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CONSENSUS STATEMENT

Drug-Induced Liver Injury in the Elderly: Consensus Statements and Recommendations from the IQ-DILI Initiative

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Abstract

The elderly demographic is the fastest-growing segment of the world's population and is projected to exceed 1.5 billion people by 2050. With multimorbidity, polypharmacy, susceptibility to drug–drug interactions, and frailty as distinct risk factors, elderly patients are especially vulnerable to developing potentially life-threatening safety events such as serious forms of drug-induced liver injury (DILI). It has been a longstanding shortcoming that elderly individuals are often a vulnerable population underrepresented in clinical trials. As such, an improved understanding of DILI in the elderly is a high-priority, unmet need. This challenge is underscored by recent documents put forward by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) that encourage data collection in the elderly and recommend improved practices that will facilitate a more inclusive approach. To establish what is already known about DILI in the elderly and pinpoint key gaps of knowledge in this arena, a working definition of "elderly" is required that accounts for both chronologic and biologic ages and varying states of frailty. In addition, it is critical to characterize the biological role of aging on liver function, as well as the different epidemiological factors such as polypharmacy and inappropriate prescribing that are common practices. While data may not show that elderly people are more susceptible to DILI, DILI due to specific drugs might be more common in this population. Improved characterization of DILI in the elderly may enhance diagnostic and prognostic capabilities and improve the way in which liver safety is monitored during clinical trials. This summary of the published literature provides a framework to understand and evaluate the risk of DILI in the elderly. Consensus statements and recommendations can help to optimize medical care and catalyze collaborations between academic clinicians, drug manufacturers, and regulatory scientists to enable the generation of high-quality research data relevant to the elderly population.

Key Points

Elderly individuals make up the fastest-growing demographic of the global population.

Because elderly individuals are often excluded from clinical trials, safety data, including data on the risk of drug-induced liver injury, is a critical unmet need.

These consensus statements and recommendations were developed by the IQ-DILI Initiative to highlight what is currently known, and to outline key knowledge gaps to inform and promote new collaborations among academic clinicians, drug manufacturers, and regulatory scientists.

Extended author information available on the last page of the article

1 Introduction

According to World Population Prospects 2022 issued by the United Nations, 1 in every 6 people will be older than 65 years of age by 2050, up from 1 in 11 in 2019. This is the fastest-growing segment of the population and the number of people older than 65 years is projected to be greater than 1.5 billion people by 2050. A consequence of this demographic shift is an increase in prevalence of chronic illness on a global scale. It comes as no surprise that the median number of prescriptions and the use of herbal and over-the-counter medications are also on the rise in adults aged 65 and older [1].

Traditionally, elderly populations (the definition of 'elderly' is described below) are underrepresented in clinical trials of pharmaceutical and biological agents. Most trials employ arbitrary upper age limits as enrollment criteria. Exclusions of defined comorbidity, and

usage of certain concomitant medication, can contribute to the poor representation of elderly patients. As a result, drug-related safety data specific to this population cohort are often limited. Relying solely on post-marketing safety data pertinent to the elderly typically suffers from inconsistent reporting, the frequent absence of complete sets of diagnostic information, and consequently, an inadequacy of interpretation.

As a result, drug safety, as it pertains to elderly populations, is poorly developed. For potentially life-threatening safety events such as DILI, understanding risk is an unmet need as well as a high priority to achieve optimal risk assessment and management of the elderly both during drug development and in clinical practice. This summary of the literature creates a framework to evaluate the risk of DILI in the elderly and has the dual objectives of (a) highlighting our current state of knowledge and (b) outlining key knowledge gaps to inform and promote new collaborations among academic clinicians, drug manufacturers, and regulatory scientists. Our current appraisal of this field underlies the consensus statements and recommendations that are presented throughout the manuscript.

The IQ drug-induced liver injury (DILI) Initiative was launched in June 2016 under the auspices of the International Consortium for Innovation and Quality in Pharmaceutical Development (also known as the IQ Consortium) to reach consensus and propose best practices on issues surrounding DILI. The IQ Consortium is a leading science-focused, not-for-profit organization addressing scientific and technical aspects of drug development and is composed of 46 pharmaceutical and biotechnology companies. The IQ-DILI Initiative is an affiliate of the IQ Consortium, composed of 19 IQ member companies, focused on establishing best practices for monitoring, diagnosing, managing, and preventing DILI. This publication is based on an extensive literature review and the consensus achieved in structured discussions between IQ-DILI members and academic and regulatory experts in a public–private partnership. It explores recent advances and identifies gaps in our present-day understanding of DILI in the elderly, a fast-growing and vulnerable population. The consensus statements and recommendations provided below are based on currently available data and informed assessments by the authors and do not imply a regulatory mandate.

2 Literature Search and Consensus Working Group

The IQ-DILI's Elderly Working Group conducted a review of published academic literature dedicated to a series of topics associated with DILI in the elderly. The following databases were searched through March 2022: BIOSIS Previews®, Derwent Drug File, Embase®, International Pharmaceutical Abstracts, MEDLINE®, and SciSearch® (a Cited Reference Science Database). Articles focused on the following concepts were targeted: chronological age, biological age, and frailty in the elderly; age-related changes in the structure, physiology, and pathophysiology of the liver in elderly; and liver diseases and DILI in older adults. Additionally, we reviewed practice guidelines related to the elderly (not necessarily related to the DILI concept). Such broadly framed information was extrapolated to the concept of DILI; this aspect of the literature review was selective and did not reflect a comprehensive search of all published general practice guidelines. The consensus statements and recommendations below were established through structured discussions of the working group. They represent expert opinions of the authors, aided by the review of pertinent literature and practice guidelines.

3 Areas of Research

3.1 Definition of 'elderly'

There is no universally accepted medical definition of "elderly," although individuals aged 65 years and older are generally considered as elderly. The line between middle age and elderly, and the strata within elderly, are becoming increasingly blurred [2].

While there is no clear medical or biological evidence to support a universal age that marks the beginning of old age, many researchers and clinicians utilize age 65 years or older to define the 'elderly.' Because there is a widespread recognition that many individuals live robust lives well beyond age 65, more granular stratifications have been proposed. Persons between 65 and 74 years have been described as 'early elderly' and those over 75 years as 'late elderly' [2, 3], and more recently, divisions of youngest-old (65–74 years), middle-old (75–84 years) and oldest-old (≥ 85 years) have been suggested [4].

3.2 Chronological age

There is significant heterogeneity in the health status and outcomes of older individuals when analyzed using only chronological age. Some studies suggest that chronological age is a poor marker of the health impact of aging for a surprisingly large number of older people today, given that different people at the same age experience vastly different adverse health outcomes. As such, for a large proportion of older people, chronological age alone is not a strong predictor of these outcomes [5].

Nonetheless, chronological age is an independent risk factor for cognitive decline [6]. Impaired memory or difficulty reading, for example, may pose a risk for inadvertent overdose or drug–drug interactions (DDI) with polypharmacy. It may be that such variables associated with chronological aging directly increase the risk for DILI, rather than the chronological age itself.

Nevertheless, organs such as the kidney can be physiologically impacted by chronological age, as a physiological decline in renal function over time generally occurs, even in healthy aging subjects. Reductions in glomerular capillary flow rate and glomerular capillary ultrafiltration coefficient contribute to age-associated decreases in the glomerular filtration rate (GFR) [7]. Reduced GFR and renal clearance can influence the half-lives of many drugs, alter their pharmacokinetic profiles, and change hepatic exposure patterns to a parent drug and its metabolites.

Parameters of liver function as well as susceptibility of the liver to injury may also be impacted by chronological age. Decreased hepatic mass, blood flow and synthetic activity have been demonstrated, but their impact on drug metabolism and risk of DILI is not well understood [8]. In addition, aging leads to a decrease in liver cell regenerative responses to a damaging event, which significantly delays restoration of liver function after injury. Moreover, age-related changes in the liver seem to affect cellular repair responses to liver injury, increasing vulnerability for serious outcomes in the elderly population [8].

Finally, there are recognized changes in body composition that are associated with chronological age, including a decrease of muscle mass and an increase of fat mass; these changes may alter both the volumes of distribution and the half-lives of many drugs. As a result, both drug exposure-related thresholds of liver toxicity and health outcomes may be impacted by aging in the elderly [9].

3.3 Biological age

The physiological decline associated with aging affects cells, tissues, and organs of the body in many ways. It has proven difficult to identify biological measures that accurately stratify individuals of the same chronological age into different biological ages. Further research is required to understand the relationship between these biological biomarkers and DILI. Table 1 highlights some of the biological age biomarkers that are being studied and their outcome predictions.

The potential value of biological determinants of age is appealing and may be especially useful as modifying predictors of chronological age. Composite biomarker panels in combination with a clinical assessment may improve our understanding of biological age in older adults and risk of DILI.

3.4 Frailty and Frailty Indices

Frailty can be defined as a multidimensional condition that makes a patient, when exposed to a stressor, vulnerable to adverse health outcomes including disability, hospitalizations, institutionalization, and death [12]. It results from aggregate declines in multiple molecular, cellular, and physiologic systems [13]. Frailty is a dynamic state that may impact reliability to predict outcomes in an elderly individual. It can be present with or without concomitant comorbidity, blurring the line between aging and illness.

Frailty, when analyzed as a syndrome, is sometimes considered to be a functional equivalent of the 'elderly state.' This may consist of (1) a physical component, such as weakness and gait instability, which predispose individuals to accidental falls, injuries, and increased use of analgesics, and (2) a nutritional deficiency component, including hypoalbuminemia due to malnutrition, which alters the free fraction of drugs, and the relative immunocompromised

Table 1 List of biological age determined biomarkers under research and outcomes that have been measured [10, 11].

Biological biomarkers	Outcome prediction markers
Cytokines and circulatory markers of inflammation: IL-6, TNF-a, CRP	Mortality, grip strength
Network analysis of inflammatory markers	Mortality
Products of glucose metabolism (HbA1c, plasma glucose)	Mortality, cardiovascular disease
Adipokines	Mortality, frailty
Thyroid hormones	Mortality/morbidity
Vitamin D (bioavailable)	Mortality/multimorbidity, cognitive impairment
NT-proBNP troponin	Mortality/multimorbidity, cognitive impairment
DNA/chromosomal damage	Aging
Telomere length	Mortality
DNA methylation and repair	Cancer development and response to therapy
microRNAs	Aging

CRP C-reactive protein, *HbA1c* hemoglobin A1c, *IL* interleukin, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *TNF* tumor necrosis factor

state that occurs with aging, which in turn increases the risk of infection and the use of anti-infectives. There are also comorbid conditions associated with frailty such as depression, osteoporosis, osteoarthritis, and fatigue, which may increase use of additional classes of drugs and herbs. Therefore, assessment of frailty in older people, along with chronological and biological age, may be important in the overall assessment of DILI risk and outcome.

More than 40 operational definitions of frailty and their related tools have been proposed [14]. Four main models that operationalize the concept of frailty include the following:

- Fried Phenotypic Model: a widely used frailty tool; examines five domains, including muscle weakness, slow walking speed, low physical activity levels, unintentional weight loss, and self-reported exhaustion [15].
- Rockwood Frailty Index: a comorbidity index; defines nine degrees of frailty from very fit to terminally ill [16].
- FRAIL questionnaire: a five-item screening scale for frailty, including fatigue, resistance, ambulation, illnesses, and loss of weight [12, 17].
- PRISMA-7: a case-finding, seven-question tool to identify older adults with moderate-to-severe disabilities [17].

These models are not interchangeable; rather, they may be used as complementary assessment tools of frailty. Thus far, agreement across these instruments has been modest, standardization is lacking, and it has been difficult for clinicians to choose the most appropriate tool to assess frailty [18]. Future clinical trial designs might include one or more frailty indices, biological biomarkers, and chronological age strata ascertained prior to study drug treatment for use in post hoc safety analyses. Such an approach would be exploratory in nature, and only validated after meta-analysis of extensive aggregate data. DILI is a rare diagnosis and therefore a large data pool will be necessary to achieve this goal.

Consensus Statements and Recommendations:

– Chronological age, biological age, and frailty are all important criteria that help to define 'elderly.'
– While there is no chronological age threshold that inherently increases an individual's risk of DILI, it is recommended to stratify the elderly into 'early elderly' (age 65–75) and 'late elderly' (age > 75).
– Biomarkers of advanced biological age have not been validated for use in DILI prediction.
– Clinically useful frailty indices have been developed, but their applicability to DILI prediction and outcomes in older people has not yet been demonstrated. The predictive value of frailty with and without concomitant illnesses needs further investigation.
– Future studies should aim to combine one or more additional criteria of old age (biological age and frailty) with chronological age stratified into 'early elderly' (age 65–75) and 'late elderly' (age > 75) to optimize DILI prediction and prognostication.

4 Effects of Aging on Liver Function and DILI Risk

4.1 Structural and functional changes

Through animal and human research, there is growing evidence that the liver undergoes both macroscopic and microscopic cellular changes in the elderly. It has been recognized that both genomic and epigenomic modifications during aging can contribute to the dysregulation of mitochondrial function and nutrient sensing pathways associated with cellular senescence and low-grade inflammation. Multiple alterations of hepatocytes, sinusoidal endothelial, stellate, and Kupffer cells within the liver may occur that can result in disturbances of hepatic physiology. Nevertheless, laboratory tests of liver function have not been shown to decline significantly with age [19].

Furthermore, current evidence suggests that reduced hepatic blood flow in the elderly is a major factor underlying the observed age-related changes in liver weight and volume [8, 20, 21]. Macroscopically, during this process the blood flow may decrease as much as 25–40% [22, 23].

The relative impact of these macroscopic changes on DILI in the elderly is poorly understood. Measures of these changes together with DILI outcomes could contribute to establishing a multifactorial DILI risk profile. In conjunction with these changes, the metabolism of certain compounds or drugs may be reduced [22]. With the age-related decline in organ volume and hepatic blood flow, the clearance of drugs with high first-pass extraction by the liver (flow-limited) is expected to decrease by 40–60% compared with young individuals [24]. Of note, changes in the clearance of low extraction drugs may be difficult to demonstrate if they are significantly bound by serum-binding proteins [24].

Microscopic changes in the livers of elderly individuals are manifold, though the specific metabolic and functional consequences of these changes are not clear yet. These changes include the following:

- Increases of brown atrophy with the accumulation of lipofuscin (the end product of lipid degradation) [25].
- Reductions of endoplasmic reticulum in hepatocytes [22, 26].
- Increases of nuclear polyploidy and binucleation in hepatocytes [22].

- Increases in the volume and number of dense bodies (lysosomes, residual bodies) [26].
- Structural and immunohistochemical changes in the sinusoidal endothelium and space of Disse resulting in increased barriers to permeability [22].
- Increases of approximately 50% in endothelial thickness and similar reductions in the porosity and number of sinusoidal fenestrations, i.e., "pseudo-capillarization" [21].
- Reductions of telomere length in hepatocytes [23].

4.2 Biochemical Changes

The liver plays a pivotal role in the metabolic regulation of many carbohydrates, proteins, and lipids that have a wide range of physiological functions. Notably, the synthesis and corresponding serum levels of some of these hepatically synthesized molecules may decrease with age. For example, decreases of serum albumin from 39.7 g/L in non-elderly subjects to 35.8 g/L in elderly subjects were consistent with a decrease in serum levels of 0.54 g/L per decade [27, 28]. Total protein synthesis is reduced by about 50% in aging rodent livers and this may be associated with impaired hepatic degradation of proteins [22]. Bile flow and bile salt formation are also reduced by about 50% [22]. Antioxidant activity in liver tissue also appears to be reduced with age, as there are declines in the activities of hepatic superoxide dismutase and glutathione peroxidase, leading to a state of increased oxidative stress [26]. In one study, a 50% age-related reduction in DNA base excision repair activity was observed in mouse hepatocytes [29]. In another study, significant increases in the levels of oxidatively damaged DNA that were identified were not due to a reduced capacity for DNA repair, per se, but rather to an age-related increase in DNA susceptibility or cell sensitivity to oxidative stress [30]. As the hepatic clearance of some drugs can be reduced by up to 30% in the elderly, it is notable that CYP-mediated phase I reactions are more likely to be impaired than the phase II metabolic reactions that are generally preserved in old age [19].

Phase I reactions consist of enzymatically mediated chemical reduction, oxidation, or hydrolysis steps that act to convert lipophilic molecules in hepatocytes into more polar molecules. The decline in the metabolism of substrates through a reduction in phase I reactions in the elderly may reflect the structural changes that occur with aging that impede oxygen diffusion and hepatic capacity for phase I oxidation, as well as reductions in cytochrome P450 activities. Phase II reactions are marked by the enzymatic addition of hydrophilic groups to a parent drug molecule or to a toxic intermediate or metabolite formed in phase I reactions to gain a further increase in drug metabolite polarity [22, 31]. As mentioned above, phase II reactions are considered relatively unaffected by aging. However, there is emerging high-level evidence for an age-related reduction in the phase II metabolism of paracetamol, valproic acid, and naproxen, and low- to medium-level evidence for a reduction in the phase II metabolism of temazepam and lorazepam [24, 32]. Other studies suggest that frailty, rather than chronological age, may independently impact phase II metabolism. There is insufficient evidence to conclude that the alterations in phase I and phase II reactions play a major role in the development of idiosyncratic DILI.

Due to age-related decreases in hepatic drug metabolism and clearance, and combined with declining renal function, there is a potential for significant pharmacokinetic changes in advanced age. For drugs with a predominant hepatic route of clearance (e.g., > 50% hepatic metabolism), a dose-related risk of DILI may be observed in the elderly [33]. Therefore, dose adjustments based on changes in the hepatic metabolism of certain drugs may be critical when prescribing some drugs in the elderly.

A study comparing drug metabolism in 226 subjects by age found differences in the microsomal drug-metabolizing enzyme system. Although both hepatic drug clearance and P450 metabolism were significantly decreased in patients > 70 years of age compared with younger subjects ($p < 0.001$), no differences in these activities were observed by sex. Given the effects of age on drug metabolism, the authors of this study suggested that the inclusion of at least three age groups—young (< 39 years), middle-aged (50–69 years), and elderly (> 70 years)—should be considered in pharmacokinetic studies of new drugs in development [31].

It still remains unclear whether increased DILI risk in the elderly is predominantly related to a global impairment in liver clearance of all drugs or to specific changes in the pharmacokinetic properties of certain drugs and DDIs. Differences in patient selection, study design, and data validation procedures have likely contributed to the variability in measures of DILI risk associated with specific study drugs in the elderly. In addition to DILI risk profiles driven by the specific properties of individual drugs and the potential for certain DDI, patient comorbidities play an important role. For example, the presence of heart failure, passive hepatic venous congestion, and systemic circulatory disturbances are likely to impact the pharmacokinetic and pharmacodynamic behavior of a hepatically cleared drug.

Thus, the comprehensive integration of structural, functional, and biochemical changes in the liver associated with aging is complex and multifaceted. Achieving adequate knowledge in this area will require rigorous research using modern techniques, not only in basic but also importantly in clinical research. Future study is necessary to provide a more complete understanding of DILI in the elderly.

Consensus Statements and Recommendations:

- Numerous macroscopic and microscopic changes in liver anatomy, physiology, and biochemical function occur in the aging liver.
- Although there is some evidence that aged livers have reduced synthetic capacity, elderly individuals defined by chronological criteria alone cannot be assumed to have uniformly impaired drug metabolism or be at increased risk for DILI.
- The severity of DILI or the time to recovery may be increased in the elderly as a result of the reduced regenerative capacity following an acute liver injury.
- Future pharmacokinetic studies and/or computational modeling that will comprehensively characterize 'early' and 'late' elderly individuals with and without comorbidities during drug development would likely increase our understanding of the impact of aging on DILI.
- In the absence of randomized controlled trials demonstrating an increased risk of DILI on the basis of chronologic age, routine (down)titration of all prescribed medications to reduce the risk of DILI in elderly patients is not recommended. However, as it relates to pharmacokinetic and pharmacodynamic alterations (i.e., changes in hepatic and renal clearance, increased DILI susceptibility, etc.), selective (down)titration of certain drugs may be indicated.

5 Epidemiology of DILI in the Elderly

Available data on the incidence of DILI in the elderly are limited. Because of the relatively small number of clinical trials that have been designed to study DILI in the elderly (stratified as a defined group or subgroup), as well as inconsistencies in the definition of 'elderly,' there are few comprehensive datasets or statistical analyses available to conduct dedicated studies in this population. The current literature provides estimates on the basis of inference from larger cohorts that include all age groups [34]. Despite this, some clinical studies have attempted to characterize liver injury in enrolled elderly patients. Relevant findings in these studies stratified by age, sex, and pattern of liver injury are highlighted in Table 2.

The clinical outcomes of DILI in the elderly are also of interest. As many elderly patients are excluded from clinical trials, and because DILI is considered a rare diagnosis, most drug development databases composed of thousands of patients exposed to a new drug will show no cases. Some data are available for marketed drugs. In the prospective Spanish DILI Registry, analysis over a 20-year time period showed that older patients with cytolytic DILI have worse outcomes, and the increased prevalence of comorbid conditions in older patients may contribute to increased severity of DILI [35]. Another study showed longer periods of hospitalization and a greater need for intensive treatment with increased age [3].

Consensus Statements and Recommendations:

- Epidemiologic evidence of DILI in the elderly has been derived from large cohorts that span multiple age groups. Epidemiologic evidence does not consistently support age > 65 years as a general risk factor for DILI.
- Gender has not been identified as a risk factor for DILI in the elderly.
- Elevated alkaline phosphatase levels may be secondary to non-hepatic etiologies (e.g., osteoporosis; biliary or pancreatic disease) and should be considered when evaluating for possible DILI in an elderly patient.
- Elderly patients often exhibit a cholestatic DILI phenotype and the oldest group is more likely to be female. These characteristics should be considered when evaluating biomarkers and when stratifying age-defined DILI populations.
- There is a specific need to develop biomarkers for cholestatic forms of DILI that may improve our diagnostic and prognostic capabilities and the way liver safety is monitored in clinical trials.

6 Impact of Polypharmacy and Inappropriate Prescribing in the Elderly

6.1 Polypharmacy

Polypharmacy with multiple prescribed medications in the elderly appears to be a common finding in the studies summarized in Table 3.

According to a literature review, data from international DILI registries urge further investigation into whether the elderly population is truly at an increased risk of developing DILI or whether the age-related liver safety profile reflects inappropriate levels of drug exposure, polypharmacy, and/or potentially toxic DDI. A higher frequency of chronic illness associated with aging, resulting in the utilization of multiple medications, can contribute to drug-exposure-related toxic outcomes. The elderly may be especially susceptible to adverse liver events associated with inappropriate drug dosing and DDIs because they have diminished hepatic blood flow and declining phase I hepatic enzymes, resulting in slower hepatic drug clearance and age- and disease-related reductions in renal clearance [51].

Functional disability related to aging has been investigated as a contributing factor to polypharmacy, including prescription and over-the-counter (OTC) analgesics. For example, the 2010 Women's Health and Aging Study reported that the majority (60%, $n = 590$) of 975

Table 2 Summary of studies evaluating the epidemiology of DILI in various age groups

[Ref]/Country	Study design/(period)	Number of patients with DILI/age	Findings
[36]/(France)	A population-based study, 1997–2000	34 confirmed DILI cases in 81,301 patients	Patients < 49 years: female/male ratio: 0.86 Patients ≥ 50 years: female/male ratio: 2.62
[37]/(Spain)	Prospective study 10-year period, 1994–2004	$N = 461$	45% (207/461) of DILI cases in patients aged ≥ 60 years No differences in gender *Pattern of injury* Intrinsic mechanism: younger patients; idiosyncratic: older patients ($p < 0.0001$) Hepatocellular injury (58%) was inversely correlated with age ($p < 0.0001$) and with worse outcome (Cox regression $p < 0.034$)
[38]/(Sweden)	Retrospective study 10-year period starting in 1995	$N = 87$ Median age: 58 years	56%: females *Pattern of injury* Hepatocellular injury: 48% Median age 53 years (range: 38–66); more frequent type in women (63% versus 29%) Cholestatic injury: 40% Median age 60 (range 48–70) years; more frequent type in men Mixed pattern of injury: 12%
[39]/(Spain)	1994–2007 (same registry as previous study 26)	603 patients with DILI; mean age 54 (range 13–88) years; 51% men	Highest incidence between 40–49 years and 60–69 years 46% of cases in patients aged > 60 years Male predominance ($p = 0.009$); < 60 years: female predominance *Pattern of injury* Cholestatic injury in older age (OR 1.025, $p = 0.001$); male/female ratio: 1.7 Hepatocellular injury in younger age (OR 0.983, $p = 0.002$)
[3]/(Japan)	Retrospective study January 1997–December 2007	142 cases of DILI confirmed in 396 patients with acute hepatitis; mean age: 60 ± 18 years	Age group < 65 years: 54% Age group 65–74 years: 26% Age group ≥ 75 years: 20% Men: 41.5% Women: 58.5% *Pattern of injury* ≥ 65 years: higher incidence of eosinophilia, higher frequency of autoantibodies, and higher number of concomitant medications Chronic cardiac failure occurred in 22.7% of cholestatic liver injury versus 1.8% in hepatocellular type and 0% in mixed type Overall: 77.5% (110/142): hepatocellular type 15.5% (22/142): cholestatic type Age ≥ 65 years: 63.6% of cases (14/22) 7.0% (10/142): mixed type

Table 2 (continued)

[Ref]/Country	Study design/(period)	Number of patients with DILI/age	Findings
[40]/(Iceland)	Population-based study 2010–2011	$N = 96$; median age 55 years	Women: 56% *Pattern of injury* Cholestatic/mixed type injury Increased with age 60 years versus 46 years, $p = 0.004$). 63% women had cholestatic/mixed injury versus 48% men Incidence of DILI increases with age. The mean prescription rate of drugs was also found to increase with age.
[41]/(Spain)	Retrospective analysis of a safety reporting database	Ages 0 to > 65 years	*Pattern of injury* Age ≥ 65 associated with 33% reporting of cholestatic injury compared with 27% in ages 18–64 and 22% ages 0–17 ($p < 0.01$)
[42]/(United States)	US DILIN Prospective DILI registry 2004–2013	1257 patients with suspected DILI, of which 1091 were adjudicated; 899 cases of definite, likely, or probable DILI	*Pattern of injury* Hepatocellular DILI: younger patients, lower likelihood of clinical jaundice Cholestatic DILI: older patients, higher levels of ALP (elderly 36% versus younger patients 21%)
[43]/(Korea)	Retrospective study 2003–2014	$N = 1835$; mean age 66 ± 16.5 (SD) years	Age ≥ 65 years: 57.4% Men: 55.8% Men: 64.4% in ≥ 65 years and 35.6% in < 65 years Women: 58.6% in ≥ 65 years and 41.4% in < 65 years *Pattern of injury* In 1420/1835 patients, clinical pattern was defined with a predominance of the cholestatic pattern (62.0%) more often observed in elderly (38.3% in age group ≥ 65 years compared with 23.7% in age group < 65 years) and in men (29.5% compared with 22.1% in women). Hepatocellular pattern occurred in (23.2%) and mixed pattern occurred in (13.7%) Cholestatic type of injury was frequently observed
[4]/ (Spain)	Prospective study from the Spanish DILI Registry	$N = 882$; 'young-old' (65–74 years); 'middle-old' (75–84 years); and 'oldest-old' (≥ 85 years)	Female predominance (> 85 years) *Patten of injury* Jaundice, DILI severity, and hospitalization more prevalent in the older age groups (> 65 years) Older patients with DILI have an increasingly predominant cholestatic phenotype across a range of culprit drugs: amoxicillin-clavulanate, atorvastatin, levofloxacin, ibuprofen, and ticlopidine
[44]/(Spain)	Prospective evaluation	$N = 458$; mean age 76.6 years	Female (54.4%) *Pattern of injury* Hepatocellular phenotype 53.3%

Table 2 (continued)

[Ref]/Country	Study design/(period)	Number of patients with DILI/age	Findings
[35]/(Spain)	Prospective Spanish DILI Registry. Analysis over a 20-year time period (1994–2018)	$N = 843$; mean age 54 years	Male (52%) *Pattern of injury* Hepatocellular injury associated with younger age Liver-related mortality more frequent in patients > 65 years with hepatocellular injury

ALP alkaline phosphatase, *DILI* drug-induced liver injury

community-dwelling disabled women were taking at least five medications, and 11.8% ($n = 115$) were on ten or more medications, with an average of 3.9 prescription and 1.9 OTC medications [52]. Specific factors contributing to and associated with polypharmacy include:

- Difficulty with activities of daily living.
- Subjective breathlessness.
- Overall subjective perception of poor health superimposed on objective chronic comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), advanced cardiac disease, and cancer.

The prevalence of moderate- to high-risk DDIs has been reported to be as high as 74% in older women; 63% of these DDIs involved non-steroidal antiinflammatory drugs (NSAIDs) [51]. A Japanese study evaluating DILI in 142 predominantly hospitalized elderly patients (defined as individuals over 75 years of age), found that they were taking significantly more concomitant medications at the time of liver injury compared with younger patients (age < 65 years) [3]. The association of polypharmacy with DILI risk may not be directly proportional to the number of concomitant medications, but rather to the specific drugs or types of drugs marked by significant DILI liability that are taken together. Unnecessary polypharmacy, in this regard, may be mitigated in the elderly [53]. The use of predictive DDI tools could prove very effective for this purpose [54].

6.2 Inappropriate Prescribing in the Elderly

Further complicating the challenges of polypharmacy and potential DDIs are patterns of inappropriate prescribing by healthcare providers. The literature provides substantial evidence that elderly patients are at increased risk for inappropriate medication prescribing. Up to 24% of community-dwelling and 40% of nursing home residents in the USA were reported to regularly receive at least one potentially inappropriate medication according to the Beers criteria, which provide guidance regarding medications that should be avoided in most elderly patients [55, 56]. These criteria have been used to assess the prevalence and trends in prescribing by providers of a list of 20 potentially inappropriate medications for older people [57].

Risk factors for inappropriate prescribing include:

- Older age.
- Polypharmacy and a high comorbidity burden.
- Multiple attending physicians and pharmacists who access different databases.

In a large retrospective epidemiological study using the modified Beers criteria, the authors found that some 23.5%

Table 3 Summary of studies identifying polypharmacy in the elderly

[Ref](Country)	Study design (year)	Age of patients (*n*)	Findings
[45]/(USA)	Cross-sectional study (2002)	Non-institutionalized ≥ 18 years ($n = 2590$)	Increased usage of all medications with advancing age, the highest prevalence of drug use being in women ≥ 65 years, with 12% taking ten or more medications and 23% taking ≥ five prescription drugs [45].
[46]/(United Kingdom)	Survey (2003)	Age ≥ 50 years ($n = 221$)	A mean number of 2.26 prescription drugs and 5.91 herbal/nutritional supplements [46].
[47]/(USA)	Cross- sectional study (2004)	Nursing home residents ($n = 13{,}403$)	The prevalence of polypharmacy (> 9 drugs) was approximately 40%; the mean number of medications taken was 8; median was 7. Higher odds for polypharmacy: female gender, white race, having Medicaid as primary payer, > 3 comorbidities [47].
[48]/(The Netherlands)	Prospective descriptive study (2005)	Age > 65 years; use of ≥ 1 drug ($n = 120$)	With a mean age of 82.3 years, 94.2 % were prescribed more than one drug and 73.3 % were prescribed ≥ 4 drugs [48].
[49]/(Germany)	Cross-sectional study (2007)	Age > 70 years ($n = 466$)	75% received at least four drugs, and 25% received ≥ 5 drugs [49].
[40]/(Iceland)	Prospective cohort study (2013)	DILI cases ($n = 96$)	Increasing number of mean prescription rate by age groups: 40–59 years: 2.4; 60– 69 years: 4.8; 70–79 years: 7.3; ≥ 80 years: 9.3 [40].
[1]/(USA)	Survey-based study (2015)	≥ 65 years in the National Health & Nutrition Examination Survey (1988–2010) ($n = 13{,}869$)	Prescription medication use among older adults (≥ 65 years) in the USA had increased dramatically from 1988 to 2010 and use of ≥ 5 medications had tripled to nearly 40% during the study time span [1].
[50]/(USA)	Cross- sectional study (2016)	Medicare elderly patients discharged to skilled nursing facilities ($n = 154$)	Overall average of 14 (± 4.7) medications prescribed in the Medicare population (≥ 65 years) [50].
[44]/(Spain)	Prospective study (2021)	$N = 458$; mean age 76.6 years	Polypharmacy was common, 86.8% were taking > 4 drugs; 39.7% were taking > 10 drugs [44]

of non-hospitalized people aged 65 years or older, or 6.64 million Americans, received at least one of the 20 contraindicated drugs [58]. While 79.6% of people receiving potentially inappropriate medications received only one such drug, 20.4% received two or more. Of the list of 20 contraindicated drugs for the elderly, the study estimated that 70,000–80,000 seniors have received dangerous combinations such as diazepam and propoxyphene, amitriptyline and chlordiazepoxide, and an NSAID in combination with dipyridamole. In another population-based, cross-sectional survey of 892 community-dwelling elderly patients, 23.9% ($n = 213$) used one or more drugs identified by the Beers criteria, and when compared with patients using no inappropriate drugs identified by those criteria, were more likely to be prescribed multiple drugs (OR 1.07, 95% CI 1.01–1.13) [57, 59]. The most frequently prescribed inappropriate medications marked by Beers criteria were long-acting benzodiazepines, dipyridamole, propoxyphene, and amitriptyline. Univariate analyses suggest the confluence of other risk factors for inappropriate medication use, including female gender and age 80 years or older [60].

Consensus Statements and Recommendations:

- Polypharmacy and inappropriate prescribing are common, well-recognized, and avoidable hazards for the elderly population and demand sustained attention of pharmacists and prescribers.
- Most studies of polypharmacy in the elderly are based on US or Western European cohorts, and further studies in non-Western populations are an unmet need.
- Polypharmacy in the elderly is a multifactorial phenomenon and is impacted by both patient behavior and prescriber practice.
- New tools are needed to consistently identify prescriptions across databases and to better inform providers and pharmacists of an elderly patient's DILI risk profile associated with inappropriate prescribing.

7 Specific Agents Associated with Increased DILI Incidence in the Elderly

Although epidemiological data have not convincingly shown that elderly people are more susceptible to DILI than younger people overall, DILI might be more common in older people taking specific drugs [9, 42, 61].

An exhaustive list of all agents implicated in causing DILI, particularly in the elderly population, is beyond the scope of this article. Of note, many classes of cancer treatments are associated with DILI, but liver safety data specific to the elderly are limited. Agents that are both frequently used by the elderly population and associated with a higher risk of DILI when used in this age group include some antimicrobials, analgesics including NSAIDs, cardiovascular drugs, and herbal supplements [3, 42]. Selected drugs belonging to these categories are described in the following section for illustrative purposes.

7.1 Anti-infectives

Anti-infectives represent the category of drugs that most frequently cause DILI in the general population and in older patients as well. In this category, DILI is most commonly caused by agents such as amoxicillin-clavulanate, isoniazid, nitrofurantoin, and flucloxacillin [9, 62–66].

7.1.1 7.1.1 Nitrofurantoin (NFT)

NFT is a commonly prescribed antibiotic for the treatment of urinary tract infections. According to some studies, DILI due to nitrofurantoin is more frequently observed in women and the elderly, probably reflecting higher use of this agent in these demographic groups due to the conditions for which these agents are usually prescribed [64, 67–69].

Liver injury due to NFT exhibits two patterns: one occurs with short-term exposure and the other due to long-term exposure. Liver injury due to short-term NFT exposure resembles acute hepatitis, whereas liver injury associated with long-term exposure resembles chronic hepatitis, characterized by moderate-to-severe hepatic inflammation, necrosis, and fibrosis.

An autoimmune-like phenotype is frequently observed with cases of long-term use of NFT. Most patients present with hepatocellular injury, often after a prolonged time to onset, which can be > 1 year. Cholestatic injury is also possible and can be associated with fatal outcomes [63, 64, 67–69]. Morbidity rates of liver disease complications with long-term use of NFT (cirrhosis, 38%) and mortality (12%) are high [69].

Presence of the DRB1*11:04 allele appears to increase the risk of NFT hepatotoxicity, particularly after long-term exposure, although the positive predictive value of this HLA allele was not replicated in the DILIGEN/iDILIC cohort [70, 71].

7.1.2 7.2.1 Anti-tuberculosis (TB) Drugs

A large proportion of anti-tuberculosis (TB) drug use occurs in the age group 65 years and older: the highest rate of TB in the USA is noted in this age group [72].

According to a systematic literature review, when exposed to anti-TB treatment, patients older than 60 years had a significantly higher risk of hepatotoxicity than younger patients

[72]. Patients aged ≥ 60 years are 2.6–3.5 times more likely to have DILI [73, 74].

The detoxification pathway NAT-2 is the main route for metabolism of anti-tuberculosis drugs; in a genome-wide association study (GWAS) of isoniazid-containing anti-TB drug regimens, ultra-slow NAT2 metabolizers are at higher risk of DILI [75, 76].

Alcohol consumption, malnutrition, viral hepatitis, and human immunodeficiency virus (HIV) co-infection are known risk factors for anti-TB drug toxicity, and other concomitantly administered drugs in the elderly may at least partially contribute to the increase in DILI risk in this age group [9].

7.1.3 7.3.1 Amoxacillin/Clavulanate (AC)

Several studies have found an association between amoxicillin/clavulanate and acute DILI [62, 77].

Prolonged therapy and older age, including the 65–75-year, 75–85 year, and > 85 year age groups were associated with cholestatic/mixed type of liver damage, while shorter treatment duration and younger age were associated with hepatocellular damage [4, 62].

Genetic factors, HLA class I allele A*02:01, and HLA class II alleles DRB1*15:01-DQB1*06:02 have been associated in GWAS with amoxicillin-clavulanate hepatotoxicity [78].

It is hypothesized that the cholestatic pattern of liver injury observed in older patients is due to slower drug elimination related to advanced age and retention of AC in the body, which would allow for a prolonged exposure of the bile duct cells to the drug metabolites through canalicular excretion. It might then trigger an immune response against haptenized duct cell proteins, and consequently, a periductular inflammatory reaction [62, 79].

7.2 Analgesics

7.2.1 7.1.2 Paracetamol (Acetaminophen)

Although most intentional and unintentional overdoses are in younger age groups, the frequency of use in the elderly, and the association with fatal DILI, deserves mention. Although hepatotoxicity due to paracetamol is dose related, cases of hepatotoxicity in older patients using therapeutic doses of paracetamol have been reported [80]. Overall, the risk of hepatotoxicity from therapeutic doses of paracetamol in older people is not well defined [9]. The pharmacokinetics of paracetamol may change with age: studies have shown increased exposure to paracetamol in older patients due to factors including decreased clearance and volume of distribution [81, 82].

Risk factors common in the elderly, such as low body weight, cardiac, pulmonary, or renal insufficiency, chronic liver disease, acute or chronic alcohol consumption, cachexia, prolonged fasting, consumption of drugs that induce hepatic metabolism such as isoniazid and classical antiepileptics, can also predispose this patient population to higher incidence of adverse effects of paracetamol.

It is prudent to consider whether a lower dose and/or reduced frequency of administration of paracetamol might be appropriate for frail people with low body weight and other risk factors for hepatotoxicity [80].

7.2.2 7.2.2 NSAIDs

NSAIDS are one of the most commonly used drug classes: their use is reported to increase with age as many chronic pain conditions, such as osteoarthritis, are age related. The occurrence of serious, overt hepatic injury caused by NSAIDs as a group is well under 0.1%; however, with upwards of 20 million patients in the USA taking NSAIDs on a regular basis, this may translate into a substantial number of affected individuals [83].

Diclofenac: aging has been associated with an increased risk of hepatotoxicity due to diclofenac use. However, when diclofenac is used at therapeutic doses, this toxicity cannot be totally explained by the decrease in hepatic clearance observed in old age [84]. It has been suggested that diclofenac may cause mitochondrial dysfunction in individuals with a reduced mitochondrial biogenesis due to the aging process, which could explain the increased susceptibility of the elderly to develop diclofenac hepatotoxicity [85]. Ibuprofen has many indications for use in an elderly population but has only rarely been associated with hepatotoxicity, including liver transplantation and death [86].

7.3 Herbal and Dietary Supplements (HDS)

There have been an increasing number of reports of liver injury associated with the use of HDS, likely due to easy access to these products and the belief among consumers that they are safer or more effective than conventional medications. They are currently used for weight loss, body building purposes, or to improve well-being or reduce symptoms of chronic diseases, among other reasons. Registries suggest that HDS-induced liver injury (HILI) may be responsible for at least 1 in 5 DILI cases, with the incidence of HDS-induced hepatic damage ranging from 1 to 3 cases per 100,000 per year [61, 87, 88]. Data from a cross-sectional British survey indicated that the average respondent older than 50 years of age takes 2.3 prescription drugs and 5.9 dietary supplements, of which 2.7 are herbal medicines [89].

The list of potential herbal hepatotoxins is long, and in the absence of reliable data on the content of herbal supplements, obtaining an accurate history of HDS use is very important, and all regularly used products should be considered when DILI is suspected. It is important to note that users frequently fail to report the use of such products to their healthcare providers [90]. To date, however, little is known about the existence or characteristics of HDS-induced liver injury in the elderly population. Further research about the specific mechanisms of liver injury, as well as more information on their pharmacodynamics, is needed. The individual's genetic background is emerging as a contributing factor in predisposing people to injury from natural products. Recent reports have demonstrated an association of the HLA-B*35:01 allele with liver injury due to *Polygonum multiflorum*, *Camellia sinensis*, and more recently, with turmeric [91–93].

Consensus Statements and Recommendations:

– Evaluation of commonly used medications has not shown that elderly people are generally more susceptible to DILI than younger people; however, DILI may be more common in older people taking specific medications.
– Changes in pharmacokinetics of drugs due to the decline in physiological functions with aging can alter the volume of distribution and half-life of certain drugs. In some cases, these changes could potentially affect the risk of DILI.
– The use of HDS is increasing worldwide and use in the elderly has been suggested, though usually underreported. A complete history of medication use, including HDS, should be taken when investigating a case of DILI. Many HDS products have been implicated in DILI cases. Further research about the incidence of DILI after use of these agents in the older population, as well as the mechanisms involved, is needed.

8 Current Regulatory Approaches in Clinical Trials

8.1 Regulatory Considerations and Guidance

As a result of too few patients older than 75–80 years of age being included in most trials, there is growing concern regarding the lack of knowledge or information concerning DILI and adverse events in the elderly population. Up to 35% of published trials excluded older people solely on the basis of age [94].

Regulatory authorities, including FDA and EMA, recognize the importance of addressing knowledge gaps in assessing DILI in the elderly. In 2012, the FDA published a *Guidance for Industry, E7 Studies in Support of Special Populations*: *Geriatrics* to highlight the importance of including the geriatric population in clinical development programs [95]. The guidance states the following:

- Elderly patients with comorbidities or those taking concomitant therapies should not be automatically excluded from enrollment in clinical trials, because including such patients in trials provides data that may help to detect DDIs.
- Eligibility criteria must be closely examined so as not to exclude patients who would be considered vulnerable or 'frail.'
- Stratification of data for the elderly into subgroups should be included in analyses; this will allow for more consistent reporting of safety profiles in the elderly, particularly the oldest-old group.
- Older adults should be allowed to enroll in clinical trials if they are stable, can be safely and ethically enrolled, and are willing to participate.

Efforts are underway to encourage sponsors to take a more rational approach to establishing eligibility criteria for clinical trials with the relaxation of specified laboratory test results as requirements for enrollment if safety is not compromised. Finally, the FDA's frequent communications with sponsors during the product development process provide interactive opportunities to remind sponsors to consider the age range and other demographic characteristics of the intended treatment population early in the development of clinical trials [96–98].

As stated in the current ICH E7 guidance, an applicant developing a drug for marketing should provide estimates of the prevalence of the disease to be treated by age as well as examination of the age distribution of usage for other drugs of the same class or for the same indication. This will characterize the expected use of the drug and should influence the number of geriatric patients to be included in the marketing application. The current guidance states, "for drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow for detection of clinically important differences" [97].

The value of product labels with sufficient information for the management of elderly patients should be considered during trial design. As a key rationale to include older adults in clinical trials, adequate labeling of liver safety information should reflect clinical trial experience as well as post-marketing experience in countries where the drug has previously been approved, if available, for the intended treatment populations of the study drug. In some cases, adequate representation of elderly patients in clinical trials may be challenging, and further safety data collection in a post-marketing setting may be required. However, the adequacy

of, and the need for, clinical trial safety data in the elderly population should be considered during drug development and discussed in the marketing application submission. Post-marketing commitments or requirements may be less urgent if these populations are adequately evaluated during clinical trials. Collection of data from all possible sources should be optimized, because adverse reactions in elderly populations are generally underreported. As stated in one article, "Sponsors and collaborative groups may also work to harness 'big data' and explore real-world outcomes to answer questions about practice patterns and safety in older adults after drug approval" [98].

The EMA and its Committee for Medicinal Products for Human Use (CHMP) commented on their perspectives on the adequacy of guidance for the elderly population regarding medicinal products for human use [99]. On the basis of their review, they proposed the following goals in drug studies in the elderly:

1. To increase the number of elderly patients participating in the clinical development programs, requiring a proportion of the efficacy and safety database to include elderly populations in relation to the indication, and mirroring the target population
2. To consider the minimum requirements for two different age groups: elderly and very elderly
3. In relation to the PK-specific considerations, an adequate representation of elderly in the efficacy and safety database would integrate and complete the PK requirements (via population PK)

There have been increasing efforts by regulatory agencies to enable the generation of high-quality research data in elderly populations.

- The FDA recommendations address the need for adequate representation of geriatric study subjects, including those with concomitant diseases, frailty state, and age subcategorization. The FDA also calls for enhanced formal PK measurements to evaluate different age-related parameters during drug development.
- The EMA encourages the inclusion of elderly patients reflective of the target population (and therefore is similar to FDA guidance), with recommendation for the stratification of the elderly target group into the two subgroups, the elderly and very elderly, and for inclusion of geriatric groups in both drug development efficacy and safety databases.
- The ICH E7 supports strategic planning of scientific evidence with clinical trials within this specific target (i.e., disease) population concerning drugs that are likely to be used by the elderly.

Studies conducted of the elderly should be aimed at safeguarding the rights and safety of elderly patients while adequately investigating their efficacy and safety in this population, analogous to the requirements for pediatric studies.

In addition to not excluding subjects solely on the basis of age, communications from regulatory authorities that support the appropriate inclusion of elderly individuals (particularly in those with multiple chronic conditions) in clinical trials are highly valued [100]. The use of adaptive strategies in clinical trial design that allow for special drug dosages in the elderly and more stringent and personalized safety monitoring rules on the basis of participants' unique characteristics, such as age, low body weight, concomitant medications, and comorbidities, might also improve participation of older patients in clinical trials.

8.2 Existing Status of Clinical Trials and Proposals for Industry

Case-control studies or other appropriate study designs may prove to be a highly pragmatic method to assess adverse drug effects in elderly populations in the future [97].

The evidence base for prescribing drugs to older people is small and clearly disproportionate to the number of prescriptions written for this group. In the year 2000, only 3.45% of 8945 randomized controlled trials and 1.2% of 706 meta-analyses reflected study populations over 65 years old [101].

Consensus Statements and Recommendations:

- On the basis of the FDA's and EMA's guidance, there is a need for adequate representation of elderly populations in clinical trials, including those with concomitant underlying diseases and/or frailty.
- Analysis of data obtained from specific age groups, including the elderly, is desirable.
- Drugs that are commonly used in the elderly require DDI studies, as this will help navigate the polypharmacy and comorbidity paradigm in this population.

9 Discussion

To meet the needs of the fastest-growing segment of the population, the elderly, a partnership of academic clinicians, industry investigators, and regulatory scientists is urgently needed. The framework for a collaboration is shaped by this summary of the current literature and identification of knowledge gaps. It is evident that these gaps are considerable and must be addressed in further studies.

Several high-level observations serve as a basis for these consensus statements and recommendations:

- Chronological age, biological age, and frailty are each essential characteristics in defining what it means to be 'elderly' and in the study of DILI during aging.
- Physiologic and biochemical changes in livers of old individuals have been observed, although the clinical implications of these changes are not fully elucidated.
- The predominance of a cholestatic DILI phenotype in the older population is consistent across several prospective and retrospective clinical studies. Thus, when an elderly patient presents with cholestatic abnormalities, DILI should be considered among the list of potential causes of injury.
- Inappropriate prescribing practices, comorbidities, and polypharmacy, compounded by multiple care providers and pharmacy sources of medications, are common in the elderly, and new tools to assure provider awareness are needed.
- Anti-infectives, analgesic medications, and herbal products are the most frequent culprits in this population.
- Guidance published by the FDA and EMA has created a roadmap for industry to foster a more inclusive approach to clinical trial enrollment.

Major gaps identified in each of the main areas of research in DILI in the elderly remain to be filled. As barriers in this endeavor are identified and addressed, effective collaborations among clinicians, industry, and regulators are expected.

Clinicians need to become aware of commonly used drug classes that are frequently associated with DILI in the elderly. Inappropriate prescribing practices and the challenges posed by polypharmacy are particularly relevant. Furthermore, clinicians can encourage elderly patient participation in clinical drug trials. They can also advise and inform industry about appropriate programs and protocol design.

Industry can take a more inclusive approach to the advanced age demographic across all phases of drug development. Guidance and recommendations that have been issued by regulatory authorities currently address many practical concerns. Clinical trial protocols that include elderly patients may consider incorporating special safety surveillance and management protocols as needed.

There remains much more to learn about DILI in the elderly, and current evidence referenced in this summary of the literature suggests that knowledge gaps remain that span many clinical and scientific aspects of this field. Two patient-centric goals should be highlighted, and serve as a focus for future, collaborative efforts. First is the optimization of safe prescribing practices in the elderly. To accomplish this, a better understanding of predictive risk factors is needed, along with effective methods to implement them in a clinical setting. Second, there is an urgent need to increase enrollment of older people in clinical trials, and regulatory authorities have laid the groundwork for this to occur.

Further studies will need to address the following critical questions: How do the pharmacodynamics in older cohorts compare with those in younger cohorts? Are the outcomes of DILI different in older versus younger cohorts? Should exclusion criteria be based primarily on liver test results? What monitoring requirements, causality assessment criteria, or discontinuation rules should be applied to older subjects?

10 Conclusion

Characterizing DILI in the elderly has been identified as a significant unmet need in clinical drug development programs. As the global population ages, the need for a broader and deeper understanding of this paradigm will intensify. This summary of the literature and the consensus statements and recommendations can help to optimize medical care for the elderly patient and to catalyze productive collaborations between stakeholders to achieve a more complete understanding of this important topic.

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