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feature

Drug repurposing in pediatrics and pediatric hematology oncology

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Drug 'repurposing', that is, using old drugs for new indications, has been proposed as a more efficient strategy for drug development than the current standard of beginning with novel agents. In this review, we explore the scope of drug repurposing in pediatric hematology oncology and in pediatrics in general. Drugs commonly used in children were identified using the *Harriet Lane Handbook* (*HLH*) and searched in PubMed for different uses. Additional drugs were identified by searching PubMed and Google.com for 'drug repurposing' or 'drug repositioning'. Almost 10% of drugs with primary uses in pediatrics have been repurposed in pediatric hematology oncology or pediatrics. The observant clinician, pharmacologist and translational bioinformatician, as well as structural targeting, will have a role in discovering new repurposing opportunities.

The path leading to a new drug becoming commercially available is long and expensive, involving an average of 13 years and as much as US$1.8 billion [1]. A more efficient strategy for drug development is to use old drugs for new indications, so-called drug 'repurposing' or 'repositioning' [2–13]. Although this process has gained application particularly for the treatment of infectious diseases in developing countries [2,4], its scope and potential are not well appreciated by many pediatric hematologist oncologists or pediatricians in general. Repurposing should be particularly attractive for treating children, given that most drugs used in adults have not been studied formally in patients under 18 years to allow for appropriate labeling information [14]. Using drugs with known safety profiles should allow investigators to bypass or streamline toxicity studies, and would make these drugs more acceptable to providers and patients.

Drug repurposing can occur serendipitously, as when a child is unlucky enough to have two medical problems that turn out to be treatable by the same drug. The use of propranolol for the treatment of hypertension in a baby whose coincident hemangioma resolved is a prototypical example [15], and propranolol rapidly has become first-line therapy for hemangiomas in many centers. More systematic approaches to drug repurposing based on mining existing drug and structural databases have also been proposed [2,4–13], although these have largely focused on diseases of adults. As background to this review, we explored the literature on drugs that have been used successfully in children or adolescents for two or more distinct indications, at least one of which is a cancer or blood disorder. Our findings confirm that repurposing has considerable potential that could be further exploited in pediatrics.

Identification of drugs commonly used in pediatrics

The 19th edition of the *HLH* [16] is a widely used manual from the Johns Hopkins School of Medicine for pediatric house officers and clinicians that includes a drug formulary. The HLH was compiled based on perceived interest to the general pediatric practitioner and, for that reason, seemed a good starting point to look at the scope of repurposing of drugs for children. Using PubMed (http://www.pubmed.gov), each drug was searched along with 'uses', 'cancer', or 'blood disorders' in an attempt to capture all of its pediatric applications. The *HLH* is not an exhaustive listing of drugs used in pediatrics, and PubMed was also screened using 'drug repurposing' and 'drug repositioning'; because of

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increasing attention to drug repurposing in the popular media, we similarly screened http://www.google.com. Drugs that were found through these searches to have primary and repurposed application to disorders seen in pediatrics were included in our results even if they were not listed in the *HLH*.

Criteria for inclusion of drugs

Drugs that had been used at least once in children or adolescents for each of two or more disorders were identified. Drugs for which the newer use was in pediatric hematology or pediatric oncology, or had likelihood of application to pediatric hematology oncology, underwent further review. We included drugs, such as cyclophosphamide, which were originally used for pediatric cancer and that were repurposed for nonmalignant hematologic processes. The commonly accepted mechanism of action for each application and the extent to which the second application had been tested (e.g. case report, series of two or more patients, or randomized trial) were noted. In some cases, the mechanism was specific (e.g. cyclophosphamide as an alkylating agent); in other cases, the mechanism was classified generally (e.g. 'immunosuppression') if this could not clearly be related to the more specific mechanism.

Drugs for which pediatric dosing is available but that might have been used only in adults for a repurposed indication were included so long as that indication was a diagnosis seen in children or adolescents. We also included drugs with a history of pediatric usage that we know are being repurposed in clinical trials or which are being used off-label but for which we could find no supportive publication. Whether the drug is US Food and Drug Administration (FDA)-labeled for any indication in the adult or pediatric age range was determined using LexiComp Online (https://www.online.lexi.com/) and Pediatric and Neonatal Lexi-Drugs Online. Drugs for which an indication was theoretical or based on preclinical studies without human data were excluded. Also excluded were corticosteroids (whose multiple applications are already well established). We did not include drugs repurposed from adult applications for which we could not document the availability of prior pediatric safety profiles (e.g. arsenic trioxide). Somewhat arbitrarily, drugs were not included for which the second application might be considered to be in the same general category of disease (e.g. two different cancers, or seizures and neuropsychiatric abnormalities). Thus, we applied a narrow definition to 'repurposing' for this evaluation.

The scope of repurposing in pediatric hematology oncology and pediatrics

Using the *HLH*, a total of 404 noncorticosteroid generic drugs with pediatric indications were identified. Drugs listed in the *HLH* under multiple trade names were included only once. Of these, publications suggesting a second use were found for 39 (10%). We identified another 24 drugs using PubMed or Google for a total of 63 drugs repurposed with applicability to pediatrics. In 39 cases, the repurposed use(s) had application to a pediatric hematology oncology diagnosis (Table 1) [17–57]. In many instances, multiple alternative applications had been investigated. However, only those indications that might be seen in pediatric hematology oncology practice were explored. These included treatment of one or more cancers, blood disorders, vascular lesions, immune dysfunction or inflammatory diseases, and supportive care. For 14 of these drugs, original applications also included hematologic or oncologic conditions. Although the mechanism of action for one or more of the indications often was unclear, it was thought to be identical in most cases but arguably different from that responsible for the original indication for 19 out of 39 drugs. FDA labeling for children has been established for 26 out of 39 of these drugs for their original purpose(s) and 3 out of 39 for the newer indication.

Table 2 is a listing of 24 drugs that have pediatric indications and that we identified as having been repurposed for at least one other, nonpediatric hematology oncology, pediatric indication. Again, several of the second applications were discovered by chance (e.g. bupropion, cimetidine and itraconazole). FDA labeling for children has been established for 14 out of 24 of these drugs for their original purpose, but not for any of the newer indications.

Discussion: implications and limitations

We identified 39 drugs that have been repurposed for one or more conditions of interest to pediatric hematology oncology. Although in 13 cases the primary indication also was for a diagnosis of interest to pediatric hematology oncology, in more than half the repurposed application was very different from the primary indication. Several of these applications were discovered fortuitously when a patient had two medical problems that turned out to be treatable by the same drug (e.g. chloroquine, lithium, nifurtimox and propranolol) or when monitoring of secondary outcomes in clinical trials suggested the new use (e.g. metformin). The potential of case reports, small series and chance observation in this context is worth emphasizing. For most of these repurposed drugs, the therapeutic mechanism was thought to be identical for both disorders. Thus, nifurtimox is reported to kill both *Trypanosoma cruzi*, which causes Chaga's disease, and neuroblastoma by generating cytotoxic free radicals. In other cases, a focus on mechanism might not have predicted the response to the second disease category, again emphasizing the value of the observant clinician. For example, the action of propranolol as a beta blocker for hypertension seems to be independent of its anti-angiogenic activity. In a few cases, the pediatric hematology oncology application was hypothesis driven and prior pediatric experience enabled testing in a child to proceed rapidly. One good example is the use of the iron chelator, deferoxamine, to treat several cancers (where high serum ferritin levels implicated iron as a tumor growth factor). Although this application has not been entirely successful, clinical trials were facilitated by prior pediatric experience. Another example is the use of nitisinone, an inhibitor of tyrosine metabolism and a primary treatment for tyrosinemia and alkaptonuria, to treat neuroblastoma, a cancer of neural crest cells that produce catecholamine metabolites from tyrosine.

As is the case for drug development in general, many of the drugs (even if already in use in children) were repurposed for other pediatric indications based upon similar repurposing in adults (e.g. aspirin, celebrex and hydroxyurea). Although most of these secondary applications were identified from case reports, small series, or single-arm pilot studies, which might not bear further scrutiny, some have been studied by meta-analyses or rigorously in randomized clinical trials. We also identified 24 other drugs, only two of which (allopurinol and mitoxantrone) are used for any childhood cancer or blood disorders, which have been repurposed for pediatric applications outside of pediatric hematology oncology.

Our lists do not include all drugs with potential for repurposing in pediatric hematology oncology or pediatrics, because we relied primarily on the *HLH* formulary, which lists only drugs commonly used in children and adolescents. Also, our secondary screenings of repurposed drugs through PubMed and Google are unlikely to be exhaustive, given that these generated almost 400 references that, in turn, referenced thousands of papers that we did not attempt to review crucially. Neither did we use the FDA website because it is less exhaustive than the HLH with fewer than 200 drugs that are FDA approved for pediatric use. In addition, neither

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TABLE 1

Drugs repurposed for pediatric hematologic and/or oncologic conditions[a,b]

Drug	Indication 1[a]	Mechanism of action	Indication 2[a,c]	Mechanism of action	Refs
Acetaminophen[a]	Fever, pain (F, f ages ≥2 years)	NSAID	Hepatoblastoma	Glutathione depletion	[17]
Aspirin[a]	Pain (F, f), fever (F, f), ischemic stroke (F)	NSAID	APLA syndrome (C, S); colon cancer prevention (S)	Antiplatelet; NSAID (cox 2 inhibition)	[18]
Caffeine[a]	Newborn apnea (f)	Adenosine antagonist, respiratory stimulant	Sarcoma treatment (S)	Inhibits DNA replication	[19]
Celecoxib	Arthritis (F, f ≥2 years)	Cox 2 inhibition	FAP (F, S, CT), desmoids (S, CT)	Cox 2 inhibition	[20,21]
Chloroquine[a]	Malaria (F, f)	Inhibition of heme crystallization, lipid peroxidation	Sideroblastic anemia (C)[c]	Inhibition of heme crystallization	[22]
Cyclophosphamide	Cancer (F, f), nephrotic syndrome (F, f)	Alkylating agent	Autoimmune disease, autoimmune cytopenias, aplastic anemia	Immunosuppressant	[23]
Danazol	Hereditary angioedema	Suppresses ovarian steroid-genesis; increases C4	ITP; hemophilia A	Unknown; increase in factor VIII:C levels	[24]
Dapsone[a]	Leprosy (F, f ≥1 month)	Antifolate	Kaposi's sarcoma (C, S), PCP (F, f ≥1 month) (S); ITP	Antifolate; unknown	[25]
Deferoxamine	Iron overload (F, f)	Chelation	Liver cancer (S), neuroblastoma (S)	Chelation	[26,27]
Doxycycline[a]	Infections (F, f ≥8 years), acne (F, f ≥8 years)	Protein synthesis inhibition; anti-inflammatory	Periodontitis, idiopathic pulmonary fibrosis (S), vascular malformations (S)	MMP inhibition	[28]
Eculizumab	PNH (F)	Anti-C5	aHUS (F, CT)	Anti-C5	[29]
Gabapentin[a]	Seizures (F, f), neuropathy	GABA mimetic, calcium channel blocker	Opsoclonus-myoclonus (S)	Inhibition of saccadic pathways	[30]
Glutamic acid hydrochloride	Achlorhydria (F)	HCl source	Vincristine neuropathy (C, CT)	Microtubule stabilization	[31]
Hydroxychloroquine[a]	Malaria (F, f); rheumatoid arthritis (F);	Antigen-processing inhibitor	Antiphospholipid syndrome, GVHD (C, CT)	Inhibition of β2GPI binding, antigen-processing inhibitor	[32,33]
Hydroxyurea	Leukemia (F)	Ribonucleotide reductase inhibition	SCD crisis prevention (F)	Increases fetal hemoglobin	[34]
Interferon alpha	Hepatitis B, C (F, f ≥1–3 years), leukemias (F), Kaposi's sarcoma (F)	Viral replication inhibitor, cell differentiation promoter, immune regulation inhibitor	Hemangiomas (CT)	Anti-VEGF	[35]
Isotretinoin[a]	Acne (F, f ≥12 years)	Vitamin A analog	Neuroblastoma (CT)	Vitamin A analog, Cell differentiation promoter	[36]
Immune globulin[a]	Hypogammaglobulinemia (F, f)	Immunoglobulin concentrate	ITP (F, f), Autoimmune hemolytic anemia (CT)	RES blockade	[37]
Lansoprazole[a]	Gastric ulcers (F, f ≥1 year), *Helicobacter pylori* eradication (F)	PPI	ITP (C, S)	*H. pylori* eradication	[38]
Lithium[a]	Bipolar disorder (F, f ≥12 years)	Calcium transport	Neutropenia (S, CT)[c]	CFU stimulation	[39]
Mercaptopurine	Leukemia (F, f)	DNA synthesis inhibitor (purine analog)	ITP (S)	Immunosuppression	[40]
Metformin[a]	Diabetes (F, f >10 years)	Biguanide	Cancer prevention (S)	Unknown	[41]
Metoclopramide[a]	Nausea and/or vomiting (F); gastric stasis (F)	Serotonin receptor antagonist; acetylcholinesterase enhancer	Diamond–Blackfan (C, S)	Prolactin release	[42]

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TABLE 1 (*Continued*)

Drug	Indication 1[a]	Mechanism of action	Indication 2[a,c]	Mechanism of action	Refs
Nitisinone	Tyrosinemia (F, f)	Blockade catecholamine degradation	Neuroblastoma (C)	Blockade catecholamine degradation	[43]
Nifurtimox	Chaga's disease	Free radical, nitrile generation	Neuroblastoma (C, CT)[c]	Free radical generation, apoptosis	[44]
Octreotide[a]	Secretory diarrhea (F),	Somatostatin analog	Neuroendocrine cancers (F) (C, CT)	Somatostatin analog	[45]
Pamidronate	Hyperkalcemia of malignancy (F)	Bisphosphonate, bone remodeling	SAPHO syndrome (S), osteogenesis imperfecta	Anti-inflammatory	[46]
Propranolol[a]	Hypertension (F, f), arrhythmias (F, f)	Beta blocker	Hemangioma (S)[c]; osteoporosis	Anti-VEGF	[15]
Pseudoephedrine[a]	Rhinorrhea (F, f ≥12 years)	Sympathomimetic	Priapism in SCA (C)	Sympathomimetic	[47]
RH_o (D) immune globulin[a]	RH disease prevention (F)	Anti-RH (D)	ITP (F, f)	RES blockade?	[37]
Rituximab	B cell lymphoma (F)	Anti-CD20	Opsoclonus-myoclonus (C,S)	Anti-CD20	[48]
Sildenafil[a]	Pulmonary arterial hypertension (F)	PDE5 inhibition	Priapism, SCD (S); vascular malformations	PDE5 inhibition	[47,49]
Sirolimus	Graft preservation, kidney transplant (F, f >13 years)	mTOR inhibition	Vascular malformations (S)	mTOR inhibition	[50]
Sulfasalazine[a]	IBD (F), JIA (f)	Anti-inflammatory	SAPHO syndrome (C, S)	Anti-inflammatory	[51]
Tamoxifen	McCune–Albright syndrome	Anti-estrogen	CNS tumors (S), desmoids (C, CT)	PKC inhibition	[52]
Thalidomide	Leprosy (F)	Immunosuppressant	Cancer, GVHD, vascular abnormalities (C, S); hepatitis C (CT)	Immunosuppression, anti-angiogenesis	[53,54]
Valproic acid[a]	Seizures (F, f)	GABA-mimetic	Anti-cancer (C, CT)	HDAC inhibition	[55]
Vasopressin[a]	Diabetes insipidus (F, f), Nocturnal enuresis (f)	ADH analog	VW, hemophilia A (C, S)	Release of endogenous factor VIII	[56]
Vincristine	Cancer (F, f)	Mitotic inhibitor	ITP (C,S), vascular lesions (C, S)	Immunosuppression	[57]

[a] Listed in the *HLH*.

[b] *Abbreviations*: C, case reports; ADH, antidiuretic hormone; aHUS, atypical hemolytic uremic syndrome; CFU, colony-forming unit; CNS, central nervous system; CT, clinical trial; CTCL, cutaneous T cell lymphoma; F, f, FDA-approved for adults/children; FAP, familial adenomatosis coli; GABA, gamma aminobutyric acid; GPI, glycoprotein I; GVHD, graft-versus-host disease; HCl, hydrochloric acid; HDAC, histone deacetylase; IBD, inflammatory bowel disease; ITP, idiopathic thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; MMP, matrix metalloproteinase; NSAID, nonsteroidal anti-inflammatory drug; PCP, pneumocystis carinii pneumonia; PDE, phosphodiesterase; PKC, protein kinase C; PPI, proton pump inhibitor; RES, reticuloendothelial system; S, series of at least two patients; SCD, sickle cell disease; TEN, toxic epidermal necrolysis; VEGF, vascular endothelial growth factor; VW, von Willebrand disease.

[c] Indication discovered by chance.

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TABLE 2

Repurposed drugs in pediatrics for nonpediatric hematology oncology indication

Drug	Indication 1[b]	Indication 2
Acetylcysteine[a]	Intestinal obstruction (F), airway secretions (F, f)	Acetaminophen poisoning (F)
Allopurinol[a]	Gout (F), Tumor lysis (F)	Metabolic syndrome
Alprostadil[a]	PDA closure (f)	Asthma
Amantadine[a]	Flu A (F, f ≥1 year)	Tardive dyskinesia (F)
Amiodarone[a]	Arrhythmia (F, f)	Fungal, parasitic infection
Azithromycin[a]	Bacterial infection (F, f ≥2 years)	Bronchiolitis
Bupropion	Depression (F)	Smoking cessation
Candesartan	Hypertension (F)	Hepatic fibrosis
Cetirizine[a]	Allergic rhinitis (F, f ≥6 months)	Sarcoid
Cimetidine[a]	Reflux (F, f)	Warts
Clofazimine	Leprosy	Multiple sclerosis
Colchicine	Familial Mediterranean fever (f ≥4 years), gout (F, f ≥12 years)	Pericarditis
Enalapril[a]	Hypertension (f)	Proteinuria
Erythromycin[a]	Bacterial infection (F, f)	Constipation
Fish oil	Hypertriglyceridemia (F)	Raynaud's, immunoglobulin A nephropathy
Formoterol	Asthma (F)	Stuttering
Itraconazole[a]	Fungal infection (F)	Cheloids
Lidocaine[a]	Pain, anesthesia (F)	Decompression sickness
Minocycline[a]	Infection (F), inflammation	Rheumatoid arthritis; viral infection; cognitive dysfunction
Mitoxantrone	Leukemia (F)	Multiple sclerosis (F)
Modafinil	Narcolepsy, sleep apnea (F)	Bipolar disorder
Phenytoin[a]	Seizures (F, f)	Epidermolysis bullosa
Ranitidine[a]	Reflux (F, f ages ≥1 month), peptic ulcer (F)	Allergic reactions
Succimer[a]	Lead poisoning (f)	Cystinuria
Terbutaline[a]	Asthma (F, f)	Tocolysis

[a] Listed in the HLH.
[b] F or f, FDA-labeled indications for adults or children, respectively.

that website nor the *Orange Book* lists approvals by age. We did not include drugs for which a second indication is speculative, based on preclinical data without supportive human data, or drugs such as corticosteroids whose repurposing seems to be infinite and well known. The use of animal models to explore pediatric drug repurposing might be a productive avenue. However, one advantage of using drugs with known dosing and toxicity profiles is that it enables one to by-pass preclinical testing for the second indication [13]. Although we included a few drugs known to be undergoing clinical trials for new indications, we did not search abstracts from proceedings of pediatric hematology oncology or hematology oncology meetings, which would probably yield more preliminary experience with repurposing of other drugs. Thus, our study probably underestimates more recent experience with drug repurposing in children.

The path to commercialization of a new drug is long, expensive and inefficient. The need to accelerate the process is clear, particularly for pediatrics, where progress in curing pediatric cancer in particular has stalled since the 1990s. The current academic approach is to generate support for a new drug against a particular target based upon preclinical work *in vitro* and in animal models, followed by the regulatory paperwork culminating in approval by the FDA to allow testing in human subjects [14]. Phase I testing to define a safe dose (the maximum tolerated dose or MTD) and toxicity profile takes on average 21 months for each new drug, which subsequently undergoes efficacy testing in phase II trials, which in turn take an average of 26 months (http://www.FDAReview.org). Drugs with activity as single agents typically undergo phase III testing in combination with other already proven drugs or regimens. In some cases, combining drugs might require more phase I testing to ensure that drug–drug interactions do not alter individual MTDs or safety profiles. During the course of phase II or III testing, FDA approval improves the likelihood that insurance will pay for the drug if prescribed for the approved indication, 'on-label use'. A 2010 analysis estimated that the average timeline for this entire process for a single drug is 13 years at a cost of $1.8 billion [1]. Some 20–30 compounds are FDA approved annually. All of these issues were presented in an excellent 2007 Commentary in *Nature* [2]. Whether the time required to get FDA approval is added to the timeline for drug development or not, the timeline is shorter when a drug with a known dose-safety profile is repurposed than when it is developed for the first time.

Drug repurposing offers an alternative timeline. It has been estimated that there are close to 10,000 commercially available drugs, not including preparations that would be considered

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to be alternative or complementary [2]. Partial lists of these drugs include the *HLH*, the *Physicians' Desk Reference* and the FDA *Orange Book*. The FDA also has a Rare Disease Repurposing Database of FDA-approved drugs with promise for orphan diseases [58]. Recently, several drug 'libraries' or repositories (usually of older and off-patent drugs), including the Johns Hopkins Clinical Compound Library (http://www.jhccsi.org), National Institute of Neurological Disorders and Stroke (NINDS), the Prestwick Chemical Library and the NCGC Pharmaceutical Collection (NPC), have made samples available for 'high-throughput screening'. Hence, the activity of thousands of drugs, including recently approved drugs that might not yet be commercially available, can be tested against specific disease targets.

Legislation such as the Food and Drug Administration Modernization Act (FDAMA) of 1997, the Best Pharmaceuticals for Children Act of 2007, and the Pediatric Research Equity Act (PREA 2003, 2007) were designed to make pediatric drug development more attractive financially by providing an incentive of a six-month extension of market exclusivity for all products containing the active agent [14]. Even with these provisions, fewer than 200 drugs have been labeled to date with pediatric prescribing information. Despite the relative lack of pediatric approvals by the FDA, most repurposed drugs in our series (26 of the 39 with secondary pediatric hematology oncology applications and 14 out of 24 with other pediatric secondary indications) had such approval for some primary pediatric indication. Most repurposing is probably to occur with off-label usage of drugs. Testing new drugs in the pediatric age range has limitations beyond those in the adult arena. Most drugs do not get to pediatric trials until an MTD has been reached in adults. Most pediatric diagnoses meet the FDA definition of an orphan disease (i.e. with a prevalence of less than 200,000 persons in the USA), so that finding children and adolescents who are eligible for a particular drug can be difficult. The Children's Oncology Group (COG) consortium might be large enough to get around this limitation, but there are fewer than 25 centers in the USA that are approved by COG to be phase I centers. Many patients and parents are unwilling to participate in toxicity studies of new drugs for which risk:benefit ratios might not be favorable [59]. Although FDA approval might not be necessary for initiating pediatric clinical trials, repurposing drugs with known safety profiles allows one to bypass or streamline phase I toxicity studies and makes these drugs more acceptable to providers and patients. The rapidity with which drugs such as propranolol have become standard of care for new indications in pediatric hematology is proof of concept. The economic and intellectual property barriers to large efforts for repurposing drugs through FDA-regulated trials remain important issues and require ongoing discussion [1,60].

Our review suggests that drug repurposing has been used already in pediatric hematology oncology and in pediatrics in general. Because most drugs have not been well studied in children, there might be more, as yet undiscovered, repurposing opportunities. We suggest that this approach be expanded by development of an online forum whereby other repurposed drugs could be added to our incomplete listings. Repurposing based on single cases or small series should lead to clinical trials to support newer indications. The observant clinician, pharmacologist and translational bioinformatician, as well as structural targeting, will have an important role in growing such a list.

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