin increases blood glucose levels. Clin Pharmacol Ther. 2011;90(1):133-142. https://doi.org/10.1038/clpt.2010.2264

110. Lorberbaum T, Sampson KJ, Chang JB, et al. Coupling data mining and laboratory experiments to discover drug interactions causing QT prolongation. J Am Coll Cardiol. 2016;68(16):1756-1764.