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Clinical Investigation

Medication Repurposing in Pediatric Patients: Teaching Old Drugs New Tricks

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OBJECTIVES: Gaps in pediatric therapeutics often result in off-label use and specifically, novel uses for existing medications, termed "drug repurposing." Drug Information (DI) queries to a Pediatric Medication Resource Center of a large metropolitan pediatric hospital in New York and inherent difficulties in retrieving evidence-based information prompted a review of current medication repurposing for pediatric patients. The objective included characterization of innovative off-label use of medications Food and Drug Administration (FDA)-approved for 1 or more indications to treat a totally different disorder or indication in pediatric patients.
METHODS: A systematic literature review was conducted to retrieve publications describing repurposed medications in pediatric patients. Excluded was FDA-approved indications used off-label in pediatric patients (e.g., different dose), preclinical data, adult use only, and experimental use. Evidence quality was classified using a modified American Academy of Neurology Level of Evidence. Results were analyzed using χ^2 at $p < 0.05$.
RESULTS: Over 2000 references were retrieved and reviewed. A total of 101 medications repurposed for novel off-label uses for pediatric patients were identified: 38 for neonates, 74 for children, and 52 for adolescents. Neonates and infants were least likely to receive a medication for a repurposed use. Strong or intermediate evidence existed in 80.2% of cases. The evidence was weak in 19.8%. No significant relationship was observed between the pediatric age group and strength of the literature. Most repurposed uses pertained to generic or widely used medications. Less than 5% of medications were first marketed after 2011.
CONCLUSIONS: While not exhaustive, the present study represents the most comprehensive listing of novel uses exclusive to pediatric patients. Further research is needed to identify the frequency of repurposed uses. The valuable DI role of pharmacists in assessing repurposed uses is of expanding and increasing importance to ensure such uses are evidence-based.

INDEX TERMS: drug information services, drug repositioning, drug utilization, off-label use, pediatrics, unlabeled indication

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INTRODUCTION

In 1963, Dr Harry C. Shirkey stated, "By an odd twist of fate, infants and children are becoming therapeutic or pharmaceutical orphans."[1] More than half a century later, most medications used

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in pediatric patients are not Food and Drug Administration (FDA) approved for use in this patient population. That is, they are used off-label. Off-label use is the mainstay of therapy in pediatric patients. Several studies have shown that between 39% and 79% of children admitted to pediatric hospitals receive 1 or more courses of off-label therapy.[2,3]

Legislative efforts to improve pediatric drug therapy include The Best Pharmaceuticals for Children Act (BPCA)[4] and the Pediatric Research Equity Act (PREA).[5] Table 1 lists similarities and differences between BPCA and PREA. Both became permanent in 2012 under the FDA Safety and Innovation Act and have resulted in about 500 pediatric labeling changes.[6] Despite this success, less than half of all products are labeled with pediatric information.[7]

The FDA does not mandate pediatric ages to be tested, and medications have received exclusiv-

Table 1. Provisions of the BPCA and PREA

BPCA	PREA
Studies voluntary (FDA can request)	Studies mandatory
Triggered by a public health need	Triggered by application for a new indication, new dosage form, dosing regimen, route of administration or new active ingredient
Studies may include unapproved different indications (on and off label)	Only indication(s) under review
Drugs and Biologics	Drugs and Biologics
Orphan indications allowed	Orphan indications exempt
Six months marketing exclusivity (added to other exclusivity only)	No extra patent extension or exclusivity (but may have an opportunity to qualify for exclusivity)

BPCA, Best Pharmaceuticals for Children Act; FDA, Food and Drug Administration; PREA, Pediatric Research Equity Act

ity by testing in 12- to 17-year-olds, extending use to adolescent but not pediatric patients. A recent study of 192 medications that were granted pediatric exclusivity by the FDA reported that studies in support of exclusivity are often not designed to meet pediatric patient needs. For example, hypertension and high cholesterol are the therapeutic category most frequently granted pediatric exclusivity.[8] Additionally, exclusivity is currently not conditioned upon studies in pediatric patients being either successful or resulting in FDA approval.

No legislation exists to incentivize pediatric research of FDA-approved medications that have no existing patent life, especially where generic versions exist. For such medications or where the medication is inexpensive, manufacturers have little financial incentive to invest in costly pediatric clinical trials. Likewise, there is no incentive to submit Supplemental New Drug Applications (SNDAs), which when approved will allow a company to make changes in a product that already has an approved new drug application (NDA) (e.g., change to FDA-approved indications). Rarely are SNDAs used to obtain FDA approval for repurposed or innovative indications. However, for high cost medications, the incentive to conduct such trials may exist. Regardless, nothing mandates manufacturers to seek FDA approval for new indications as they become established. Even for NDAs, pharmaceutical companies are reluctant to include extra indications that might further complicate their application's approval.[9]

Contributing factors for the extensive lack of pediatric clinical trials include, for example, difficulty recruiting pediatric patients, especially where the risk:benefit ratio is unclear or there is limited pediatric prevalence for the condition. Even with Orphan Drug Act[10] drug development incentives, it still may be financially unattractive to conduct research in the pediatric population where contradictory evidence may be found and the manufacturer is already profiting from a medication's recognized off-label use. For monoclonal antibodies, for example, twice as many off-label uses as FDA-approved indications exist. Under the Federal Food, Drug, and Cosmetic Act, manufacturers are prohibited from directly marketing a medication for a use other than FDA-approved indications.[11] However, the FDA does not have the legal authority to regulate the practice of medicine, and prescribers may prescribe a medication off-label.

Off-label use can be classified into 2 broad categories: 1) using an FDA-approved medication for 1 or more indications to treat an entirely different disorder or indication, or 2) prescribing a medication for an indication it was FDA-approved for, but outside certain specifications (age, weight, route of administration, doses, or patient populations).[12] In the first instance, the off-label use can be classified as innovative or novel where, for example, the benefit was serendipitously clinically observed. In other cases, these uses have been discovered through mining chemical structure or pharmacogenomics databases, clinical research, or trial and error.

While studies have been conducted in hospitalized pediatric populations to determine incidence of off-label use,[13–15] and to investigate pediatric off-label use of unapproved medications,[6,16] few studies have investigated either the incidence or characterization of repurposed or

innovative off-label medication use in pediatric patients. The focus of this article is innovative off-label use of medications approved for 1 or more indications in adult and/or pediatric patients to treat a totally different disorder or indication in pediatric patients.

METHODOLOGY

A literature search was performed to retrieve all publications describing repurposed medications in pediatric patients. Patient ages were categorized as: infant (< 1 year), child (1 to < 12 years), and adolescent (12-18 years). This classification closely follows FDA age categories for exclusivity studies. The search was conducted in PubMed (1966 through January 2015), EMBASE, Ovid, The Cochrane Library, and Google Scholar using the search terms "pediatric," "off-label," "repurposed medications," "repositioning medications," "drug repositioning," "drug rediscovery," and "drug repurposing." No language or date restrictions were considered. The FDA "Pediatric Labeling Database,"[17] FDA "Rare Disease Repurposing Database,"[18] Off-Label Drug Facts,[19] and Harriet Lane Handbook were also reviewed.[20] To ensure the latest prescribing information was reviewed, the FDA Web site (Center for Drug Evaluation and Research) listing of marketed medications was used.

Off-label was defined as an indication not listed in the current prescribing information (i.e., package insert). For the purposes of this study, repurposed uses were defined as those involving different categories of diseases (e.g., asthma and epilepsy), rather than merely different diseases in the same category (i.e., eczema and boils). Both prescription and over-the-counter (OTC) products were included.

Clinical observations of innovative uses from a large metropolitan pediatric hospital were included, and further literature searches were conducted to obtain publications reporting the novel use. Additionally, included were Drug Information requests received at a Pediatric Medication Resource Center pertaining to the need for information about dosing, supporting literature, and administration for innovative uses.[21]

An effort was made to locate the best and most recent evidence (e.g., randomized clinical trials versus anecdotal case reports). Included were randomized controlled trials, cohort and case control studies, professional guidelines or recommendations, case reports, case series, and studies conducted on small numbers of pediatric patients. Preclinical and chemical screening studies, review articles (other than meta-analysis or systematic reviews), letters to the editor, editorials, and commentaries were excluded. Both positive and negative evidence were included. For each repurposed use identified, a second search was conducted both in the databases above as well as by reviewing the bibliography of each article to locate the best evidence possible.

To identify the strength of the evidence and evaluate evidence quality, a modified American Academy of Neurology (AAN) Level of Evidence classification for therapeutic intervention was employed.[22] Our modified classification involved a 3-tiered system (i.e., strong, intermediate, weak). Strong evidence involved prospective randomized controlled trials or prospective matched group cohort studies directly relevant yielding positive findings or inclusion in a Pediatric Association Guideline. Intermediate evidence involved conflicting data in randomized clinical trials or cohort studies, case-control studies (including well-defined natural history controls or patients serving as their own controls), some evidence in the form of small or pilot (preliminary) trials or case series, or consensus recommendation in the absence of relevant clinical trials and better evidence than case reports. Weak evidence involved isolated or anecdotal case reports, expert opinion, or where the results of strong or intermediate evidence indicated the medication was not clinically useful for the repurposed usage. Only a few key citations were included in the citation column even where multiple existed. Finally, we reported out the specific ages of the pediatric patient population or subpopulation (e.g., adolescents) for which the novel use was either most likely to be used or was reported as used. Results were analyzed using χ^2 and significance was set at $p < 0.05$.

Excluded were FDA-approved indications used off-label in pediatric patients; innovative uses which were used in both adult and pediatric patients but primarily in adult patients or where the literature pertained solely to adult patients; where the use was only described in adults and the literature pertained only to adults; and where no literature support was located or where the only available literature regarding the novel off-

label use pertained to preclinical studies. In such cases, the use would be experimentation requiring informed consent or perhaps submission of an Investigational New Drug Application (IND) to the FDA.

RESULTS

The search retrieved over 2000 references, many of which were excluded as either not pertinent or related to pediatric off-label, but not necessarily repurposed, use of medication FDA approved for the indication in adults. No single source contained all the repurposed indications, but Off Label Drug Facts identified the most. Tables 2 to 4 detail repurposed uses of medications for pediatric patients, and provides the medication name, the repurposed indication, patient age ranges, strength of evidence, and reference(s). Table 2 represents medications for which strong published evidence was retrieved based on a modified AAN Level of Evidence.[23–78] Tables 3 and 4 represent intermediate[79–129] and weak[130–156] evidence, respectively. A total of 101 medications used in a repurposed manner in pediatric patients were identified; 38 medications for neonates and/or infants; 74 for children; and 52 for adolescents. The majority (i.e., 58) involved multiple age categories; thus the total adds up to 164. Medications repurposed for multiple pediatric categories were as follows: 11 infants and children; 42 adolescents and children; and 5 infants, children, and adolescents. Neonates and infants were least likely to receive a medication for an innovative off-label use.

Strong or intermediate evidence existed in a majority of cases (81/101) (80.2%); that is, the use was supported by the published literature. The evidence was strong in 40/101 instances (39.6%); intermediate in 41/101 instances (40.6%); and weak in only 20/101 (19.8%). While only about 20% of the evidence was considered weak, this may have been a result of failure to identify every repurposed usage. Table 5 identifies the strength of the evidence by age group. Using χ^2 analysis, no significant relationship was observed between the pediatric age group and strength of the literature.

Most references provided the dosages used; most often weight-based, but sometimes fixed dosing was used. In a number of cases, the doses differed for the same repurposed indication. Dosing information was not included in Tables 2 to 4, as it was felt very important for clinicians to retrieve and review the latest primary literature.

Our research also revealed the fact that, in almost every instance, the medical record did not indicate that patients or their guardians/parents were informed that a drug was being prescribed for an unlabeled indication.

DISCUSSION

Due to resource constraints, we did not attempt to produce the most exhaustive list possible. Rather, our list represented the most extensive list of repurposed medications in pediatric patients published to date. A recent study by Blatt and Corey[157] identified 63 repurposed medications used in pediatric patients with emphasis on pediatric hematology/oncology. The authors looked for medications having at least 1 pediatric indication for which a newer use was in hematology/oncology. The present study differed in that it did not focus on hematology/oncology. Additionally, repurposed medications were excluded if the use was also found in adult patients (e.g., aspirin for colon cancer prevention).

Some studies have shown that off-label use is extensive in hospital as well as outpatient settings.[13–15] The present study was limited to the literature and hospital setting and did not seek to answer the question of frequency of off-label prescribing in either inpatients or outpatients. Further research is needed to determine the extent of novel off-label use of medications in pediatric populations.

A recent study revealed that few drug-labeling changes made under pediatric legislation include neonates.[158] Previous research has revealed that hospitalized neonates and infants receive the greatest proportion of off-label use of medications.[12] Although this may be true for all off-label use (e.g., age, dose, weight, and route of administration), the present study reveals that this pediatric subpopulation is actually least likely to receive an off-label use for a repurposed indication. Our results reflect other literature that has found neonates to be less likely to receive medications off-label and attributed this to the scarcity of reliable dosing information, as well as a more conservative approach in this pediatric subpopulation.[159]

Results presented in this paper validate that

Table 2. Repurposed Medications for Pediatric Patients With Strong Evidence for Use

Reference	Drug	Novel Indication	Ages
Go et al[23]	ACTH	Infantile spasms	< 1 yr
Madenci et al[24] Ward et al[25]	Alendronate	Osteogenesis imperfecta	3-7 yr 1.8-15 yr
App et al[26]	Amiloride, via inhalation	Cystic fibrosis	2-18 yr
Eleftheriou et al[27]	Aspirin	Kawasaki's disease	< 5 yr; Peak 18-24 mo
Omari et al[28]	Baclofen	Gastroesophageal reflux disease	2 mo-17 yr
El Shaded et al[29]	Beractant	Meconium aspiration syndrome	Infants
Mintz-Hittner et al[30]	Bevacizumab	Retinopathy of prematurity	< 54 wk PMA
Furuta et al[31]	Budesonide	Eosinophilic esophagitis	Children
Lemonnier et al[32]	Bumetanide	Autism	3-11 yr
Schmidt et al[33] Mueni et al[34] Rhein et al[35]	Caffeine	Newborn apnea Intermittent hypoxia preterm	Median PMA 31 wk
Takeuchi et al[36]	Caffeine	Sarcoma (potentiation of chemotherapy)	7-21 yr
Richmond et al[37] Gil-Ad et al[38]	Clonidine	Growth hormone stimulation test	Prepubertal < 17 yr
Rotig et al[39] Parikh et al[40]	Coenzyme Q	Metabolic acidosis (secondary to mitochondrial disease)	3 mo-2 yr
Yazigi et al[41]	Colchicine	Recurrent pericarditis	4-14 yr
Ahn et al[42] Choodhry et al[43]	Danazol	Childhood chronic idiopathic thrombocytopenia purpura	>10 yr
Hedlund-Treutiger et al[44] Neunert et al[45]	Dexamethasone	Idiopathic thrombocytopenic purpura	3-17 yr
Zheng et al[46] Yang et al[47]	Dexamethasone	Infantile hemangioma	Infants
Ohlsson et al[48]	Epoetin alpha	Anemia of prematurity	Premature infants
Sahni et al[49] Prabhu et al[50]	Furosemide, nebulized	Broncho-pulmonary dysplasia	Neonates, preterm
Moody et al[51]	Haloperidol	Refractory nausea and vomiting	Not for children < 3 yr
Kim et al[52]	Helium-oxygen therapy with racemic Epinephrine	Bronchiolitis	2-12 mo
Heyman et al[53] Ohlsson et al[54]	Ibuprofen	Patent ductus arteriosus	Preterm infants; GA < 35 wk
Johnston et al[55]	Indomethacin	Patent ductus arteriosus	Preterm infants; GA < 35 wk
Mangla et al[56] Del-Pozzo-Mangla et al[57]	Intravenous immunoglobulin	Toxic epidermal necrolysis	3 mo-15 yr
Mangla et al[56]	Intravenous immunoglobulin	Stevens–Johnson syndrome	3 mo-15 yr

ACTH, adrenocorticotropic hormone; GA, gestational age; PMA, postmenstrual age

Table 2. Repurposed Medications for Pediatric Patients With Strong Evidence for Use (*cont.*)

Reference	Drug	Novel Indication	Ages
Pinto et al[58]	Isotretinoin	Neuroblastoma	9-18 mo
Pope et al[59]	Methylprednisolone	Infantile hemangioma	Infants
Chen et al[60]	Montelukast	Perennial allergic rhinitis	2-11 yr
Ballard et al[61] Mercier et al[62]	Nitric oxide	Bronchopulmonary dysplasia	Preterm
Fenichel et al[63]	Oxandrolone	Duchenne muscular dystrophy	2-18 yr
Brousseau et al[64]	Prochlorperazine	Pediatric migraine	5-18 yr
Hagman et al[65]	Risperidone	Anorexia	12-21 yr
Joung et al[66] Anand et al[67]	Sucrose	Pain management	Newborn infants
Lazzerini et al[68] Felipez et al[69]	Thalidomide	Crohn's disease	Mean age 14 yr
Galeotti et al[70]	Tocilizumab	Castleman's disease	6.5-7 yr
Winner et al[71] Lakshmi et al[72]	Topiramate	Pediatric migraine	6-17 yr
Rumore et al[73] Hall et al[74]	Vitamin A	Measles	≥ 6 mo
Gabbay et al[75] Zipitis et al[76]	Vitamin D_3	Preserve pancreatic B-cell function in newly diagnosed T1DM	7-30 yr
Marchisio et al[77]	Vitamin D	Otitis media	1-5 yr
Milgrom et al[78]	Xylitol	Dental caries prevention	9-15 mo

ACTH, adrenocorticotropic hormone; GA, gestational age; PMA, postmenstrual age

the majority of the literature pertained to studies in small numbers of children and that several therapeutic categories had multiple repurposed medications. For example, medications were repurposed more than several times for cerebral palsy, muscular dystrophy, insomnia, cystic fibrosis, migraine, apnea, and stuttering. Our data also revealed that research may be needed on older medications. Most innovative uses pertained to medications that had been on the market for years; that is, older generic medications or widely used medications for which little evidence exists of harm to children. Few new medications were used for innovative uses. In fact, depending upon the definition of a new medication, less than 5% of the medications in Tables 2 to 4 were first marketed after 2011 and could be considered new medications (i.e., exenatide, letrozole, and tocilizumab). Possible reasons for this may include lack of experience on the part of clinicians even in adult patients to use new medications, fear of liability, and/or the fact that novel uses often emerge from postmarketing experience.

In some cases, promising novel uses reported by clinicians to the manufacturer may prompt a clinical trial with subsequent FDA approval. For example, while conducting this research, propranolol, used for pediatric hemangioma, received FDA approval for this indication. Similarly, imipramine is now FDA-approved for nocturnal enuresis in pediatric patients and does not appear in Tables 2 to 4. However, in other cases uses identified decades ago in the literature were not followed up upon and more recent studies could not be located. In a number of cases, the early literature was strong but FDA approval was never sought nor were later clinical studies conducted.

This paper highlights the difficulty in locating information on medications repurposed for pediatric patients. There are few resources that enable a clinician to locate drug information on prescribing, dosing, and dispensing of approved medications for unlabeled repurposed pediatric indications. Such uses can no longer be discussed at symposia or professional meetings. Most of

Table 3. Repurposed Medications for Pediatric Patients With Intermediate Evidence for Use

Reference	Drug	Novel Indication	Ages
Apt et al[79] Vargus et al[80]	Allopurinol	Chagas disease	9-18 yr
Lewis et al[81]	Amitriptyline	Pediatric migraine	3.9-18 yr
Rino et al[82]	Ascorbic acid	Methemo-globinemia	Infants < 3 mo
Goebel et al[83]	Azathioprine	Atopic dermatitis	2-18 yr
Kanellopoulos et al[84] Coutinho et al[85]	Botulinum toxin type A	Cerebral palsy	2.5-12 yr
Gordon et al[86]	Clomipramine	Stuttering	9-21 yr
Ingrassia et al[87] Prince et al[88]	Clonidine	Insomnia	4-18 yr
Phua et al[89]	Cromolyn sodium	Insulin induced lipoatrophy	Mean 16.1 ± 5 yr
Lewis et al[81]	Cyproheptadine	Pediatric migraine	3.9-18 yr
Gordon et al[86]	Desipramine	Stuttering	9-21 yr
Dawson et al[90] Sui et al[91]	Dextromethorphan	Adjunctive postoperative pain control	3-13 yr
Kelly et al[92] Kelly et al[93]	Exenatide	Obesity	9-19 yr
Kallepalli et al[94]	Fluoxetine	Insomnia	13-17 yr
Wheeler et al[95] Eiland et al[96]	Gabapentin	Migraine	7-17 yr
Robinson et al[97]	Gabapentin	Refractory insomnia	Mean age 7.2 yr
Mokhtar et al[98]	Glutamic acid hydrochloride	Achlorhydria	≤18 yr
Scahill et al[99] Cummings et al[100]	Guanfacine	Tourette syndrome	7-16 yr
Florin et al[101] Wu et al[102]	Hypertonic saline	Acute bronchiolitis	2- < 24 mo
Rodriguiz et al[103]	Interferon	Kasabach Merritt Phenomenon	< 2 yr
Kim et al[104] Ezekowitz et al[105]	Interferon	Infantile hepatic hemangio-endothelioma	< 1 yr
Johnston et al[106] Shankar et al[107]	Isoflurane	Status asthmaticus	1-16 yr
Wickman et al[108]	Letrozole	Delayed puberty	Adolescent males
Miller et al[109]	Levetiracetam	Pediatric migraine	Mean age 11.9 yr
Winter et al[110]	Levocarnitine	Cardiomyopathy	Neonates
McDonagh et al[111]	Metformin	Obesity	≤ 18 yr
Tofil et al[112]	Naloxone, orally	Opioid-induced constipation	Children
Glare et al[113]	Olanzapine	Nausea, vomiting	4-18 yr
Glorieux et al[114] Salehpour et al[115]	Pamidronate	Osteogenesis imperfecta	3-16 yr
Sung et al[116]	Probiotics	Excessive infant crying	< 3 mo
Hao et al[117]	Probiotics	Upper respiratory tract infections	0-7 yr
Parodi et al[118] DelVecchio et al[119]	Rituximab	Immune thrombocytopenia	2-19 yr
Senniappan et al[120]	Sirolimus	Persistent hyperinsulinemic hypoglycemia	Infants
Van Hove et al[121]	Sodium benzoate	Nonketotic hyperglycemia	1 mo-13 yr
Arnold et al[122]	Sodium benzoate & dextromethorphan	Nonketotic hyperglycemia	24 day-9 yr
Brock et al[123] Neuwelt et al[124]	Sodium thiosulfate	Platinum-induced ototoxicity	17 mo-12 yr
Laue et al[125] Leschek et al[126]	Spironolactone	Precocious puberty	2.3-7.7 yr
Eugster et al[127]	Tamoxifen	McCune-Albright syndrome	3-11 yr
Ondo et al[128]	Tetrabenazine	Tourette's syndrome	5-16 yr
Kallepalli et al[94]	Trazodone	Insomnia	13-17 yr
Zipitis et al[76]	Vitamin D	Influenza A	1-5 yr
Magge et al[129]	Zinc protoporphyrin	Iron deficiency screening	8-18 mo

Table 4. Repurposed Medications for Pediatric Patients With Weak Evidence for Use

Reference	Drug	Novel Indication	Ages
Hammerman et al[130]	Acetaminophen	Patent ductus arteriosus	Preterm GA <35 wk
Amendola et al[131] Jubelirer et al[132]	Ascorbic acid	Idiopathic thrombocytopenic purpura	4-16 yr
Geobel et al[133]	Azathioprine	Uveitis	3 mo-19 yr
Sulheim et al[134]	Clonidine	Chronic fatigue syndrome	12-18 yr
Treem et al[135]	Cyclosporine	Ulcerative colitis	7-20 yr
Treem et al[136] Seidman et al[137]	Cyclosporine	Autoimmune enteropathy	< 15 mo
Gerloni et al[138]	Cyclosporine	Juvenile idiopathic arthritis	2-18 yr
Hauer et al[139]	Gabapentin	Apnea	2 mo; 5 mo
Pistoia et al[140]	Gabapentin	Pediatric opsoclonus-myoclonus syndrome	1-2 yr (mean age diagnosis 18 mo)
Coakley et al[141] Griggs et al[142]	Mazindol	Duchenne muscular dystrophy	5.8-7.5 yr
Bhalla et al[143] Flynn et al[144]	Methylene blue	Refractory hypotension; vasoplegic syndrome	22 mo; 5 yr
Karabulut et al[145]	Octreotide	Enterocutaneous fistulas	Neonates
Lavid et al[146] Boyd et al[147]	Olanzapine	Stuttering	9-16 yr
Holbrook et al[148]	Ondansetron	Enterocolitis	3-12 yr
Freedman et al[149]	Ondansetron	Acute gastroenteritis	Children
Frigon et al[150] Feng et al[151]	Ondansetron	Pruritus (associated with nevi)	3 yr; 7 yr
Van Wattum et al[152]	Risperidone	Stuttering	4 yr
Costa et al[153]	Sertraline	Stuttering	9-21 yr
Schmitt et al[154]	Valproic acid	Insomnia	2-17 yr
Moore et al[155] Perez et al[156]	Vincristine	Vascular tumor of infancy	3 mo

GA, gestational age

the uses noted in Tables 2 to 4 did not appear in the Harriet Lane Handbook or other pediatric textbooks (e.g., Nelson's Textbook of Pediatrics). Prescribers frequently consult pharmacists regarding complex pediatric pharmacotherapies and the role of pharmacists as drug information experts in facilitating evidence-based prescribing for unlabeled pediatric use of medications is of increasing importance.[160] Pediatric Drug Information practice today entails more and more requests for information about off-label uses. In a recent study of drug information queries to a Pediatric Medication Resource Center conducted by the author, safety and efficacy of off–label uses, dosages, and regimens constituted a large number of requests.[21] Pharmacy clinicians need to be knowledgeable as to where to locate information. Table 6 provides a listing of drug information resources that include unlabeled pediatric indications.

This study underscores the need for clinical trials. A number of specific repurposed medications did not appear on the FDA list of medications requiring further study in children. It is hoped that our results will assist in further prioritizing certain medications for additional pediatric study. Where evidence is weak, perhaps IND applications would be needed or clinicians could not obtain institutional review board approval to conduct a study in the first place. Repositioned medications do not require the typical 7 to 9 years required for new drug development but

Table 5. Summary of Strength of the Evidence for the Age Categories

	Infants	Children	Adolescents	Total
Strong	20	26	18	64
Intermediate	12	33	25	70
Weak	6	15	9	30
Total	38	74	52	164

go directly to preclinical testing and clinical trials thus reducing risks and costs.[161]

The BPCA and PREA have increased the study of drugs in children. Prior to these laws, more than 80% of drugs approved for adult use were being used in children, even though safety and efficacy had not been established in children. The FDA estimates that today that number is about 50%. The FDA often requests that manufacturers conduct pediatric studies and it gives the manufacturers a deadline for them. In some cases (e.g., prostate cancer drug), the FDA will waive pediatric study requirements. In other cases, if the manufacturer does not perform the studies, the FDA can grant extensions. But, if a company does not conduct the study or ask for extensions, since August 2013, the FDA has published the non-compliance letters it issues together with the company's response on its Web site…a type of public humiliation.

The BPCA Priority List of Needs in Pediatric Therapeutics is an important initiative to promote pediatric research. The BPCA requires that the National Institutes of Health, and specifically the National Institute of Child Health and Human Development (NICHD), identify drug needs in pediatric therapeutics. The NICHD sponsors relevant clinical trials and is responsible for submission of resulting clinical trial data to the FDA for pediatric labeling changes. Although progress has been made, revisions to the BPCA and the PREA are essential for these laws to achieve their original intent. Clinical studies in pediatric patients should actually be required to include pediatric patients (as opposed to adolescents), be meaningful, and successful to result in exclusivity.

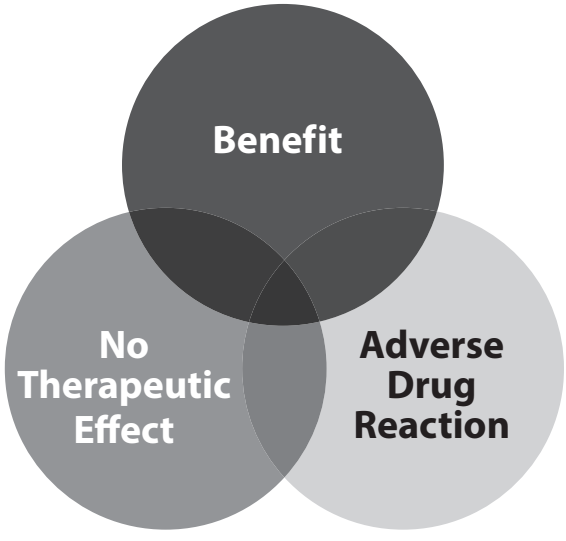

Figure. Benefit-to-risk spectrum for off-label use: patient benefit or therapeutic roulette.

Our results indicate that despite evidence of the benefits of off-label usage, many off-label indications lack scientific support or literature of efficacy or safety. Some have only anecdotal or case report data. Although the vast majority of repurposed indications were for older medications, research for safety and efficacy is, nevertheless, required. Prescribers are often unaware that the medication does not have FDA approval for a use when they prescribe it. Even worse, off-label use can have no therapeutic effect resulting in wasteful medication use and worst-case scenario the off-label use can harm the patient (Figure). For example, codeine for postoperative analgesia after pediatric tonsillectomy and/or adenoidectomy was used for years before it was discovered that cytochrome P4502D6 ultrarapid metabolizers were at risk of life-threatening or fatal adverse effects from normal doses. Similarly, promethazine, commonly used previously in pediatric patients, received a black box warning in 2005 for children less than 2 years due to respiratory depression and death. Therefore, a procedure that yields information on safety and pharmacovigilance on off-label uses remains imperative to avoid therapeutic roulette.

Moreover, legal implications of prescribing and dispensing a medication for non-approved uses will be minimized if the prescriber and

Table 6. Drug Information Resources Which Include Unlabeled Pediatric Indications

- AHFS Essentials
- AHFS Drug Information
- American Academy of Pediatrics Practice Guidelines and Policy Statements
- FDA Rare Disease Repurposing Database
- Harriett Lane Handbook
- Off-Label Drug Facts (Facts & Comparisons)
- Neofax
- Pediatric Dosage Handbook
- Peer-reviewed journal articles and case reports
- Pharmaceutical Manufacturer's Drug or Medical Information Departments (Unsolicited requests only)
- The Teddy Bear Book. Guidelines for Administration of Intravenous Medications to Pediatric Patients

AHFS, American Society of Health-System Pharmacists; FDA, Food and Drug Administration

pharmacist, in the exercise of sound professional judgment conclude the use is rationale, safe, and reasonable.[162]

Some hospitals have policies and procedures for innovative use of medications. Table 7 provides an example of possible elements to include in such a policy. When the use of a medication is experimental, then the patient (or guardian) should be informed of its experimental status. According to the American Academy of Pediatrics Policy Statement, off-label use is neither incorrect nor investigational if based on sound scientific evidence, expert medical judgment, or published literature; when use is truly investigational, or when the prescriber proposes to treat a group of patients rather than a single patient, the use should be performed in conjunction with well-controlled clinical trials.[163]

Guidelines for appropriate off-label prescribing would help to inform clinical practitioners. In February 2013, the FDA issued a guidance entitled "Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling," which provides recommendations for placement and content of pediatric information in prescription drug labeling when available data support a pediatric indication and when data do not support a pediatric indication (i.e., data are negative or inconclusive). This is a step in the right direction but does not address repurposed uses.

The fact remains that there is no central repository for comprehensive data on pediatric off-label uses for policy makers, regulators, payers, and clinicians. Recently, it has been suggested that an online forum be developed to share novel uses of medications for pediatric patients.

It is apparent that an enormous research agenda exists that begs to be addressed to permit more repurposed uses with strong evidence on the product label. Further research should also focus on determining the circumstances of off-label prescribing and its appropriateness. The FDA has perceived its role with regard to identification of important supplemental indications to be somewhat passive. There is a growing recognition that the FDA should adopt a much more active role, facilitating research, evaluation, and labeling revisions for off-label uses. Perhaps preliminarily assessing the available data or providing some other regulatory mechanism for accelerated approval for pediatric indications should be considered. The use of an application similar to an Orphan Drug Act (ODA) request or actually providing ODA designation for all pediatric SNDAs might be beneficial to accelerate approval for pediatric indications. Ideally, an FDA-mandated efficacy assessment of innovative off-label uses could be established to collect data on clinical effectiveness and adverse events (AEs).[164] This would involve the FDA systematically collecting postmarketing data to quantify the risk:benefit of innovative off-label uses; synthesizing evidence regarding these uses and disseminating requests. Grant funding would assure proper study and monitoring. Such a model has been applied to clinical/surgical registries, AE reporting, and medical device failures. Alternatively, manufacturers could be made responsible for collecting efficacy data and develop pharmacovigilance plans to detect and report AE associated with innovative off-label use. Importantly, however, all

Table 7. Policy Title: Innovative Use of Medications

Policy: For medications that are:

1. FDA approved for adults with no supporting data for the use in patient's age group
2. FDA approved for adults with no supporting data for an innovative (or repurposed) use in patient's age group

Procedure: For medication orders received that fall into 1 or 2 above, the following steps will be taken:

- The pharmacist will search the following references to locate appropriate literature regarding the innovative use: (List of references here)
- If there is no information in those references, the pharmacist will contact the prescriber and ask for supporting literature. The prescriber can be directed to the Pediatric Medication Resource Center for assistance.
- If there is no data, the pharmacist will page the Pharmacy Clinical Coordinator on call.
- The prescriber must document the rationale for use in the progress notes and supporting literature is placed in the chart.
- A medication consent form will need to be completed by the prescriber for the following situations:
  - A medication that does not have data available for the use in pediatric patients in either the references in #1 above or in the primary literature.
- The Clinical Coordinator is responsible for completing an Evaluation of Safety Form prior to dispensing. The pharmacist who reviews and processes the order is responsible for ensuring the informed consent has been signed and a copy resides in the pharmacy.

FDA, Food and Drug Administration

this must be accomplished without compromising rigorous efficacy or safety standards.

The use of medications for repurposed uses plays an important role in pediatric pharmacotherapy. When package inserts lag behind clinical practice, clinicians must critically evaluate the entire body of evidence available, become familiar with the strength of the literature on the proposed use, and carefully weigh the potential therapeutic benefits against the risks. Rigorous literature evaluation by pharmacists is of increasing importance to ensure that innovative uses are evidence-based. The valuable role of pediatric clinical pharmacists in assessing novel off-label uses continues to expand and is established in most of the approximately 175 US children's hospitals.

By describing drug repurposing in pediatric patients, the hope is clinicians, industry, academia, and government will continue to cooperate so that Dr Shirkey's phrase pediatric "therapeutic orphan" becomes a colloquialism.

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