Translational Article

Special Issue on Drugs and Drug Metabolism

Guest Editorial

Aging, Drugs, and Drug Metabolism

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In this series of special themed editions of the Journal of Gerontology Biological Sciences and Medical Sciences, reviews and commentaries have been solicited that focus on the basic biology, animal models, translational research, physiology, epidemiology, and public health aspects of aging. This emphasizes the multidisciplinary and translational nature of modern aging research. Aging is stochastic, complicated, and complex; therefore, answers and solutions to the problems of old age will almost certainly require multidisciplinary teams that focus on translating research into outcomes that are ultimately beneficial for humans. In this edition, our theme is “Drugs and Drug Metabolism.”

Why should biogerontologists be interested in drugs and drug metabolism? These topics would seem, superficially at least, to be very medical and quite distant from the cellular and physiological focus of most aging biologists. In fact, there are many reasons. First, old age is associated with marked changes in the response to medications, which are a consequence of age-related changes in both the pharmacokinetics and the pharmacodynamics of drugs. These pharmacological changes are caused by the same biological mechanisms as other aging changes, including altered gene expression, oxidative injury, and mitochondrial dysfunction (1). Thus, age-related changes in drug metabolism should be considered a typical phenotypic characteristic of the aging process. Generally, older age is associated with increased blood concentrations of drugs and altered metabolism, reduced effectiveness, and increased risk of adverse reactions for many medications (2). Impaired response to pharmacotherapeutic interventions is a critical yet underemphasized aspect of older age. If medical therapies for disease were effective in old age, then it would not matter that old age is the main risk factor for disease because diseases would still be able to be treated and cured. Impaired responsiveness to therapeutic interventions has such important implications for older people that we believe it should be included in any definition of aging.

Furthermore, by studying the effects of old age on drug disposition, we can gain insights into the aging process itself. For example, age-related changes in the hepatic microcirculation were discovered as a direct consequence of research into the effects of age on hepatic drug metabolism (3, 4). It should also be recognized that drug metabolism is only one aspect of the body’s response to any potentially toxic and disease-causing xenobiotic. Therefore, age-related changes in drug metabolism and elimination have much broader implications for disease susceptibility. For example, age-related changes in hepatic cytochrome P450 enzymes not only increase drug concentrations but also increase an older person’s susceptibility to pesticide neurotoxins thought to contribute to the risk of developing Parkinson’s disease (5).

There is no doubt that a major aim of many scientists involved in aging biology research is to develop pharmacological therapies that delay aging, diseases and disabilities that accompany older age, and, ultimately, improve function. Recent research into the biology of aging has led to an increased understanding of the cellular mechanisms and pathways involved in generating the beneficial effects of caloric and protein restriction on aging, such as the target of...
rapamycin, insulin/insulin-like growth factor-1, and sirtuins 
(6–8). Application of the principles of drug discovery to
these novel aging targets has led to major advances in ther-
apies to delay aging. Regardless of controversy, resveratrol 
and rapamycin have provided proof of principle that aging 
is plastic and a valid target for drug discovery (9, 10). Now, 
every scientist involved in biogerontological research could 
be considered to be undertaking early phase drug discovery 
that will potentially benefit all humans, not just those with 
a particular disease.

Notwithstanding the biological significance, the use of 
drugs in older people is one of the most important issues for 
the practice of medicine this century. However, it is also a 
minefield, often without a map. Old age is the main risk factor 
for disease, and accordingly, most medications are used in 
older people, and it is usually conceded that over one half of 
medications in the Western world are used by this group of 
patients. On one hand, it is well established that there are 
marked aging changes in drug disposition and harm from 
medications is much more common in older people. On the 
other hand, there is only limited evidence to support the effi-
cacy and safety of many medications in older people, espe-
cially frail older people taking multiple medications (2). Much 
clinical geriatric research is needed to provide the evidence 
base for the future quality use of medicines in older people.

In this issue, Le Couteur and colleagues (11) point out 
that recent dramatic advances in drug discovery technology 
have not been rewarded by any increase in the rate of dis-
covery of new drugs and drug targets for specific diseases. 
However, research into the biology of aging is generating 
many potential targets for drug development that may delay 
all age-related diseases and be used long term by the entire 
population—clearly “blockbusters” for the pharmaceutical 
industry. Aging biology is a promising arena for new drug 
targets—the current focus is on pathways that mediate the 
effects of caloric restriction (11). Rodents are the usual 
model for establishing the proof of principle for a novel 
drug target or drug for most diseases, and as Lebel and col-
leagues (12) have shown, this is also the case for aging. 
There are 68 genetic mouse models with either premature 
ageing or extended life span as well as dietary manipulation 
with caloric restriction and high-fat diets—these all provide 
useful models for testing new drugs. They emphasize that 
there are many phytochemicals, antioxidants, and other 
drugs that have been shown to be effective in delaying aging 
in rodents. Unfortunately, as Smoliga and colleagues (13) 
note in their review on resveratrol, there is often a very long 
journey in translating promising drug targets in experimen-
tal animal models to successful human medications that im-
prove outcomes. After the initial excitement associated with 
the discovery of a new target or drug, subsequent translation 
into human pharmacotherapy generates new and frustrating 
issues around intellectual property, non-availability of com-
mercially sensitive clinical trial data, and industry’s interest 
only in those chemicals that can be protected by patent. Ap-
parently, mundane (but essential) issues such as pharmaco-
kinetics, toxicology, regulatory requirements, and commercial interpretation of market opportunities deter-
mine go/no-go decisions in subsequent drug development.

The first three reviews in this series focus on the develop-
ment of therapies to delay aging and age-related diseases. 
Such therapies are likely to be used by people in mid-life 
before the onset of age-related pathologies and perhaps ex-
tended into later years. Of course, today most medication is 
utilized by older people for treatment of individual diseases. 
Lindley (14) concludes that it is a failure of modern medical 
research that clinical trials have rarely recruited those older 
frail participants with comorbidities who are most likely to 
be prescribed medication in real life. Lindley has been a 
strong proponent for the removal of age as an exclusion cri-
terion in clinical trials and for the recruitment of frail older 
population (or at least the measurement of frailty in partici-
pants) in clinical research. One of the key considerations in 
achieving optimal outcomes with medicines in older people 
is the effect of aging on drug metabolism. McLachlan and 
Pont (15) describe how biological aging processes influence 
hepatic drug metabolism and provide evidence that the age-
related changes in the liver decrease the clearance of any 
unbound drug and also influences variability in response to 
medicines in older people. In the absence of good quality 
evidence on prescribing in older people, the principles of 
pharmacokinetics can be utilized to individualize and hope-
fully optimize new and existing pharmacotherapies. How-
ever, too often we must rely on postmarketing data to 
determine whether medications are effective or indeed 
causing harm in older people. Hilmer and colleagues (16) 
report that pharmacoepidemiology can be used to assess 
medication outcomes in real-life older people and the chal-
gen of therein. Few clinical trials are appropriately designed 
to establish medication safety, and regulatory guidelines 
have yet to come to terms with the needs of older people. 
Therefore, it has been left to the pharmacoepidemiologists 
to provide us with evidence about risk, and less frequently 
efficacy, of medications in older people.

It is certainly an exciting time to be a scientist working in 
the field of geriatric pharmacology but perhaps not such a 
good time to be an older person needing pharmacother-
apies. There is an overwhelming and unmet demand, driven 
by demographic change, for effective and safe medications 
that delay aging and/or treat diseases in older people. As the 
reviews in this special issue indicate, the demand will only 
be met by a coalition including pharmaceutical industry, 
government regulators, biogerontologists, clinical pharma-
cologists, and of course older people themselves.

References
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