Analysis of Pediatric Clinical Drug Trials for Neuropsychiatric Conditions

WHAT'S KNOWN ON THIS SUBJECT: Neuropsychiatric conditions comprise a substantial and growing disease burden among children. Pharmacotherapy represents an important treatment option for these conditions, although most drugs are not approved for use in children.

WHAT THIS STUDY ADDS: Very few drug trials studying neuropsychiatric conditions focus on children. Furthermore, these trials examine and provide pediatric evidence for only a fraction of all available drugs in the treatment of common neuropsychiatric conditions.

BACKGROUND AND OBJECTIVE: Neuropsychiatric conditions represent a large and increasing disease burden in children. A number of drugs are available for the treatment of these conditions, but most drugs have not been adequately tested in children, and off-label drug use remains widespread. We sought to define and quantify recent and ongoing clinical research on the use of neuropsychiatric drugs in children.

METHODS: Drug trials registered in ClinicalTrials.gov between 2006 and 2011 and studying neuropsychiatric conditions were selected and classified based on the drug's Food and Drug Administration (FDA) approval status in children. We measured the proportion of trials seeking to expand the use of a drug to pediatric patients and the proportion of available drugs studied in children.

RESULTS: Only 10% of neuropsychiatric trials focused on children. Of 303 drugs studied in both pediatric and adult populations, 90% lacked FDA approval in children and 97% were not approved in children for the indication studied. However, only 19% of all neuropsychiatric drugs were under study in pediatric populations, with as few as 8% of either antidepressant or antipsychotic drugs. Overall, 76% of pediatric drug trials examined a drug previously unapproved in children and 26% explored the use of a drug for a new indication.

CONCLUSIONS: Despite the rising prevalence of neuropsychiatric disease and the paucity of FDA-approved pediatric drugs, only a small proportion of trials focus on pediatric populations and these trials cover only a fraction of available drugs. This deficiency is most pronounced for depression and schizophrenia. Pediatrics 2013;131:1125–1131
Despite metabolic and pathophysiologic differences between children and adults, only 46% of drug labels provide information on pediatric use.¹⁻⁴ Clinicians often treat children with off-label and unlicensed medications that have been tested in and approved for adult populations without pediatric-specific guidelines, with as many as 78% of hospitalized children receiving medications lacking age-specific approval.²⁻⁷

The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), both of which were permanently reauthorized in May of 2012, seek to increase the study of drugs in children and address some of the concerns with the pediatric research infrastructure that have long been recognized.⁸⁻¹ⁱ The Institute of Medicine reports that these efforts have led to improvements in pediatric research, but also points to persistent deficiencies, including continued reluctance by providers to enroll children in clinical drug trials and limited long-term data collection.¹²

Neuropsychiatric conditions represent a large and increasing disease burden in children.¹³ In the United States, the prevalence of emotional, behavioral, and neurologic disabilities has even surpassed physical impairments in children and represents the leading cause of limitation in their usual activities.¹³,¹⁴ In a 2009 survey, close to 1 in 5 parents reported that their child suffered from a neurologic or psychiatric condition, whereas the most common physical condition, asthma, was cited by only 8% of parents.¹³,¹⁵ These increases have been mirrored by a dramatic rise in the use of neuropsychiatric drugs in children.¹⁶⁻¹⁸ Antipsychotic use increased from 8.6 per 1000 children to 39.4 per 1000 children from 1995 to 2002, for example, and antidepressant use increased from 9.4 per 1000 to 21.3 per 1000 children between 1994 and 2003.¹⁸⁻²¹ The lack of clinical evidence to support the use of these agents in children has resulted in a number of controversies, including concerns over increased suicidality among adolescents treated with selective serotonin reuptake inhibitors and antipsychotic side effects in young children.²²⁻²⁵

We define the current state of pediatric research activity for neuropsychiatric disease, including the underrepresentation of certain drug classes and conditions. Specifically, we determine the proportion of clinical drug trials for neuropsychiatric conditions seeking to expand the evidence base for children and compare pediatric and adult research on these conditions.

METHODS

Clinical Conditions

We focused on the 5 neuropsychiatric conditions representing the highest disease burden of children, measured by comprehensive morbidity and mortality measures for diseases and injuries based on national and regional information on the prevalence and incidence of specific conditions. The overall burden of disease is calculated by using disability-adjusted life years (DALYs), which incorporates both years of life lost due to premature death and life spent in less than full health. This measure has previously been used to evaluate the adequacy of research activity pertaining to a condition.²⁶²⁷ The conditions selected in this study were depression (10 845 134 DALYs), schizophrenia (4 397 896 DALYs), migraine (4 143 821 DALYs), bipolar disorder (3 390 134 DALYs), and epilepsy (3 376 590 DALYs). Because disease burden data are collected by WHO in predefined age groups (0–4 years, 5–14 years, and 15–19 years), we combined data for the younger age groups with three-fifths of the 15- to 19-year age group to generate disease burden estimates for children 0 to 17 years.²⁸

Trial Selection

Clinical drug trials relating to the conditions of interest were identified in ClinicalTrials.gov, the largest and most comprehensive registry of clinical trials.²⁹ This trial registry contains both domestic and international clinical trials and is estimated to include records for as many as 89% of all registered trials.³⁰,³¹ Given frequent delays in publication and failure to publish trials, clinical trial registries are preferable to using published research to evaluate current and complete research activity.³²,³³ Trial records were selected and downloaded on November 1, 2011, using the following inclusion criteria: the trial studied 1 of the 5 conditions of interest, the trial was a drug intervention study addressing the efficacy and/or safety of an agent (ie, pharmacokinetic/dynamic and dose-finding trials were excluded), and the start date was on or after January 1, 2006. In defining drug trials, we referred to the WHO Anatomic Therapeutic Chemical Classification System and included trials studying substances listed in this database. Drugs not included in this database, but for which we found documentation in the form of company documents or press releases that the substance was a drug in development at the time of study start, were included for separate analyses as “new drugs.” All trials were manually reviewed by 1 of the authors (S.M.) to ensure that they met all inclusion criteria. Trials were excluded if the registry records indicated trial termination or withdrawal before subject enrollment. If a trial compared a drug to an active comparator drug, then the primary drug under study was considered the index drug. If 2 or more drugs were studied in head-to-head comparisons,
then both drugs were included and examined separately.

Trial data were extracted from ClinicalTrials.gov, including study start date, minimum and maximum age eligibility, and conditions and drugs under study. A trial was classified as a pediatric trial if it enrolled only patients younger than 18 or if it also enrolled patients 18 and older but the midpoint of the age range for enrolled participants was younger than 18. Two trials were missing minimum age eligibility and therefore could not be classified and included in the analysis. There were also 35 trials that did not specify an upper age limit for enrollment (of which 24 had a lower age limit of 15 years or older) and these were classified as adult trials.

Food and Drug Administration Approval Status

For each drug under study, we determined the Food and Drug Administration (FDA) approval status using publicly available drug labels and the Physician’s Desk Reference. A drug that has received FDA approval is considered adequately tested for efficacy and safety for a specific indication and the drug label provides detailed information on proper dosage and administration, contraindications, and potential adverse events. Data elements abstracted for every drug included FDA-approved patient ages, indications for drug use, and the dates of approval for each of the approved age groups and indications. Drugs in development were not considered approved for any age group or indication. New formulations of previously approved drugs were considered non-FDA approved because these require FDA review and approval. Drugs that obtained FDA approval for pediatric use between 2006 and 2011 were individually reviewed and, using available FDA databases, we determined whether results from the trials examined in this study contributed to their approval.

Statistical Analysis

For each of the neuropsychiatric conditions examined, we calculated descriptive statistics on the proportion of trials that sought to expand the use of a drug to pediatric patients, the proportion that explored the use of a drug for a new indication in this population, and the proportion that supported the development of a new drug or formulation for use in children. For comparison, we also calculated these values for adult trials. Overall proportions are reported with 95% confidence intervals (CIs). All statistical analyses were performed by using SAS software (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

A total of 2824 trials were identified and, of these, 1778 were excluded (958 because they did not study interventional use of a drug, 752 because they were not efficacy and/or safety trials, and 68 because they were terminated before subject enrollment), yielding a final cohort of 1046 trials for analysis. Of these trials, only 10% (108/1046) were pediatric trials (Table 1). The smallest proportion of pediatric trials was for depression (6%, 17/308) and schizophrenia (6%, 16/290), whereas the largest proportion was for epilepsy (26%, 42/163).

Drugs Studied in Neuropsychiatric Conditions

A total of 303 drugs were studied in the pediatric and adult trials and, of these, 90% (273/303) did not have FDA approval for use in children and 97% (293/303) did not have FDA approval for use in children for the specific neuropsychiatric condition studied (Table 2). No drugs studied for bipolar disorder, depression, or migraine were FDA approved for use in children. Despite the limited amount of previous pediatric research, as demonstrated by FDA approval status, only 19% (57/303; 95% CI 15%–23%) of all drugs were under study in the pediatric trials, compared with 95% (288/303; 95% CI 93%–97%) of drugs among adult trials. Drugs to treat depression and schizophrenia were the most poorly represented in pediatric trials with only 8% (8/107 and 8/104, respectively) of drugs studied in either condition. Antiepileptics were the most broadly studied in children, with 51% (25/49) of drugs included in pediatric trials.

Trials Supporting Pediatric Use, New Indications, or New Drugs and Formulations

Overall, 76% (74/97) of pediatric trials were expanding drug use to pediatric age groups by testing a drug that was not previously FDA approved for use in children (Table 3). At the same time, 26% (25/97; 95% CI 17%–35%) of trials were also exploring the use of

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**TABLE 1** Safety and Efficacy Drug Trials for Neuropsychiatric Conditions, 2006–2011

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Trials</th>
<th>Pediatric Trials</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>308</td>
<td>17 (6)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>290</td>
<td>16 (6)</td>
<td></td>
</tr>
<tr>
<td>Migraines</td>
<td>110</td>
<td>12 (11)</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>179</td>
<td>24 (13)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>163</td>
<td>40 (25)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1046</td>
<td>106 (10)</td>
<td></td>
</tr>
</tbody>
</table>

* Top 5 neuropsychiatric conditions based on global pediatric burden of disease (DALYs).

* Defined as trials with maximum age criteria of 17 y as well as trials with a maximum age criteria of ≥18 y but where the midpoint of the age range is <18 y.

* Total does not represent sum of rows, as some trials study >1 condition.
a drug for an unapproved indication. The proportion of trials studying new indications ranged from 12% (2/16) for trials studying schizophrenia to 42% (5/12) for trials addressing migraine. Only 8% (9/106; 95% CI 3%–13%) of all trials studied the use of a new drug or formulation in children and all of these trials were for new antiepileptic agents.

By comparison, trials conducted in adult populations were more likely to explore the use of a drug for a new indication, with 42% (95% CI 38–46) examining unapproved indications. Adult trials were also more likely to support the development of a new drug or formulation, with 32% (95% CI 29%–35%) of trials investigating new agents (Table 3).

Because new drugs are typically first tested in adults before being examined in children, we conducted a separate analysis that excluded the 314 trials supporting the development of a new drug or new drug formulation, and obtained similar results. Overall, 13% (97/732) of trials for neuropsychiatric conditions were pediatric. Depression and schizophrenia remained the least studied with only 9% (17/192) and 8% (16/193) of trials studying these respective conditions in children, compared with 21% (16/76), 15% (24/165), and 27% (31/115) of trials studying migraines, bipolar disorder, and epilepsy, respectively. Excluding new drugs and formulations, 83% (142/170) of the drugs were not FDA approved for use in pediatric patients and 94% (160/170) were not approved in children for the indication studied. However, only 29% (49/170) of available drugs were under investigation in clinical trials in children.

Among the 106 pediatric trials, we identified 6 that contributed to the subsequent FDA approval of a drug for use in pediatric age groups as of June 2012: 3 trials supported the approval of rizatriptan for migraine relief in children 6 to 17 years; 2 trials provided evidence for the approval of paliperidone in the treatment of schizophrenia in children 12 to 17 years; and 1 trial supported the approval of aripiprazole in children 13 to 17 years with schizophrenia.

**DISCUSSION**

Only 10% of clinical drug efficacy and safety trials registered between 2006 and 2011 for neuropsychiatric conditions focus on studying children, despite most psychotropic drugs lacking pediatric FDA approval. The small number of trials that do study pediatric populations examine only a fraction of currently available drugs, with the aim of expanding an indication approved in adults to a pediatric age group. This is in contrast to adult drug research, which includes safety and efficacy studies for almost all available drug options.

The BPCA and PREA have led to a number of drug label revisions to include pediatric information, based on clinical trial and postmarketing surveillance data. As such, these legislations hold great promise in improving the scientific evidence supporting rational use of drugs in children. However, there has also been

### TABLE 2 Drugs Studied in the Treatment of Neuropsychiatric Conditions, 2006–2011

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Drugs</th>
<th>Drugs Studied in Pediatric Trials, n (%)</th>
<th>Drugs Studied in Adult Trials, n (%)</th>
<th>Drugs Not FDA Approved in Children, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not Approved for Any Condition</td>
<td>Not Approved for Studied Condition</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>107</td>
<td>8 (8)</td>
<td>103 (96)</td>
<td>97 (91)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>104</td>
<td>8 (8)</td>
<td>103 (99)</td>
<td>96 (77)</td>
</tr>
<tr>
<td>Migraines</td>
<td>58</td>
<td>8 (1)</td>
<td>56 (97)</td>
<td>53 (91)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>60</td>
<td>18 (30)</td>
<td>53 (88)</td>
<td>49 (82)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>49</td>
<td>25 (51)</td>
<td>40 (82)</td>
<td>38 (78)</td>
</tr>
<tr>
<td>Total</td>
<td>303</td>
<td>57 (19)</td>
<td>288 (95)</td>
<td>273 (90)</td>
</tr>
</tbody>
</table>

| Representative                | n/N (%) | | | |
|--------------------------------|---------| | | |
| Depression                   | 12/17   | | | |
| Schizophrenia                | 16/16   | | | |
| Migraines                    | 12/12   | | | |
| Bipolar disorder             | 16/24   | | | |
| Epilepsy                      | 16/31  | | | |

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Drugs</th>
<th>Drugs Studied in Pediatric Trials, n (%)</th>
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<tr>
<td>Total</td>
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<td>57 (19)</td>
<td>288 (95)</td>
<td>273 (90)</td>
</tr>
</tbody>
</table>

### TABLE 3 Drug Trials for Neuropsychiatric Conditions, 2006–2011

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pediatric Trials</th>
<th>Adult Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials Expanding</td>
<td>Development of New Drug or New Formulation of Existing Drug</td>
</tr>
<tr>
<td></td>
<td>Drug Use to Pediatric Age Groups</td>
<td>Drug for a New Indication</td>
</tr>
<tr>
<td>Depression</td>
<td>88 (15/17)</td>
<td>0 (0/17)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>94 (15/16)</td>
<td>0 (0/16)</td>
</tr>
<tr>
<td>Migraines</td>
<td>100 (12/12)</td>
<td>0 (0/12)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>67 (16/24)</td>
<td>0 (0/24)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>52 (16/31)</td>
<td>22 (9/40)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (74/97)</td>
<td>8 (8/108)</td>
</tr>
</tbody>
</table>

| Representative                | n/N (%) | | | |
|--------------------------------|---------| | | |
| Depression                   | 15/17   | | | |
| Schizophrenia                | 16/16   | | | |
| Migraines                    | 12/12   | | | |
| Bipolar disorder             | 16/24   | | | |
| Epilepsy                      | 16/31  | | | |

Values are % (n/N).

a Excludes drugs in development.

b Represents trials studying a drug that is not FDA approved for any indication in the pediatric population.

c Represents trials studying a drug for a new indication that is not FDA approved in any age group.

d Total does not represent sum of rows, as some drugs are studied in >1 condition.
concern that the significant economic benefits used to incentivize pharmaceutical companies to undertake pediatric research has led industry to concentrate their efforts on drugs that represent a large adult market share and have greater potential for profitability.\(^1\)\(^2\) Consequently, the drugs studied under the exclusivity program may more closely mirror adult than pediatric medical needs. Nonetheless, the BPCA and PREA have succeeded in encouraging both efficacy and safety studies in children and in expanding indications for existing adult drugs to pediatric populations.\(^3\)\(^9\)\(^4\)\(^3\) Furthermore, the Pediatric Formulations Initiative, established in 2005 in response to the BPCA, aims to systematically evaluate pediatric formulations and improve the development of these.\(^4\)\(^4\)

Increasing the development of new drugs for common childhood conditions, however, will likely require specific legislation.\(^4\)\(^5\) The recent Creating Hope Act of 2010 was designed to incentivize industry to develop drugs for child-specific diseases, but the focus of the act is on rare conditions and therefore excludes the childhood conditions examined in this analysis.\(^4\)\(^6\)

Our results suggest that, given the extensive burden of neuropsychiatric disease, research activity is currently not adequately addressing these conditions in pediatric populations.\(^4\) Depression and schizophrenia, which pose the greatest neuropsychiatric disease burden in children, are the most underrepresented in terms of the proportion of trials studying children and the proportion of available drugs under study in children; only 6% of all trials and 8% of all drugs for these conditions are studied in the pediatric population. These deficiencies have been previously described and our findings indicate that, despite a number of programs encouraging drug studies in children, further efforts are needed to address the gap in pediatric drug research.\(^1\)\(^1\)\(^4\)\(^7\) It is possible that our analysis is too early to fully assess the effects of stimulation programs on pediatric neuropsychiatric research. However, as of 2012, the only drug that is FDA approved for the treatment of depression in children younger than 12 is fluoxetine. Additionally, between 2007 and 2011, 4 drugs were approved for the treatment of schizophrenia in adolescents, but there continues to be no approved treatment of children younger than 12.\(^5\)\(^8\)

There are substantial ethical and practical barriers to the inclusion of children in clinical drug trials, and children with neuropsychiatric disease may be particularly difficult to study. Complex consent procedures are required for research in children and there is a general unwillingness to perform first-in-human trials in children.\(^5\)\(^8\)\(^4\)\(^9\) Age-group–specific drug studies are required because of pathophysiologic changes as children mature and, compared with adult studies, there is a relative lack of qualified investigators to perform such trials.\(^4\)\(^5\)\(^0\) Patients with psychiatric conditions also require additional attention concerning their ability to provide informed consent or assent.\(^5\)\(^1\) Overall, the pediatric population represents a small market size and potential for profitability compared with adults, creating a disincentive for pharmaceutical companies to develop and market drugs targeted at children.\(^5\)\(^0\)\(^5\)\(^2\) A limitation of our study is that the ClinicalTrials.gov registry may not include all relevant neuropsychiatric trials; however, this is the most accessible and comprehensive registry for domestic clinical research.\(^3\)\(^0\) We also could not verify the information provided by investigators in the trial record and encountered records with some missing data. For the drug data, we could not ensure that our sources provided the most recently approved drug labels, although 2 separate references were used and all searches were performed separately by 2 of the investigators (S.M. and F.B.).

CONCLUSIONS

We have quantified current drug research for neuropsychiatric conditions in children in the era of regulatory incentivization of pediatric research. We find that despite the rising prevalence of neuropsychiatric disease, only a small proportion of trials focus on pediatric populations and these trials cover only a fraction of the available drugs. This deficiency is most pronounced for depression and schizophrenia, which also represent the conditions with the greatest neuropsychiatric disease burden in children. Current strategies need to be strengthened to overcome persistent barriers to research activity in children and to increase evidence-based treatment options for children with neurologic and psychiatric disabilities.

ACKNOWLEDGMENTS

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GOING GREEN: I travel a lot and stay at many different types of hotels. Recently, I gave a series of talks for a continuing medical education course, and the program director put my wife, daughter, and me in a room at a luxury hotel. Similar to almost every hotel I have stayed at in the past year, there were information placards scattered across the room to remind me that the hotel was environmentally conscious and that—if I wanted to help save the environment—I should reuse the towels and sheets (“go green”). We are fairly environmentally conscious at home, but what to do at a hotel is a bit more problematic. For example, within two days we had made our previously lovely hotel room look remarkably like our own home, with various towels slung over doors to dry and the sheets a bit dusty from our hiking gear. The room no longer looked much like a luxury hotel room. As reported on CNN (Travel: March 6, 2013), many hotel guests struggle with how environmentally conscious to be. After all, travelers are spending a lot of money to stay in the room, and “going green” involves a sacrifice. Moreover, the hotel (not the consumer) reaps the direct benefit. Some hotels recognize their guests’ sacrifices and reward those who participate in the linen reuse programs with food or drink discounts or additional awards program points. According to CNN, of the nearly 90% of hotel guests offered the chance to participate in a sustainable use program during their stay, approximately two-thirds agree. Remarkably, travelers who participate in the “go green” programs report greater satisfaction with their stay than those who do not. Personally, I am all for reducing energy expenditures and water consumption associated with frequent hotel linen washing, and I am quite happy to “go green” (even without any financial inducements).

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