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Research Article

Leveraging Electronic Health Data to Evaluate Pediatric Medication Use and Health Outcomes

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Abstract

Objective: To examine how electronic healthcare data can be leveraged to support large-scale pharmacoepidemiologic research on pediatric medication use and related efficacy and safety outcomes.

Methods: We searched MEDLINE, EMBASE, and CINAHL databases using text words and appropriate filters for literature published in English since 2000 that evaluated the use of electronic health data sources to research medication use and outcomes in children. Abstracts were searched for age <=20, electronic data source, medicines, and efficacy/safety. Information on study population, data source(s), country of origin, and study type was extracted. From 843 abstracts, 33 full-text papers were selected for review.

Results: Most studies (77%) estimated trends in medication use; others evaluated medication-related efficacy or safety outcomes. Most studies acknowledged specific limitations to use of these data.

Conclusions: Pediatric medication-related studies using electronic health data can provide valuable and timely information about use, benefits, and risk, but should be approached with caution. To the extent possible, investigators should address known limitations using established methods

Keywords: children; electronic health record, medication use, medication outcomes, medication safety.

Introduction

Increased disease incidence in children has accelerated pediatric medication use. Despite successful efforts to intensify pediatric pharmacologic research, many medications continue to be used off-label in pediatric patients and lack evidence describing appropriate use. Conducting research in pediatric populations raises unique ethical and methodological challenges, limiting the number of pediatric patients available to participate in studies. Given these issues, the use of electronic health data to generate evidence of short- and long-term benefits and risks of medication treatment is attractive [1]. Improvements in the collection, integration and availability of large volumes of electronic health data (e.g.

administrative claims, medical records, and pharmacy data) have transformed researchers' ability to conduct patient-oriented clinical research, particularly studies in pediatric populations. Prior to the availability of computerized health data, conducting comprehensive drug studies in children was difficult and costly. Descriptive data generated from large, unselected cohorts of youth may have great potential to improve treatment by uncovering important patterns that otherwise would not be captured in smaller settings.

The purpose of this review is to examine how electronic healthcare data from automated sources (e.g. medical and pharmacy claims, electronic health records, retail pharmacy) can be leveraged to support large-scale pharmacoepidemiologic research on pediatric medication use and related efficacy and safety outcomes. We aim to describe the types of studies conducted using these data, summarize their outcomes, and propose suggestions for appropriate selection and use.

Methods

A literature search was conducted to identify recent articles (published from 2000-2015) that used automated data sources to examine medication use and/or outcomes in pediatric subjects (age <= 20 years). Several online databases were queried, including MEDLINE, EMBASE, and CINAHL. The following search terms were used in combination to identify articles for consideration: pediatric, drug, retrospective, medical or health, records or claims, and efficacy or effectiveness or safety. Initial searches yielded 843 unique results. We excluded studies of the following nature: case reports/series, medical record reviews, studies restricted to health resource use, and studies using data from a single state (e.g. Texas Medicaid). After applying additional exclusion criteria (non-English language, manuscripts not available as full-text), 33 articles remained. Information on data source(s), patient population, therapeutic area, drug/class, and outcomes were extracted. Since the therapeutic areas and outcomes examined in these studies varied, articles were grouped and summarized by study type (medication use and medication outcomes) and therapeutic area (i.e. neuropsychiatry, asthma).

Results

Characteristics of studies are summarized in two tables. Most studies (n=25) used large data sources to evaluate medication use patterns Table1:

Authors	Therapeutic Area	Data source(s); year(s)	Age Range	Study focus	Country
Arellano et al	Asthma	Phar Metrics Integrated Outcomes; June 1995-Sept 2008	6-18 y	Prescription patterns for asthma	USA
Bali et al	Neuropsychiatry	IMS Health Life Link claims data; 2004-2007	6-16 y	Trends in ADHD use and persistence of long-acting stimulants and concomitant use of atypical antipsychotic agents	USA
Barron et al	Gastrointestinal	Administrative claims from four US health plans; 1994-2004	< 12 m	Trends in proton pump inhibitor use in infants	USA
Bennett et al	Neuropsychiatry	Pediatric Health Information System database (PHIS); 2001 - 2008	< 18 y	Trend in use of hypertonic saline and mannitol in children with traumatic brain injury	USA
Delate et al	Neuropsychiatry	Express Scripts administrative pharmacy claims; 1998-2002	<18 y	Trend in use of antidepressants in commercially insured youth	USA
DeVries et al	Analgesia	Health Core Integrated Research Environment, claims data for 14 major commercial health plans; 2007-2008	13-17 y	Use of opioid therapy in adolescents treated for headache	USA
Dusetzina et al (2011)	Neuropsychiatry	Thomson Reuters Market Scan Commercial Claims and Encounters; 2005-2007	6-17 y	Receipt of guideline-concordant pharmacotherapy	USA
Dusetzina et al (2012)	Neuropsychiatry	Thomson Reuters Market Scan Commercial Claims and Encounters 2005-2007	<18 y	Prevalence and treatment patterns of bipolar disorder	USA
Garfield et al	Neuropsychiatry	IMS Health National Disease and Therapeutic Index (NDTI); 2000-2010	<18 y	Trends in diagnosis and treatment of ADHD	USA
Hodgkins et al	Neuropsychiatry	PHARMO medical record linkage database; 2003-2006	6-17 y	Trends in treatment with and adherence to ADHD medications	Netherlands

Kemper et al	Endocrine	Market Scan Commercial Claims database, Market Scan Multi-State Medicaid database; 2002-2006 (commercial), 2001-2005 (Medicaid)	<1 y	Discontinuation of hormone treatment in children with congenital hyperthyroidism	USA
Korelitz et al	Asthma	Ingenix LabRx Database; 2004-2005	<18 y	Trends in asthma prevalence and use of asthma-related medications	USA
Kornfield et al	Neuropsychiatry	IMS Health National Disease and Therapeutic Index (NDTI); 2004-2008	<18 y	Effect of FDA advisories on treatment patterns for ADHD	USA
Mandell et al	Neuropsychiatry	Medicaid Analytic eXtract files; 2001	<=20 y	Characteristics of psychotropic medication use in children with autism spectrum disorders	USA
O'Sullivan et al	Neuropsychiatry	Irish Health Service Executive (HSE) pharmacy claims database; 2002-2011	<=15 y	Trends in antidepressant use in Irish children	Ireland
Raffini et al	Cardiology	Pediatric Health Information System database; 2001-2007	<=18 y	Trends in inpatient venous thromboembolism and related treatment	USA
Sen et al	Asthma	Pedianet database (Italy), Integrated Primary Care Information database (Netherlands), Medi plus Disease Analyzer-Medi plus database (UK); 2000-2005	<18 y	Trends in use of asthma medications in three European countries	Netherlands, Italy, United Kingdom
Spencer et al	Neuropsychiatry	Administrative claims from a large health plan; 2001-2009	<=20 y	Trends in psychotropic use and poly pharmacy in children with autism spectrum disorders	USA
Stallworth et al	Asthma	Administrative claims data; 2000-2002	5-18 y	Inappropriate use of antibiotics in children with asthma	USA
Star et al	Analgesics	IMS Health Data Analyzer; 1988-2005	2-11 y	Demographic and medication-related factors influencing variations in dosing of NSAIDs	United Kingdom
Stempel et al (2005)	Asthma	PharMetrics Integrated Outcomes; 2001	1-17 y	Treatment of pediatric asthma pre- and post-ED visits	USA
Ziller et al	Gynecology	IMS Disease Analyzer; 2007 and 2011	12-18 y	Patterns in gynecologists' prescribing of contraceptive medications	Germany
Zito et al	Neuropsychiatry	Medical record data from Midwest and Mid-Atlantic Medicaid programs and a group HMO; 1988-1994	2-19 y	Trends in antidepressant use	USA

Table1: measured the impact of guidelines or guidance on medication use trends.

Of these, four studies measured the impact of guidelines or other guidance on these trends. Eight studies assessed medication outcomes (Table 2) succinct summaries of the scope and findings of these publications follow.

Authors	Therapeutic Area	Data source(s); year(s)	Age Range	Study focus	Country
Elder et al	Infectious disease	PharMetrics Integrated Outcomes; 2000-2004	<11 y	Comparative efficacy of endoscopic injection versus antibiotic prophylaxis to treat urinary tract infection (UTI)	USA
Love grove et al	Toxicology	National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance, IMS Health Vector One: National and Total Patient Tracker; 2007-2011	<6 y	Characteristics of emergency hospitalizations for unsupervised prescription medication ingestions	USA
Parikh et al	Asthma	Pediatric Health Information System (PHIS); 2007-2012	4-17 y	Comparative effectiveness of Dexamethasone and prednisone/prednisolone	USA

Rubin et al	Neuropsychiatry	Medicaid Analytic eXtract files; 2003-2007	10-18 y	Incidence of type 2 diabetes mellitus after initiation of second-generation antipsychotics	USA
Stempel et al (2007)	Asthma	PharMetrics Integrated Outcomes; 2001-2003	4-17 y	Comparative efficacy and costs of asthma care for fluticasone propionate and montelukast	USA
Sturkenboom et al	Analgesia	Pedianet (electronic patient records); 1998-2001	<15 y	Mucocutaneous reactions associated with use of niflumic acid, NSAIDs, and non opiod analgesics	Italy
Verstraeten et al	Infectious disease	Administrative claims from two HMOs; 1993-1999	1-6 y	Incidence and associations of varicella breakthrough with asthma, steroid use, and other vaccine-related factors	USA
Wu et al	Asthma	Administration claims from Population-based Effectiveness in Asthma and Lung Diseases (PEAL) Network; 2004-2010	4-17 y	Comparative of leukotriene receptor antagonists and inhaled corticosteroids	USA

Table 2: Studies Using Large Databases to Evaluate Medication Outcomes (Safety/Efficacy) in Children

Medication Use

Neuropsychiatry

Fourteen studies used large datasets to evaluate pediatric medication use patterns related to neuropsychiatry, including bipolar disorder, attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and traumatic brain injury. Garfield et al used pharmacy data and physician visits to examine trends in diagnosis and treatment of ADHD from 2000-2010among children and adolescents < 18 years [2].They evaluated physician visits with mentions of ADHD-related diagnoses and treatments. Visits with ADHD mentions increased during initial years before plateauing, while the proportion of treatment visits remained relatively stable over the study period. Trends by treatment type varied and diagnosis and treatment of ADHD shifted from pediatricians to psychiatrists. Korn field et al used the same data to assess the effect of U.S. Food and Drug Administration (FDA)public health advisories issued from 2005 to 2007 on treatment patterns for attention-deficit hyperactivity disorder (ADHD) in children and adolescents (ages < 18 years) [3].

Although market shares for atomoxetine and Adderall® declined as use of non-Adderall® stimulants increased, study results suggest that health advisories had no significant impact on these trends. Bali et al linked medical and pharmacy claims to concomitant use of long-acting stimulants (LAS) and antipsychotics in youth (ages 6-16 years) with ADHD [4]. Their analysis as curtained correlates of concomitant use and its effect on persistence with stimulant medications. Concomitant use of LAS and atypical antipsychotics was influenced by diverse factors and was associated with increased persistence. Hodgkins et al performed a similar analysis of patterns in incidence, prevalence, and treatment of ADHD, using linked medical, pharmacy, and hospital claims from a nationally representative sample of Dutch children [5]. Additionally, the authors calculated measures of persistence and adherence to ADHD therapies. Over the study period, incidence and prevalence of ADHD and its treatment increased; persistence and adherence with ADHD treatment declined in the year following treatment validation. Using linked commercial medical and pharmacy claims, Sikirica et al analyzed treatment patterns, related health resource use, and costs of atypical antipsychotics (AAPs) in youth with ADHD and prior stimulant use [6]AAP and non-AAP users were propensity matched, then compared in regards to therapeutic substitutions and additions and its impact on outcomes. ADHD patients using AAPs experienced more frequent augmentation of therapy, greater rates of outpatient, ED and hospital use, and higher costs.

Mandell et al employed national Medicaid claims from 2001claims data to illustrate widespread use of psychotropic medications and relevant contributing factors in pediatric Medicaid patients with ASD [7]. More than half (56%) of all children with ASD used psychotropic medications; numerous factors were significantly associated with prescribing of these agents (e.g. older age, white race, disability or foster care eligibility, inpatient utilization, etc.). Spencer et al used linked commercial medical and pharmacy claims to evaluate prevalence and duration of interclass poly pharmacy in ASD patients [8]. Their analysis centered on prevalence and duration of interclass poly-pharmacy. Half of all children with ASD diagnoses used psychotropic medications in two or more classes. Shatin and Drinkard also performed an analysis of psychotropic medications, using a sample of children in a large national health plan [9]. They reported decreased use of tricyclic antidepressants (TCAs) and increased use of central nervous system stimulants (CNSSs), selective serotonin reuptake inhibitors (SSRIs), and other antidepressants (OADs) in their analysis of pe-

diatric psychotropic medication use trends in a large health plan.

Dusetzina et al used commercial medical and pharmacy claims to examine the extent to which children with bipolar I disorder received recommended drug treatment during 2005-2007 [10] .They determined that only 20% of children received recommended first-line treatment within 90 days of diagnosis and 32% of children received no medications. Most children taking non-recommended pharmacotherapy used antidepressants. Dusetzina et al used the same source to estimate the treatment prevalence of bipolar disorder in privately insured population and described patient characteristics and patterns of psychotropic drug therapy [11]. They found that 35% of children used no psychotropic drug therapy in the 30-day period following their most recent diagnosis. The most commonly used drug regimens were antipsychotics and mood stabilizers.

Delate et al used prescription claims to report trends by sex and drug class in antidepressant use among commercially insured youth over a five-year period [12]. A near 10% annual increase in antidepressant use was observed; the rate of increase in girls was twice that of boys. Zito et al also examined trends in antidepressant use in youth receiving care through Medicaid and health maintenance organizations (HMOs) [13]. From 1988 to 1994, prescribing of antidepressants increased three- to four-fold across care settings. O'Sullivan et al analysis of national pharmacy claims revealed declines in use of antidepressants (except fluoxetine) in Irish children from 2002 to 2008, following the issuance of an Irish Medicines Board (IMB) warning on use of SSRIs [14]. Results suggest that practitioners heeded the advice of IMB.

Finally, Bennett et al used discharge data from children's hospitals to evaluate characteristics and patterns and the impact of guidelines in use of hypertonic saline and mannitol among children with traumatic brain injury [15]. Osmolar therapies were used principally among children of older age or with advanced injury and did not always include intracranial monitoring. Hypertonic saline and mannitol use decreased following publication of guidelines in 2003.

Analgesia

Two studies reported medication trends for non-steroidal anti-inflammatory drugs (NSAIDs). Star et al used prescription claims to evaluate the impact of key demographic and medication-related factors on variations in dosing of NSAIDs among children ages 2-11 years in the United Kingdom [16]. Ibuprofen was almost always prescribed and dosing varied by dosage form, with tablets being prescribed at significantly higher doses than liquids. Age was positively associated with dosing among ibuprofen users; an opposite trend was observed for other NSAIDs. DeVries et al relied on commercial medical and pharmacy claims data to evaluate trends in the prevalence and predictors of opioid prescribing in adolescents (ages 13-17) with newly diagnosed headache [17].Results revealed common opioid use (46%) among adolescents with headache despite guideline disparagement.

Asthma

Five studies evaluated trends in asthma medication use. Korelitz et al used medical and pharmacy claims to determine the prevalence of asthma and the proportion of children with asthma receiving asthma-related medications [18].While only6% of the patient population had a diagnosis of asthma, 15% used asthma-related medications. Asthma medication use was much higher among children with asthma (86%) than those without a diagnosis (10%). Stempel et al used integrated medical and pharmacy data to examine treatment of pediatric asthma prior to and following emergency department (ED) visits [19]. Children with an asthma-related ED visit, but no prior ED or inpatient visits for asthma in the previous year, were identified. The results showed substantial increases in dispensing of oral and inhaled corticosteroids and rescue short-acting β_2-agonists in the month following ED visitation; however, all returned to pre-event monthly levels by the second month post-visit. Arellano et al evaluated asthma prescription patterns for privately insured children [20]. Analysis showed that short-acting β_2-agonists were used most frequently and that health service use and use of multiple medications was greater for youth with severe vs. non-severe asthma. Nearly 40% of children and adolescents with asthma did not receive any asthma medication. Sen et al utilized a linked dataset to examine trends in use of asthma medications among children with and without asthma in three countries [21]. The authors evaluated patterns by country, age, asthma diagnosis, and approval status. Rates varied widely by country, but β_2-agonists and inhaled steroids were most frequently prescribed. Stall worth et al used administrative claims data from 2000-2002 to evaluate inappropriate antibiotic use in youth with asthma [22]. After matching children (ages 5-18 years) with asthma to non-asthma controls, rates and predictors of antibiotic use were examined. The results showed that asthma patients had greater use of antibiotics.

Miscellaneous

Kemper et al used commercial and Medicaid data to evaluate discontinuation of thyroid hormone treatment according to guidelines in children with congenital hypothyroidism [23]. One-third of treatment discontinuations did not conform to guidelines; the reasons for discontinuation could not be ascertained. Raffini et al examined trends in occurrence of venous thromboembolism (VTE) and use of anticoagulant medications in children discharged from children's hospitals [24]. Over a seven-year period, the authors observed substantial increases in diagnosis of VTE; enoxaparin use increased, while warfarin use decreased during the study

period. Ziller et al used patient-level pharmacy claims to define patterns in gynecologists' prescribing of contraceptive medications to adolescent girls (ages 12-18 years) in Germany in 2007 and 2011[25]. The proportion of adolescent girls receiving contraceptives increased significantly over the study period; varying patterns in use of combination medications were observed. Contraceptive management was the most common indication for prescribing across years. Barron et al extracted administrative claims data from four health plans to observe trends in use of proton pump inhibitors (PPI) in infants and neonates documenting common diagnoses and patient characteristics associated with PPI use [26]. PPI use increased four-fold over the study period and was most strongly associated with gastrointestinal and feeding issues.

Medication Outcomes

Asthma

Three studies evaluated comparative effectiveness of asthma therapies. Stempel et al used encounters from the Phar Metrics Integrated Outcomes Database to evaluate efficacy and costs of asthma care for fluticasone propionate (FP) and montelukast (MON) therapies in asthma patients ages 4-17 years [27]. Children with an asthma diagnosis were propensity-matched 1:1 by treatment type for analysis. After accounting for differences in prior health resource use, MON patients had higher costs and were more likely to experience treatment failure, therapy changes, and asthma-related hospital admissions than FP patients. Parikh et al analyzed discharges from children's hospitals to compare the effectiveness of dexamethasone versus prednisone/prednisolone in children (ages 4-17 years) hospitalized with asthma [28]. Primary outcomes included length of stay (LOS), readmissions, cost, and transfer to ICU after admission. Dexamethasone was associated with significantly shorter LOS and lower cost versus prednisone, but rates of transfer to ICU or readmission at 7 and 30 days did not differ. Wu et al used data from six health plans to examine asthma exacerbations among new initiators of asthma controller medications across three groups: (inhaled corticosteroids (ICS), Leukotriene antagonists (LTRA), and ICS long-acting β-agonist (LABA) combination therapy [29]. Overall, use of controller medications was low and exacerbations did not differ by drug type.

Miscellaneous

Five studies evaluated efficacy and safety outcomes of various drugs. Elder et al used integrated medical and pharmacy claims to evaluate comparative efficacy of endoscopic injection (dextranomer/ zhyaluronic acid (D x/HA)) versus antibiotic prophylaxis to treat urinary tract infection (UTI) in children with vesicoureteral reflux (VUR) [30].After matching antibiotic prophylaxis and Dx/HA patients, Dx/HA was associated with fewer UTIs. Verstraeten et al used medical and pharmacy records from two HMOs to examine incidence and characteristics contributing to varicella breakthrough in the period following vaccination [31]. Children vaccinated during the study period were followed to identify breakthrough cases. Authors did not observe any significant associations between proposed risk factors (asthma, steroid use) and varicella breakthrough. Rubin et al used data from Medicaid medical and pharmacy claims to demonstrate increased incidence of type 2diabetes associated with initiation of second-generation antipsychotics and concomitant therapy with antidepressants and certain newer antipsychotics [32].

Sturkenboom et al used electronic patient records from Pedianet network to evaluate mucocutaneous reactions arising from use of niflumic acid, non-opioid analgesics, and other NSAIDs in children [33]. The authors identified episodes of mild and severe reactions to studied treatments and related demographic and clinical factors. Multiple analyses concluded that the use of niflumic acid did not increase risk of mild or severe mucocutatneous reactions. Lovegrove et al used the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance and national retail pharmacy prescription data from IMS Health to evaluate emergency hospitalizations for unsupervised prescription medication ingestions in young children (<6 years) [34]. Three-quarters of hospitalizations for unsupervised prescription medication ingestions involved 1- or 2-year-old children; one in five hospitalizations involved ingestion of two medications. Opioids and benzodiazepines were the most commonly implicated medication classes.

Discussion:

Our review demonstrates the utility of large automated data sources to conduct medication-related research for pediatric populations. Most (77%) of the reviewed studies focused on medication trends, including analyses of adherence, persistence, and discontinuation. The remaining studies addressed drug/treatment safety, comparative effectiveness, and dosing. Beyond these designs, automated health data is also useful for evaluating healthcare resource use, adoption of new therapies, and effects of policy and guidelines. Several of these studies were noted as the first or largest (in scope) of its kind in their respective fields. In the studies we reviewed, a variety of large databases were utilized, incorporating data from medical and pharmacy claims, health records, and pharmaceutical retail outlets. These databases can contain numerous clinical and demographic variables for, in some cases, millions of unique pediatric patients. Authors noted several strengths of automated health data including large sample size, long follow-up periods, and real-world clinical settings. More specifically, pharmacy claims data are noted as reliable and valid sources to document

patterns in treatment, adherence, and persistence, while medical claims provide reliable information on disease incidence and prevalence as well as health resource use. Such data expand the bounds of clinical research to include study of rare events, heterogeneous treatment effects, short- and long-term outcomes, and other topics otherwise infeasible for exploration through RCTs. Moreover, the use of such databases for critical hypothesis testing can uncover previously unrealized events and outcomes.

In contrast, limitations to the use of observational data for research are widely cited (Table 3)[35].

Advantages:	Disadvantages:
Large sample size	Uncertain validity of diagnosis date (more for claims, less for EHR data)
Relatively inexpensive	Lack of confounding variables
Potential to link to external or other electronic health records	Instability of population
–	Limited availability for longitudinal analysis

Table 3: Advantages and Disadvantages of Electronic Health Records

In general, medical records and claims systems are designed largely for patient care and billing purposes; they are not always capable of supporting extraction or aggregation of data or identification of patient groups. Second, unstructured data (e.g. free-form text) require additional coding and reformatting to facilitate use for research. Accuracy and completeness of data are important factors that impact the inferences that can be made from analysis [36]. Errors of omission and commission occur in these data arising from data entry, transfer, and extraction. In addition, these data cannot capture patient mobility in and out or across multiple systems, nor do they capture individuals experiencing barriers to care. These data are also subject to misclassification bias, due to reliance on diagnosis codes and other criteria to ascertain cases. Most studies mentioned limitations to generalizability for the specific datasets used. Studies also frequently cited the absence of diagnoses or indications for pharmacologic treatment as a limitation of pharmacy databases (including those linked to medical claims). Though authors often attributed prescribed treatments to the particular conditions studied, use outside of assumed indications cannot be ruled out. Several studies also specifically noted limitations to use of diagnosis codes for disease ascertainment, including the potential for misclassification bias and the inability to determine severity or differentiate sub types. Of note, most de-identified sources restrict the number of diagnosis codes reported, leading to underestimation of disease. Dosing data (depending on the source) are often unreliable or nonexistent, and many sources do not capture over-the-counter medication use or prescriptions filled through mail-order or purchased without claims. Finally, these data rarely include critical variables (e.g. race/ethnicity, income, education, smoking status, etc.) that may likely influence outcomes, leading to residual confounding.

While observational data are less costly and potentially useful when randomized controlled trials are not feasible or ethical, studies using these sources must be approached with caution. Researchers should make every effort to address the aforementioned limitations to the extent possible through appropriate study design and statistical methodologies. Diagnosis codes used to identify conditions of interest should have clear definitions. The reviewed studies employed various methods to reduce biases arising from use of specific observational data sources. Dusetzina et al required presence of multiple claims with a diagnosis of interest and Barron et al and Verstraeten et al abstracted validation data from a subset of medical charts to reduce misclassification bias [11,26,31]. Zito et al used multiple sources of data to corroborate findings [13].Parikh et al, Sikirica et al, Stempel et al (2007), and Wu et al applied propensity score matching in their comparative analyses [6,27-29], while Stall worth et al and Elder et al relied on other matching techniques to minimize residual confounding [22,30].These approaches substantially improve validity and reliability of estimates. Investigators should also acknowledge other data-related limitations that cannot be addressed and their impact on study results. Continued improvements in internal and external integration of electronic health information systems, accuracy and methods of data capture and storage, and open access/sharing of de-identified data will ultimately increase the value and utility of automated health data to improve human health.

Conclusions

Findings from the studies reviewed demonstrate the significant potential of leveraging electronic healthcare data to systematically evaluate patterns of medications use in children, especially for therapeutic areas with limited approved therapies. The use of large healthcare data bases has the capability to support evidence based use of medications with a well-founded understanding of effectiveness and risk.

Contributions

BEF designed and conducted the review of studies and lead in the writing of the article. EP assisted in the literature search and abstraction of data for each included article. ZB, RLD, MDR and DRM guided the design of the study, guided the literature search, contributed to interpretation of results, and provided critical review on all drafts of the manuscript. MLC contributing to the design of the review, interpretation of results and provided critical review on all drafts of the manuscript.

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