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Authors

Slattum, Patricia W
Schwartz, Janice B

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COMMENTARIES

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A challenge: The American Geriatric Society needs to address the lack of inclusion of older adults in new drug evaluation

Patricia W. Slattum PharmD, PhD[1] | **Janice B. Schwartz MD**[2]

[1]School of Pharmacy, Pharmacotherapy and Outcomes Science, Geriatrics Workforce Enhancement Program, Virginia Commonwealth University, Richmond, Virginia, USA

[2]School of Medicine, Department of Medicine, University of California, San Francisco, San Francisco, California, USA

Correspondence
Janice B. Schwartz, MD, University of California, San Francisco, 490 Illinois Street, Floor 08, UCSF Box 1265, San Francisco, CA 94143-1265, USA.
Email: janice.schwartz@ucsf.edu
Patricia W. Slattum, PharmD, PhD, Virginia Commonwealth University, Richmond, VA, USA.
Email: pwslattu@vcu.edu

We decry the lack of evidence for the efficacy or safety of new drugs for conditions common in older adults,[1–6] but this will not change until we participate in the process of new drug evaluation. Currently, neither the American Geriatric Society (AGS) nor its members play a role in the US Food and Drug Administration (FDA) evaluation process for new drugs for conditions that may be common in older adults. There are 17 Human Drug Advisory Committees that review safety and efficacy data contained in new drug applications and make recommendations to FDA regarding marketing approval.[7] Only three of 189 current voting members of these committees are affiliated with a Geriatrics Division or an Aging Center, and none of the three are geriatricians. In addition, while almost every other specialty of medicine is listed in the FDA Network of Experts Program: Connecting the FDA with External Expertise,[8] as are dental, engineering, pharmacy, and physical therapy disciplines, no geriatric- or gerontology-focused society appears. Our absence may partially explain the lack of information regarding older adults when new drugs are approved.

Geriatricians, geriatric pharmacists, and advanced practice geriatric nurses are experienced practitioners, researchers, and teachers of geriatric pharmacotherapy. In clinical practice, geriatricians and the interdisciplinary team constantly address issues related to choices of drugs, dosing for older adults, and safety and efficacy considerations in older adults with varying comorbid conditions and polypharmacy. The AGS publishes "Geriatrics at your Fingertips" that provides information to guide drug choices and dosing,[9] has co-sponsored a series of workshops (to identify gaps and research priorities for older adults with cancer, cardiovascular disease,[10] cognitive disorders, delirium, fatigue, frailty, inflammation, incontinence, osteoporosis, sleep disorders, and urinary tract disorders),[11] and includes research and educational sessions on medication-related issues at its annual scientific meetings. AGS also publishes criteria for drugs that may be potentially inappropriate for use in older adults[12] and AGS members currently lead efforts to reduce burdens and complications of polypharmacy, have established research center collaborative networks to increase enrollment of older adults in clinical research such as Claude D Pepper Older Americans Independence Centers,[13] the Research Centers Collaborative Network,[14] the US Deprescribing Network,[15] and the Palliative Care Research Cooperative,[16] among others. However, participation in the process of evaluating new drugs has been largely absent.

We recently co-chaired a public FDA Workshop, "Roadmap to 2030 for new drug evaluation in older adults, a virtual workshop." We invited members of AGS, academic colleagues, pharmaceutical industry and

patient representatives, the European Medicines Agency (EMA) and FDA, to speak.[17] There was consensus on several points:

1. Data obtained during clinical trials of new drug applications should be representative of the real-world population of older adults with the proposed treatment indication but currently it is not. There was no agreement on what would be "representative." One author (JBS) proposed that enrollment targets could begin with chronologic age and the proportion of older adults enrolled within specific age subgroups should mirror the prevalence of older adults within specific age subgroups of the clinical population with the disease/indication. This proportional enrollment was termed "Representative Patient Enrollment." In Figure 1, we present the age distribution of trial participants for several categories of new drugs approved for marketing in the United States during 2010–2020 and the age distribution of patients with the treatment indication in the United States. The age distribution imbalance is apparent and most marked for those over 80 years of age. Older adults (or children) would not be mandated for inclusion in trials for disorders that are not present in that age group and thus not exposing them to risk for no potential benefit to them or society. Exceptions in target sample sizes could be made to address safety or specific concerns for any group.
2. A second point of agreement was that representativeness should extend beyond chronologic age acknowledging the variability within any older age group. Importantly, patients with multimorbidity, such as multiple chronic conditions, polypharmacy, or with functional impairment or frailty, largely excluded from participation previously, should be included.
3. There was also consensus that trials should include patient-centered endpoints important to older adults (e.g., functional and cognitive endpoints).

Consensus on these principles is encouraging, but the key will be implementation. How can we as members of AGS help assure that truly representative older adults are enrolled in clinical trials of new drugs likely to be prescribed to older adults, that the clinical trials strike the right balance between the potential risks and benefits, and that the appropriate outcome measures are included? In other words, how can we act and participate to assure that the information needed to optimize use in older adults encountered in clinical practice is available at the time of drug approval?

We would like to encourage the society and its members to participate in the new drug approval evaluation process at the FDA and share currently missing geriatric expertise and data on older adults with the FDA (Table 1). Specifically, we call for AGS to take the following actions:

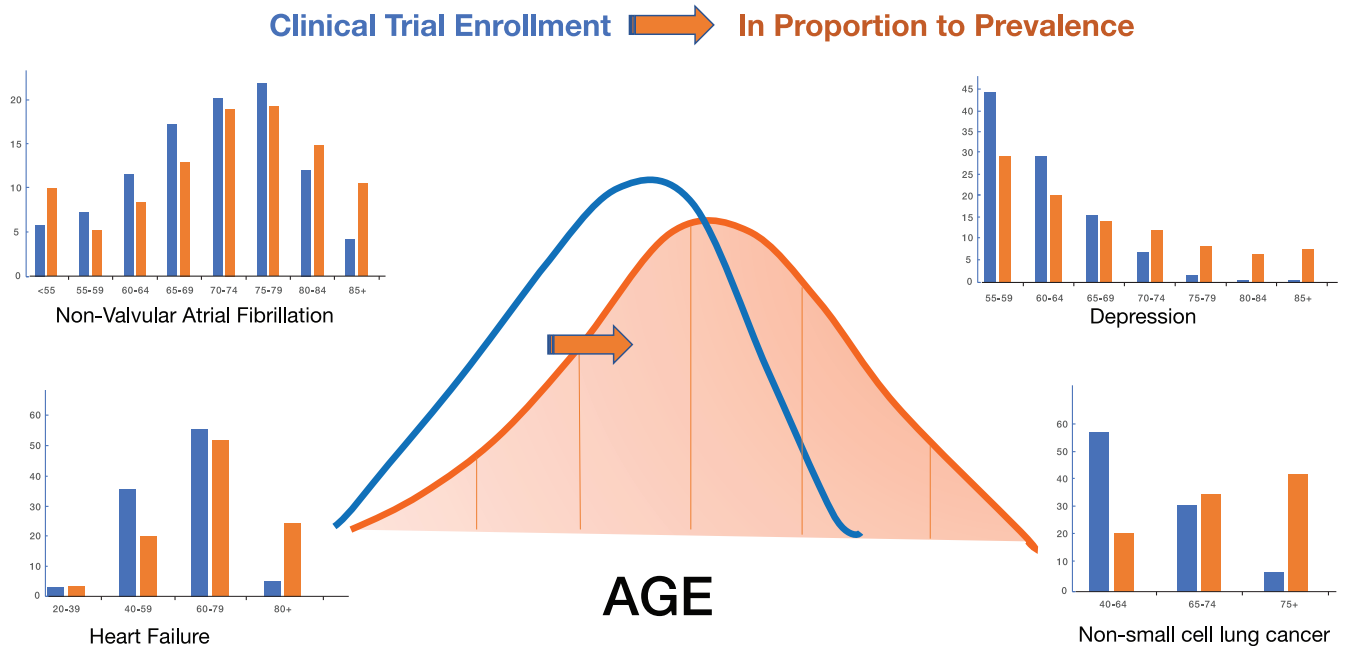

FIGURE 1 The figure presents percentages (on the y axis) in relation to age (on the x axis) for patient registration trial enrollment (in blue) versus the prevalence of the condition in community-dwelling older adults in the United States (in orange) for several disease categories of new drug applications approved for marketing by the Food and Drug Administration from 2010 through 2019. To achieve clinical trial enrollment that is proportional to the prevalence of the disease in the US population by age, enrollment generally needs to be shifted to include older age groups as indicated in the center schematic

TABLE 1 Call to action for the American Geriatric Society and its members

Participate
In the Food and Drug Administration advisory groups and expert panels
In design and performance of clinical trials that facilitate enrollment of representative older adults
Develop guidelines and standards/benchmarks
To define representative clinical populations of older adults for new drug evaluations
To define and measure geriatric conditions and syndromes to be used in new drug evaluations
To define and measure patient-centered outcomes
Advocate
For greater inclusion of older adults in clinical trials
For legislative action to improve drug evaluation for older adults

Participate

1. AGS should nominate qualified individuals for the FDA Advisory Committees. These committees have a major influence on the subsequent decisions by the FDA on whether to approve medications for marketing in the United States and whether to request or require additional premarketing or postmarketing studies. At the time of this writing, there are current vacancies on the Antimicrobial Drugs, Bone, Reproductive and Urologic Drugs, Gastrointestinal Drugs, Oncologic Drugs, and Pharmaceutical Science and Clinical Pharmacology Advisory Committees—all of which have relevance to the treatment of older adults.
2. AGS needs to join the list of societies in the FDA Network of Experts program so that participation will be ensured for the future.
3. AGS and its members should engage in research efforts and novel designs for clinical trials that allow for participation of older adults and enroll representative older adults in clinical trials of new drugs.

Develop guidelines, standards, and benchmarks

The society should compile and disseminate clinically relevant and operational definitions and best practices for participation of representative older adults in drug evaluation research. The workshop identified the need for criteria for:

a. *Definitions of "Older" Adult*. While it is recognized that chronologic age alone does not reflect the variability seen in older adults, it is likely to remain the administrative classification definition; thus, clinically meaningful definitions are needed. Current FDA Drug Trials Snapshots that present trial data for all new drug approvals[18] and current FDA-approved drug labels define geriatrics as people over age 65 years and this clearly is inadequate. The 2020 FDA Geriatric Labeling guidance[19] defines the geriatric population as patients aged 65 years and older and that additional age cutoff points may be needed for subgroup effectiveness and safety analyses (e.g., 65–74, 75–84, and 85 years of age and older) as recommended by the International Council on Harmonization.[20] However, these groupings are arbitrary, may not reflect ages at which changes in physiology become greatest, changes in physiology become more prevalent versus variable, and enrollment of people over age 85 years is likely too small to allow meaningful conclusions.
b. *Definitions of "Representativeness"*. Chronologic age subgroups for proportionality testing are a beginning but lack consideration of variability in function within subgroups. Before variability can be assessed, standardized definitions and measurements are needed. There are multiple definitions for many common geriatric conditions. Standardized definitions, preferred assessment tools, and definitions for meaningful changes in measures are needed for:
   - Polypharmacy
   - Drug burden assessments (for specific drug categories, systemic, and organ-specific adverse effects)
   - Multimorbidity
   - Function and frailty
   - Cognition
c. Prevalence estimates for diseases and geriatric syndromes across the older age span are needed to assess representativeness and inform sample size estimates for studies of new drugs. Nationally representative longitudinal studies of older adults are ongoing but new measures and collation of data across studies may be needed to provide a complete profile of older adults. Funding to expand, merge, and update datasets regularly is needed.
d. Guidance regarding inclusion and consequences for exclusion of older adults with comorbidities, functional limitations, and multiple comedications needs development.

Advocate

AGS and it members should join with other organizations advocating for greater inclusion of older adults in clinical trials and addressing obstacles.[21] Another possibility is to advocate for legislation, although legislation may take decades to enact.[22]

AGS should create a group to work on these issues soon if we are to have an impact on the direction moving forward as other societies, White Paper recommendations,[23] and the pharmaceutical industry are voicing recommendations without the input or expertise of geriatricians and interprofessional geriatric specialists. The COVID pandemic experience has highlighted the need for healthcare professionals caring for older adults to have a loud voice to ensure that older adults are represented in trials of new medical therapies that they are likely to receive. We realize these are only the first steps toward creating an ecosystem to optimize pharmacotherapy for older adults, but we need to act now or we perpetuate the problem.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Patricia W. Slattum and Janice B. Schwartz were involved in conception and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the manuscript.

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Sponsors had no role in the design, methods, subject recruitment, data collections, analysis, or preparation of the paper.

ORCID

Patricia W. Slattum https://orcid.org/0000-0003-1858-5089

Janice B. Schwartz https://orcid.org/0000-0002-5171-7824

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