

Polypharmacy and Therapeutic Inertia in Extreme Longevity: A Potential Clinical Ageism Scenario Secondary to Important Gaps in Clinical Evidence

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Population aging is a global health priority due to the dramatic increase in the proportion of older persons worldwide. It is also expected that both global life expectancy and disability-free life expectancy will increase, leading to a significant rise in the proportion of individuals with extreme longevity, such as non-agenarians and centenarians. The inaccuracy of clinical evidence on therapeutic interventions for this demographic could lead to biased decision-making, influenced by age-related beliefs or misperceptions about their therapeutic needs. This represents a potential clinical ageism scenario stemming from gaps in clinical evidence. Such biases can result in 2 significant issues that adversely affect the health status and prognosis of older persons: polypharmacy and therapeutic inertia. To date, documents on polypharmacy in non-agenarians and centenarians account for less than 0.35% of the overall available evidence on polypharmacy. Furthermore, evidence regarding therapeutic inertia is non-existent. The purpose of this letter is to discuss polypharmacy and therapeutic inertia as potential clinical ageism scenarios resulting from the clinical evidence gaps in extreme longevity.

Key words: Nonagenarians, Centenarians, Polypharmacy, Ageism, Secondary prevention

Population aging is recognized as a global health priority, driven by a significant increase in the proportion of older persons worldwide. The World Health Organization (WHO) projects that within the next 30 years, at least one-fifth of the global population will consist of older persons, with over 80% living in low-income regions [1]. Furthermore, both global life

expectancy and disability-free life expectancy are expected to rise, leading to a higher number of individuals achieving extreme longevity, including non-agenarians and centenarians [1]. This rapid increase in the aging population has profound implications for public health and healthcare systems [2]. There is a pressing need for precise clinical evidence to support the development and implementation of preventive models and evidence-based interventions. These strategies are essential to enhance health outcomes in this population.

Recently, Ungar et al. [3] published a manifesto addressing the issue of ageism in healthcare, specifically highlighting various instances of clinical ageism. Clinical ageism involves discrimination or the creation of dilemmas in clinical care based on a patient's age, predominantly affecting older individuals [3]. While the primary focus of the discussion is on decision-

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making for clinical interventions in hospital settings, it is interesting to note another potential scenario that has remained underexplored, despite evidence supporting its existence [4]. This scenario likely relates to the interplay between clinical ageism and the clinical evidence gap, particularly in terms of polypharmacy and therapeutic inertia in the treatment of individuals with extreme longevity, such as non-agenarians and centenarians.

Polypharmacy is a significant risk factor primarily associated with the risk of falls in older individuals. However, in non-agenarians and centenarians, although there are very few studies, those available have reported varied prevalence rates of polypharmacy, mainly related to falls [5,6]. These studies, however, have not investigated the causality between polypharmacy and other health outcomes, which could be more crucial in predicting morbidity and mortality in those of extreme longevity, such as functionality, frailty, sarcopenia, and nutrition [7]. Furthermore, the criteria for initiating medication in this population have not been thoroughly examined. This lack of scrutiny could explain why at least 70% of drug prescriptions in this demographic might be inappropriate and could significantly affect key health outcomes [4]. As Ribera-Casado [8] has noted, significant gaps exist in the availability and certainty of evidence regarding pharmacological interventions in this age group. Typically, clinical intervention recommendations for septuagenarians and octogenarians are inappropriately extrapolated to non-agenarians and centenarians, despite important biological and clinical differences between these groups, as previously demonstrated in intergenerational cohort studies [5,6]. Due to the absence of clear evidence-based criteria, the efficacy and safety of such interventions over the medium and long term remain uncertain. Currently, there are no randomized controlled trials for pharmacological interventions in non-agenarians or centenarians listed on ClinicalTrials.gov.

Closely related to the absence of randomized controlled trials and the limited information on the efficacy and safety of pharmacological interventions, as well as clinical predictors of healthy lifespan and overall survival in extreme longevity, therapeutic inertia may occur [9]. In scenarios where necessary therapies are not initiated, negative or even fatal outcomes can result. It is crucial to note that this situation should not automatically be attributed to intentional clinical ageism. The challenges in training general practitioners to care for older individuals and the scarcity of high-quality evidence complicate the management of clinical conditions in extreme lon-

gevity. However, it could be inferred that the absence of precise clinical evidence might lead to decision-making biases based on assumptions about chronological age rather than biological considerations and specific predictors of extreme longevity [7]. Therefore, in light of the needs and challenges posed by demographic transitions and global health objectives, there is a pressing need for a larger proportion of healthcare providers trained in geriatric and gerontological care.

Intervention studies and long-term prospective cohort studies are particularly needed in regions with a high demand for primary data evidence, such as low-income and middle-income areas [1]. These studies are essential for developing truly evidence-based geriatric care. Issues such as polypharmacy and therapeutic inertia in individuals of extreme longevity are poorly evidenced. A brief original bibliometric analysis conducted to evaluate the impact of polypharmacy and therapeutic inertia showed that the existing literature on polypharmacy among non-agenarians and centenarians accounts for less than 0.35% of all the evidence available on polypharmacy. Furthermore, there is no evidence concerning therapeutic inertia (Table 1).

Until this evidence gap is resolved, there may be speculation about the presence of clinical ageism related to polypharmacy and therapeutic inertia in the care of those with extreme longevity. This could potentially bias clinical decision-making and highlight a new dilemma associated with ageism. However, there remains an ethical dilemma regarding the conduct of clinical trials in this population, which can pose significant challenges due to the prognosis and risk of death associated with their extreme age. This would undoubtedly have significant repercussions on this population's health and preventive medicine for the oldest-old [2]. These dilemmas underscore

Table 1. Current status of research on polypharmacy and therapeutic inertia in extreme longevity

Database	Publications		
	Polypharmacy n (%)	Therapeutic inertia (n)	All (n)
PubMed	11 (0.34)	0	3168 (Polypharmacy) 181 (Therapeutic inertia)
Scopus	2 (0.05)	0	3590 (Polypharmacy) 207 (Therapeutic inertia)

The number of results was obtained by searching for (Nonagenar*[Title], Centenar*[Title], "Extreme Longevity"[Title], Polypharmacy[MeSH], Therapeutic inertia[Title]) on PubMed and Scopus [retrieved 4 Jul 2024]; Book chapters, books and conference papers were excluded; The accuracy of the results was not confirmed; "All" refers to all published research on polypharmacy or therapeutic inertia unrelated to extreme longevity.

the need to enhance funding and incentives for institutes and international networks dedicated to research in aging and extreme longevity, aiming to find reproducible solutions that significantly impact the global population.

Ethics Statement

This paper is a perspective, so it did not need ethical approval.

NOTES

Conflict of Interest

The authors have no conflicts of interest associated with the material presented in this paper.

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Both authors contributed equally to conceiving the study, analyzing the data, and writing this paper.

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