INTRODUCTION

The long-held belief that information about pediatric drugs (e.g., efficacy, safety, and dosage) is often lacking in manufacturers’ product labeling in the U.S. has been recently confirmed; only 41% of medications approved from 2002 to 2008 have labeling specific to pediatrics. Similar suspicions apply to the content of the prescribing information about medications intended for geriatric patients.

In 2012, the U.S. Government Accountability Office (GAO) indicated that few patients older than 65 years of age were enrolled in drug trials for New Drug Applications (NDAs) from January 2001 through June 2004, and it encouraged a re-examination of the guidance and regulations governing drug approvals. It is well established that older patients show considerable differences in drug tolerance and in pharmacokinetic and pharmacodynamic responses to medications, compared with non-geriatric groups. Further, the U.S. Census Bureau anticipates a doubling of the geriatric population by 2040. With the projected rapid increase in the number of elderly people needing health care, clinicians must have sufficient knowledge about new drugs so that they can safely prescribe them to this patient population and avoid unnecessary adverse effects and hospitalizations.

An editorial published in 2011 underscored the problem by emphasizing the inadequacy of current guidance for medication use in the elderly, particularly individuals older than 75 years of age. Because some adverse effects, as well as the potential for exaggerated clinical, biobehavioral, or functional consequences of drug therapy, may be more prevalent in the elderly,

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Figure 1: Schema of study data flow.

<table>
<thead>
<tr>
<th>235 drugs approved 2002–2011</th>
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</thead>
<tbody>
<tr>
<td>12 excluded by researchers as “not relevant in geriatrics”</td>
</tr>
<tr>
<td>174 sent to be reviewed by expert</td>
</tr>
<tr>
<td>49 with sufficient geriatric information</td>
</tr>
<tr>
<td>9 with unlikely use in geriatrics and, therefore, excluded</td>
</tr>
<tr>
<td>165 have potential use in geriatrics</td>
</tr>
<tr>
<td>22 have sufficient geriatric information</td>
</tr>
</tbody>
</table>
adequate information is essential in guiding drug selection, dosage regimens, and monitoring. Modeling and simulation studies often fail to provide sufficient data to ensure drug safety in geriatric patients.

We conducted a study to assess the labeling content in the product information of drugs approved relatively recently in the U.S. (from 2002 to 2011). We were primarily interested in reviewing the adequacy of the labeling used to inform prescribers and other health care professionals about medications for elderly patients. Our goal was to determine whether a knowledge gap existed in the labeling of drugs intended for older patients.

METHODS

For this investigation, we adopted the definition of the term “geriatric,” as used by the FDA, to mean patients 65 years of age or older.8 We obtained a listing of all new molecular entities (NMEs) and biologics approved by the FDA in the previous decade from the agency’s Web site (www.fda.gov). Drug indications, geriatric information, and dosages were extracted from current FDA-approved labeling, as found in the National Library of Medicine’s DailyMed repository.9

Drugs were reviewed to determine whether they would be expected to have a geriatric use or whether age-specific dosing might be required. Of a total of 235 medications, 12 drugs (contraceptives and sunscreens) were excluded from further analysis because a lack of geriatric labeling was unlikely to constitute a knowledge gap. A schema of the study flow is provided in Figure 1.

Two of the authors (T. H. and J. K.-U.) rated the 223 drugs remaining as having either sufficient or insufficient information in the manufacturer’s FDA-approved labeling to be prescribed safely to a geriatric patient. The schema shown in Table 1, created by the authors, was based on the premise that labeling information might be helpful but not always explicit regarding how medicine is practiced in the “real world.” We based the classifications in Table 1 on the adequacy of prescribing information specifically related to the geriatric population.

We evaluated the product information (the FDA-approved label) of each medication and gave a score based on points assigned for three rating criteria:

1. reference to a sample of studied geriatric patients, such as from the package insert for cetuximab (Erbitux, Bristol-Myers Squibb/ImClone): “363 patients were ≥65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.”
2. inclusion of geriatric-specific information about dosage, such as from the package insert for vilazodone (Viibryd, Forest): “no dose adjustment is recommended on the basis of age.”
3. availability of focused information on the safe use of the drug in patients with renal insufficiency, such as from the prescribing information for cabazitaxel (Jevtana, Sanofi-Aventis): “no significant difference was observed in the pharmacokinetics of cabazitaxel between patients >65 years ... and older.”

The maximum score for a well-studied drug could be 5 points. A score of 3 or lower was considered to constitute a knowledge gap, and a score of 4 or higher was considered to constitute no knowledge gap.

We subsequently sent product information from medications that were rated preliminarily as having inadequate labeling to be reviewed by four clinicians with expertise in geriatric medicine. All of these experts had at least 15 years of clinical practice in geriatrics, were board-certified in geriatric pharmacy, and had written review articles and research publications in the geriatric and pharmacy literature. The reviewers were asked whether the drug (1) had potential use (i.e., relevance) in geriatric patients and (2) was an “important” entity for the geriatric population.

All drugs that were considered by at least two experts to have potential use were included in the analysis. We excluded some drugs if fewer than two experts considered them to have a geriatric use. Therefore, we excluded nine more drugs (in addition to the 12 previously excluded) that were not considered to be associated with a geriatric knowledge gap. The excluded drugs and their indications can be found in Table 2.

RESULTS

Our expert panel considered 214 of the 235 drugs (91%) that were approved by the FDA within the previous decade to be relevant for geriatric patients. The year-by-year breakdown for NMEs is presented in Table 3.

Of the 214 medications that underwent further evaluation, 143 (67%) were considered to be associated with a labeling knowledge gap, as determined by a score of 3 or less by our rating schema. Of the drugs associated with a knowledge gap, 90 of the total number evaluated (42%) were considered to be “important” by the experts (Table 4). The summary “point score” of the medications judged to be relevant to geriatrics and with a knowledge gap is depicted in Table 5.

Medications that were considered to be both associated with and not associated with a geriatric knowledge gap are categorized by therapeutic class in Table 6.

Figure 2 displays the annual number of geriatric-relevant medications associated with a knowledge gap, approved by the FDA between 2002 and 2011, compared with the total number of NMEs approved in the same time period. A knowledge gap was judged to apply to more than one-third of geriatric-relevant NMEs approved each year during this time period.

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**Table 1: Rating Schema for Adequacy of Labeling Information in Medications for Geriatric Patients**

<table>
<thead>
<tr>
<th>No. of Geriatric Patients Studied</th>
<th>Available Geriatric Dosing Guidance</th>
<th>Renal Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comment/none studied = 0 point</td>
<td>No comment = 0 point</td>
<td>No comment = 0 point</td>
</tr>
<tr>
<td>Small number, but some information described = 1 point</td>
<td>Geriatric caution advised = 1 point</td>
<td>Information available = 1 point</td>
</tr>
<tr>
<td>Adequately studied = 2 points</td>
<td>Explicit recommendation = 2 points</td>
<td>—</td>
</tr>
</tbody>
</table>
DISCUSSION

In our analysis, two-thirds of medications (143/214) relevant to geriatrics and FDA-approved in the previous 10 years were found to lack adequate prescribing information about efficacy and safety data for use in older populations. With the anticipated exponential growth of the baby-boomer age group, health care practitioners must have sufficient data on safety and efficacy when they prescribe or monitor newly approved drugs often indicated for patients older than age 65 or 75. Federal legislation and FDA regulations require that drugs be tested for safety and efficacy in specific populations, at a specific dosage, and for a specific time period before they are approved for clinical use.

Knowledge Gaps in Labeling of Drugs for Geriatric Patients

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisdexamfetamine dimesylate (Vyvanse)</td>
<td>Treatment of attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>Nitidine (Orfadin)</td>
<td>Adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type-1</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Topical treatment of head lice infestation in patients 6 months of age and older</td>
</tr>
<tr>
<td>Spinosad (Natrobe suspension)</td>
<td>Topical treatment of head lice infestation in patients 4 years of age and older</td>
</tr>
<tr>
<td>Mecasermin rinfabate [rDNA origin] injection (Iplex); preservative-free</td>
<td>Treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone (not for long-term treatment)</td>
</tr>
<tr>
<td>Mecasermin [rDNA origin] injection (Increlex); benzyl alcohol, sodium chloride, polysorbate 20, and acetate</td>
<td>Treatment of growth failure in children with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone (long-term treatment)</td>
</tr>
</tbody>
</table>
| Estradiol valerate/dienogest (Natazia)                                    | • Used by women to prevent pregnancy  
• Treatment of heavy menstrual bleeding in women without organic pathology who use an oral contraceptive                                                                                           |
| Ulipristal acetate (ella)                                                 | Prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure; not intended for routine use as a contraceptive                                                        |
| Hyaluronidase (Hydase; Vitrase)                                           | Adjuvant  
• Used to treat hypodermoclysis  
• Used to increase dispersion and absorption of other injected drugs  
• Used in subcutaneous urography to improve resorption of radiopaque agents                                                                 |
| Hyaluronidase, human [recombinant DNA] injection (Hyenex)                 | Adjuvant  
• Used in subcutaneous fluid administration to achieve hydration  
• Used to increase dispersion and absorption of other injected drugs  
• Used in subcutaneous urography to improve resorption of radiopaque agents                                                                 |
| Hyaluronidase, ovine (Amphadase)                                         | Adjuvant  
• Used in subcutaneous fluid administration to achieve hydration  
• Used to increase dispersion and absorption of other injected drugs  
• Used in subcutaneous urography to improve resorption of radiopaque agents                                                                 |
| Avobenzone (Parsol), ecamsule (Mexoryl), octocrylene                      | Sunscreen lotion protection against ultraviolet A and B light                                                                                                                                             |
| Alglucosidase alfa (Myozyme, Lumizyme)                                   | Treatment of Pompe disease (acid alpha-glucosidase deficiency)                                                                                                                                               |
| Idursulfase (Elaprase)                                                    | Treatment of Hunter syndrome (MPS type-II)                                                                                                                                                                  |
| Galsulfase (Naglazyme)                                                    | Treatment of Maroteaux–Lamy syndrome (MPS type-VI)                                                                                                                                                         |
| Clofarabine (Clolar)                                                     | Treatment of pediatric patients 1 to 21 years of age with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens                                                           |
| Pentetate calcium trisodium (pentetic acid) injection                    | Treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination                                                                 |
| Pentetate zinc trisodium (Zn-DTPA)                                       | Treatment of individuals with known or suspected internal contamination with plutonium, americium, or curium to increase the rates of elimination                                                                 |
| Ferric hexacyanoferrate (Prussian Blue)                                   | Treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase rates of elimination                                    |
| Carglumic acid (Carbaglu)                                                 | • Adjunctive therapy for acute hyperammonemia caused by a deficiency of the hepatic enzyme NAGS  
• Maintenance therapy for chronic hyperammonemia caused by a deficiency of the hepatic enzyme NAGS                                                                                       |

IGF = insulin growth factor; MPS = mucopolysaccharidosis; NAGS = N-acetylglutamate synthase; rDNA = recombinant DNA.
### Table 3: Results of the Geriatric Knowledge Gap Analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of NMEs approved</td>
<td>17</td>
<td>21</td>
<td>36</td>
<td>20</td>
<td>22</td>
<td>18</td>
<td>24</td>
<td>26</td>
<td>21</td>
<td>30</td>
<td>235</td>
</tr>
<tr>
<td>NMEs considered relevant for geriatrics</td>
<td>16</td>
<td>20</td>
<td>31</td>
<td>15</td>
<td>19</td>
<td>17</td>
<td>24</td>
<td>25</td>
<td>18</td>
<td>29</td>
<td>214</td>
</tr>
<tr>
<td>NMEs with a geriatric knowledge gap (%)</td>
<td>9 (56)</td>
<td>12 (60)</td>
<td>20 (65)</td>
<td>11 (73)</td>
<td>13 (68)</td>
<td>14 (82)</td>
<td>14 (67)</td>
<td>16 (64)</td>
<td>15 (83)</td>
<td>19 (66)</td>
<td>143 (67)</td>
</tr>
<tr>
<td>NMEs considered important with a knowledge gap (%)</td>
<td>4 (25)</td>
<td>8 (40)</td>
<td>15 (48)</td>
<td>9 (60)</td>
<td>8 (42)</td>
<td>9 (53)</td>
<td>11 (52)</td>
<td>8 (32)</td>
<td>8 (44)</td>
<td>10 (35)</td>
<td>90 (42)</td>
</tr>
</tbody>
</table>

*Percentage of new molecular entities (NMEs) considered relevant for geriatrics.

### Table 4: Drugs Associated With a Knowledge Gap but Considered Important in Geriatrics (n = 90)

- Trypan Blue (e.g., VisionBlue)
- Retapamulin (Altabax)
- Gadoxetate disodium (Eovist)
- Difluprednate (Durezol)
- Lapatinib (Tykerb)
- Romiplostim (Nplate)
- Tetrabenazine (Xenazine)
- Ambrisentan (Letaris)
- Eltrombopag olamine (Promacta)
- Natalizumab (Tysabri)
- Etravirine (Intelicence)
- Vigabatrin (Sabril)
- Panitumumab (Vectibix)
- Cetrotizumab pegol (Cimzia)
- Golimumab (Simponi)
- Ixabepilone (Ixempra)
- Regadenoson (Lexiscan)
- Pralatrexate (Folotyn)
- Temsirolimus (Torisel)
- Gadofosveset trisodium (Ablavar)
- Dalfampridine (Ampyra)
- Crizotinib (Xalkori)
- Degarelix (Firmagon)
- Gabapentin enacarbil (Horizant)
- Periflexane (Imagent) and perflutren (Definity)
- phospholipid microspheres
- Tolvaptan (Samsca)
- Nepafenac (Nevanac)
- Icodextrin (Extraneal, Adept)
- Romidepsin (Istodax)
- Alfuzosin HCl (Uroxatral)
- Fulvestrant (Faslodex)
- Pazopanib (Votrient)
- Pegaptanib sodium (Macugen)
- Enfuvirtide (Fuzeon)
- Tocilizumab (Actemra)
- Aliskiren (Tekturna)
- Aflbercept (Eylea)
- Abarelix (Plenaris), withdrawn
- Enbulin mesyate (Halaven)
- Dronedarone HCl (Multaq)
- Gefitinib (Iressa)
- Fingolimod HCl (Gilenya)
- Denosumab (Prolia)
- Bortezomib (Velcade)
- Cabazitaxel (Jevtana)
- Afibercept (Eylea)
- L-Glutamine
- Rapilivirine (Edurant)
- Rasagiline mesylate (Azilect)
- Omega-3-acid ethyl esters (Lovaza, Vascepa)
- Belatacept (Nulojix)
- Ranolazine (Ranexa)
- Lanthanum carbonate hydrate (Fosrenal)
- Abiraterone acetate (Zytiga)
- Rotigotine (Neupro)
- Bevacizumab (Avastin)
- Ipilimumab (Yervoy)
- Silodosin (Rapaflo)
- Palifermin (Kepivance)
- Ioflupane l-123 injection (DaTScan)
- Prasugrel (Effient)
- Tipranavir (Aptivus)
- Treprostinil sodium (Tyvaso)
- Ticagrelor (Brilipta)
- Pramlintide acetate (Symlin)
- Emtricitabine (Emtriva)
- Memantine HCl (Namenda)
- Tigecycline (Tigacil)
- Palonosetron HCl (Aloxil)
- Liraglutide (Victoza)
- Conivaptan HCl (Vaprisol)
- Acamprosate calcium (Campral)
- Solifenacin succinate (Vesicare)
- Darunavir (Prezista)
- Iloprost (Ventavis)
- Insulin glulisine (Apidra)
- Lubiprostone (Amitiza)
- Apomorphine HCl (Apokyn)
- Ramelteon (Rozarex)
- Dextabine (Dacogen)
- Ziconotide (Prialt)
- Exenatide (Byetta, Bydureon)
- Sunitinib malate (Sutent)
- Gadozamine dimeglumine (Multihance)
- Insulin detemir (Levemir)
- Maraviroc (Selzentry)
- Abatacept (Orencia)
- Dabigatran etexilate (Pradaxa)
- Raltegravir potassium (Isentress)
- Vorinostat (Zolinza)
- Rivaroxaban (Xarelto)
CONCLUSION

Clinicians are left with few options other than to start elderly patients with the lowest doses available and to titrate the doses upward slowly. Although recent efforts by the American Geriatrics Society to update a long-stagnant list of potentially inappropriate drugs for use in the elderly are helpful, perhaps the time has come for additional incentives (e.g., tax credits, extended patent protection) to be provided to drug manufacturers to study and incorporate more robust prescribing information into their product labels for drugs used in geriatric patients.

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REFERENCES