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Expanding the scope of drug repurposing in pediatrics: The Children's Pharmacy Collaborative™

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Abstract

Drug repurposing is the use of "old" drugs for new indications, avoiding the need for time- and cost-intensive toxicity studies. This approach should be particularly attractive for pediatrics, but its use in this population has been limited. One obstacle has been the lack of a comprehensive database of drugs for which there already is at least one indication in children. We describe the development of The Children's Pharmacy Collaborative™, which should grow over time, serve as a resource for professionals and families, and stimulate drug repurposing efforts for a range of pediatric disorders.

Keywords

drug repositioning; drug repurposing; pediatrics; pharmaceutical

The development of new drugs is a long and expensive process [1]. Drug repurposing has been increasingly applied over the past decade to the use of "old" drugs with known safety profiles for new indications. Unlike new drug development, drug repurposing allows investigators to bypass or streamline toxicity studies [2], so that it appears to be a cost- and time-efficient strategy. This approach should be particularly attractive for pediatrics [3], where phase I (dose finding and toxicity) studies often are not initiated because small patient numbers keeps them from being economically viable [4].

Some 500 drugs have been approved by the Food and Drug Administration (FDA) for use in children. Thus, most medications are used off- label without having been through rigorous

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Teaser: To address one obstacle to drug repurposing in pediatrics, we offer a comprehensive drug database which will grow over time and serve as a resource for professionals and families.

phase I/II testing. Nonetheless, there often is a published experience of dosages and side effects to guide pediatric prescribers. Partial listings of such drugs are included in the Harriet Lane Handbook, Micromedex, Lexicomp, hospital formularies, and other commonly used references. Repurposing of these drugs should be acceptable to providersand patients' families who may be reassured that they are "less experimental" than are most drugs in phase I studies. The rapidity with which the anti-hypertensive agent propranolol has become standard of care for treatment of infantile hemangiomas is one proof of concept [3, 5]. That these drugs are often less expensive should make them appealing to third-party payers.

Although many available databases include drugs which have been used in children, they do not include *all* drugs which have been used in children. Conversely, for investigators with an interest in pediatric disorders, most of the listings have not been used in children. Thus, while some compounds might potentially be of interest, they could not be repurposed without going through the phase I process. We offer a solution in the development of The Children's Pharmacy Collaborative™, a comprehensive database of drugs for which there already is at least one indication for individuals under 18 years of age.

Available compound databases and repositories

Databases

The largest publicly accessible list of existing drugs is the Johns Hopkins Clinical Compound Library (JHCCL, www.jhccsi.org) [6]. As of 2007 the database included close to 10,000 agents, and in turn, had been derived from drugs which had been approved by the FDA, drugs listed in the FDA Orange Book, the Physicians' Desk Reference, as well as drugs which had entered phase II clinical trials in the United States or which had been approved abroad. This database listed 9,991 compounds by generic name, together with categories of primary indications (e.g., antiinflammatories, antineoplastics).

Repositories

Johns Hopkins and a number of other organizations have assembled repositories of drugs, a subset of those listed in their databases, which are publically (National Institute of Neurological Disorders and Stroke [NINDS], Prestwick Chemical Library, National Institutes of Health Chemical Genomics Center [NCGC] Pharmaceutical Collection [NPC) or commercially (Sigma's Library of Pharmacologically Active Compounds [LOPAC]) available [7]. Several of these are limited to FDA-approved and marketed drugs. The National Center for Advancing Translational Sciences (NCATS) also has its Mechanism Interrogation PlatE (MIPE) library of oncology-focused, mechanistically annotated agents—many of which are still investigational. Over the past 10 years, these compound collections have been used for preclinical screening with a view toward repurposing these old drugs.

Limitations of existing resources for pediatric drug development

Screening of these libraries against *in vitro* models of childhood diseases likely would identify active compounds. However, it also is likely that many of the "hits" would be with drugs which have not been used in children. Importantly, many drugs with known dosage and safety profiles in children may not be included in any of these databases.

Development of the Children's Pharmacy Collaborative™

Identification of drugs with pediatric indications

In order to identify all drugs which already have indications for patients under 18 years of age, we searched for each of the almost 10,000 compounds listed in the JHCCL database [6] online in **MICROMEDEX**® 2.0 (www.micromedex.com), against PubMed (using the generic drug name with "childhood" or "pediatrics"), and in the formulary of the Harriet Lane Handbook [8]. www.ClinicalTrials.gov also was searched and drugs included in our database which had been in phase II or III pediatric trials (i.e., for which phase I data were available). Although we have not yet performed a systematic review of published literature and abstracts, we included other agents which came to our attention and for which we confirmed published experience.

Information in the database

Where pediatric usage was identified, we noted whether the drug was FDA-approved for any indication in adults or children using www.FDA.gov and the FDA's New Pediatric Labeling Information Database (http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase), labeled and unlabeled adult and pediatric indications, and recommended age ranges. Drugs were listed under one of the more than 80 categories in the JHCCL, in order to allow comparison with that database: e.g., analgesic, anesthetic, appetite stimulants, antacids, antibacterial/antibiotic, antiamoebic. Some drugs were listed as "unclassified". These categories did not necessarily reflect what most clinicians would consider the primary category for which the drug is used in children. Drugs which did not appear in the JHCCL were assigned to one of the categories.

Data were recorded in an Excel spreadsheet which also includes columns for trade names, chemical names and structures [represented as Simplified Molecular-Input Line-Entry System (SMILES) strings], mechanism(s) of action, and one or more pharmaceutical companies which manufacture the drugs. The chemical structures for most of the compounds listed in the spreadsheet were automatically retrieved from several chemical databases (e.g., the National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/), whereas additional manual searches were conducted using in-house and web-accessible [e.g., Chemspider (http://www.chemspider.com/) and PubChem (http://pubchem.ncbi.nlm.nih.gov/)] databases. All drugs, except large biologics and natural products presented as complex mixtures, are stored as an sdf file (see Supplementary Material) with initial composition and stereochemistry preserved. Chemical structures of all the compounds in our database are under manual verification and curation according to previously described guidelines (8). Many of the columns in our spreadsheet are not yet complete but data will be added over time. In order to allow multiple users to access the database, this was saved as a Google Cloud document that can be accessed by anyone but edited only by the authors (https://docs.google.com/spreadsheet/pub?key=0AgsQROeRaJo8dHB2TXFBcnlMMDRjOUNhTUtpMFdTLWc&output=html). The database has been trademarked as "The Children's Pharmacy Collaborative ™".

Results

We identified almost 1250 drugs which had been reported series or case reports as ever having been used in children. 464 of these were listed in the HLH, most of which had been captured in **MICROMEDEX**® 2.0. We were able to confirm that 790 of the drugs with a history of pediatric usage were listed on the FDA website as having achieved FDA-labeling for at least one indication in adults; 456 of the drugs had any pediatric indication which was FDA-approved. These numbers may be overestimates, since the FDA site lists several drugs in duplicate or even triplicate when these have multiple brand names. In many cases, the FDA-approval was limited to specific age ranges (e.g., older than 10 years) despite common usage for a wider pediatric age range. Although these age ranges did vary for individual drugs depending on the indication, our database lists the youngest age for which usage is FDA-approved for any indication. Pediatric indications were variable, and fell into each of the 81 JHCCL categories. The 10 most common categories were antibiotics (n=117), which were listed separately from antibacterials, (n=27), antineoplastics (n=93), antihypertensives (n=45), antiviral (n=48), antiinflammatory drugs (n=38), anithistamines (n=34), anitconvulsants (n= 33), vitamins (n=27), and antipsychotics (n=24). To illustrate the arbitrariness of the categories, a listing of drugs which have been used in children for treatment of any infectious disease is given in Table 1.

Discussion

We have used a large online database of drugs as the starting point for development of a comparable listing which includes only drugs for which there is some experience in children, and which we have called The Children's Pharmacy Collaborative™. Of the almost 10,000 drugs listed in the JHCCL, we confirmed that some 1250 have been used in individuals under the age of 18 years, the definition of a "child" commonly used by most pediatricians and by the FDA, and based upon the Best Pharmaceuticals for Children Act (BPCA) of 2002 and Pediatric Research Equity Act of 2007. While there already are a number of handbooks and on-line listings of drugs, our database is both more comprehensive (including drugs which are or have been used anywhere in the world) and designed specifically for pediatrics, as it includes only drugs for which there is experience in children. It is not meant to be a formulary with dosing or safety information, which already is available elsewhere. It is meant to eliminate the "background" noise of "only-used-in-adult" drugs which which we believe clutter other drug databases. This focus should make the database useful to a broad audience including physicians and scientists, parents of children with a range of illnesses, and to pharmaceutical companies interested in drug repurposing for children.

Limitations to the database

There are limitations to the database. The drugs which have been used in children include drugs whose primary indications have been previously categorized into one of the more than 80 categories listed by JHCCL. These categories were sometimes arbitrary in that drugs could have been assigned to one or another (e.g., antibacterials were separated from antibiotics and antiseptics; many of the immunosuppressants could have been categorized as antineoplastic or antiinflammatory). We have kept the same categories for ease of

comparison between the two databases. There is some duplication in the JHCCL (e.g., five insulin formulations are listed separately). We have maintained some of these in our registry as well, both for comparability between databases and because it seems possible that different formulations or chemical variants might have different activities with respect to new indications.

The CPC listing does not include unpublished proprietary data. Our intent is to add drugs as data are published or become available online. Although a number of complementary or alternative medicines are included in our database, this is probably not a comprehensive listing, as we have not yet critically examined the relevant literature.

To date, we have not listed every indication for each of the drugs in our own database. Our listing of indications is not meant to be complete or perfect at this time, but is simply a scaffold on which to build. Similarly, the FDA-approval status of drugs may change over time and users of the database will need to check for updated prescribing recommendations. Undoubtedly, there will be other criticisms of the database. We hope that ultimately the open access nature of the database will permit community-based improvements. The goal of developing a list of drugs for which there is pediatric information remains the same as for developing the original comprehensive database. As stated by the Johns Hopkins investigators, this is “to bridge the gap between lab and the clinic by finding new uses for existing drugs” [6].

Conclusion

“The Children’s Pharmacy Collaborative™” is the first database to focus on pediatrics, and confirms that drug development and labeling for children lag far behind that for adults. As additional new and old drugs with pediatric safety profiles are reported, these will be added to the database. Thus, this will grow and should be useful to a broad audience including physicians and scientists, parents of children with a range of illnesses, and to pharmaceutical companies interested in drug repurposing. A curated Wiki-website is under development, which we hope will allow others to participate in this process. A drug repository derived from the database can serve for high throughput screening and drug repurposing for a range of indications for which there are *in vitro* models such as childhood cancer, vascular anomalies, and chronic inflammatory disorders are only a few of these.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Drugs with Pediatric Applications to Infectious Diseases

Category	Number of drugs
Anthelminthic	14
Antiamebic	1
Antibacterial	27
Antibiotic	123
Antifungal	23
Antiinflammatory	38
Antimalarial	17
Antiseptic	12
Antiviral	48
Immunomodulator	9
Immunosuppressant	11
Vaccines	19