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POLYPHARMACY AND ANXIETY IN ELDERLY: A NARRATIVE COMPREHENSIVE REVIEW

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ABSTRAK

Prevalensi polifarmasi pada pasien lanjut usia meningkat setiap tahun. Hal ini mungkin berkaitan dengan proses penuaan yang menyebabkan meningkatnya komorbiditas, sehingga jumlah obat yang dibutuhkan oleh lansia juga bertambah. Kecemasan merupakan salah satu gangguan mental yang paling umum pada lansia, dengan penyebab yang bersifat multifaktorial, meliputi faktor biologis, lingkungan, dan psikologis. Predisposisi genetik serta disregulasi pada poros hipotalamus–pituitari–adrenal (HPA) berperan penting dalam pengelolaan stres dan turut berkontribusi terhadap timbulnya kecemasan. Kecemasan pada lansia juga dapat berkaitan dengan penyakit seperti aritmia, diabetes, gangguan tiroid, atau penggunaan obat-obatan seperti albuterol, kafein, dan steroid. Lansia yang mendapatkan banyak resep obat cenderung mengalami peningkatan stres. Polifarmasi dapat memicu kecemasan antisipatif yang berkaitan dengan keamanan dan pengelolaan penggunaan obat. Tinjauan pustaka ini bertujuan untuk menilai pentingnya evaluasi terhadap dampak polifarmasi terhadap kecemasan pada populasi lanjut usia. Tinjauan Pustaka ini dilakukan dengan menggunakan data dari *PubMed, Google Scholar, ScienceDirect* untuk memilih artikel yang sesuai dengan kriteria serta relevan dengan topik kami. Polifarmasi dapat berkontribusi terhadap tekanan psikologis pada lansia dengan meningkatkan kompleksitas pengelolaan obat serta memicu kecemasan yang berkaitan dengan keamanan dan kepatuhan pengobatan. Hubungan antara tekanan psikologis dan polifarmasi bersifat kompleks, dua arah, dan multifaktorial.

Kata kunci : *polifarmasi; lansia; ansietas; multimorbiditas*

ABSTRACT

The prevalence of polypharmacy among elderly patients is increasing each year. This might be related with the aging process, that leads to increase comorbidities, hence increased number of medications required by elderly. Anxiety is one of the most common mental disorders in the elderly, and its causes are multifactorial, involving biological, environmental, and psychological factors. Genetic predisposition and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis have an important role in managing stress and contribute to anxiety in general. Anxiety in elderly is associated with arrythmias, diabetes, thyroid disease, or medications such as albuterol, caffeine and steroids. Elderly that are given multiple prescriptions adds to stress. Polypharmacy can induce anticipatory anxiety associated with the safety and management of medications. This literature review aims highlight the importance of evaluating the effects of polypharmacy on anxiety among the elderly population. This literature review was conducted via PubMed, Google Scholar, ScienceDirect databases to identify articles that were eligible according to our criteria and relevant to our subject. Polypharmacy can contribute to psychological distress in elderly individuals by increasing the complexity of medication management and triggering anxiety related to treatment safety and adherence. The relationship between psychological distress and polypharmacy is complex, bidirectional, and multifactorial.

Keywords : *polypharmacy; elderly; anxiety; multimorbidity*

INTRODUCTION

Polypharmacy is often defined as an individual concurrently using multiple medicines including prescription by clinicians and over the counter drugs. According to World Health Organization (WHO), there is no generally accepted definition for polypharmacy but the most

common definition of polypharmacy in the literature is the concurrent use of 5 or more drugs. Excessive polypharmacy is defined as using 10 or more drugs concurrently (Cheng & Bai, 2022; Wongpakaran et al., 2018). The prevalence of polypharmacy ranges variously. A study done across 17 European countries and Israel involving 34,232 older adults (aged 65 years or more) found the prevalence of polypharmacy ranges from 26.3 to 39.9% (Pazan & Wehling, 2021). Other studies reported the prevalence of polypharmacy in elderly to be 86.4% in Korea, 40% in United States (US), and 83.5% in Taiwan (Cheng & Bai, 2022; Wongpakaran et al., 2018).

In the past twenty years, the number of elderly (≥65 years) receiving multiple medications has increased by more than 300% in the US. This could be attributed to increased life expectancy, which leads to higher comorbidity, and guidelines encouraging the use of multiple drugs to manage multiple health conditions (Ngcobo, 2025b; Thompson & McDonald, 2024). However, pharmacological management of multiple comorbidities in elderly, while often necessary, is associated with several clinically significant risks. These include harmful drug–drug interactions, increased likelihood of medication-related hospital admissions, and deterioration in cognitive function as well as physical and psychological well-being. Beyond its impact on individual patients, polypharmacy also places a substantial burden on healthcare systems by contributing to higher hospitalization rates, more frequent emergency department visits, and escalating healthcare expenditures.

Evidences from retrospective analyses indicates that adverse drug events account for approximately 10% of emergency department visits among individuals aged 65 years and older. Another retrospective data demonstrates that elderly prescribed more than five medications have a fourfold increased risk of hospitalization related to adverse drug events. (Dale & Kashid, 2025; Doumat et al., 2023) Polypharmacy also contributes to malnutrition, weight loss, medication non-adherence, drug-drug interactions (DDIs), falls, fractures, disability, frailty, anxiety and even depression (Aktaş & Sarıaslan, 2025; Ngcobo, 2025b).

Anxiety is an emotional response triggered by an undesired situation, leading to a series of reactions in cognitive, physiological, and behavioural domains. This emotion can manifests as fear, excessive worry, anticipatory anxiety, and avoidance behaviours (Grajeda-León et al., 2025). Among geriatric population, anxiety is the second most common mental disorder, with a global incidence of 3.8% (Grajeda-León et al., 2025). Around fourteen percent of elderly live with mental disorder, with depression, anxiety and stress being most common in elderly. A meta-analysis by Jalali, et al. reported that prevalence of anxiety in older adults is 14.6% (Jalali et al., 2024).

Anxiety occurs in the elderly due to changes with the aging process. Anxiety in elderly may arise as a consequence of age-related changes. Psychological stress in this population is influenced not only by life stressors but also by progressive declines in functional capacity, chronic pain, frailty, mobility impairment, social isolation, loneliness, chronic conditions, financial difficulties, and major life transitions such as retirement, caregiving responsibilities, and personal losses. (Aktaş & Sarıaslan, 2025). Psychological distress such as anxiety and depression has been found to be associated with polypharmacy. Anxiety in elderly is associated to memory impairment and difficulties performing tasks such as organization and planning. Additionally elderly often refuse treatment and along with other comorbidities they have, contribute to increased risk mortality. Elderly receiving polypharmacy tend to experience a diminished quality of life, which is associated with impairments in activities of daily living.(Grajeda-León et al., 2025).

The association between anxiety and polypharmacy has emerged as a topic of growing research interest; however, the underlying mechanisms linking these conditions remain insufficiently elucidated. The prevalence of anxiety disorders secondary to medical illnesses is also increasing among older adults. Diagnosing anxiety and related conditions in this

population is particularly challenging, as older individuals often underreport psychological symptoms and attribute them to physical illness, age-related comorbidities, or cognitive decline. In addition, psychological symptoms arising in the context of chronic disease are frequently perceived as a normal aspect of aging, and because anxiety commonly coexists with depression, its recognition and diagnosis may be overlooked.(Aktaş & Sarıaslan, 2025)

This literature review summarizes the impact of polypharmacy in elderly to anxiety despite the positive outcomes for treating elderly with multimorbidity. This review also provides guidance for clinicians and highlights for further research opportunities for this topic.

METHODS

This study is a narrative literature review that provides overview about anxiety in elderly with polypharmacy. We used PubMed, Google Scholar, and ScienceDirect to search for related publications from the last 10 years. The search terms were the following: “polypharmacy” OR “multiple medications” OR “multiple drugs” OR “multiple medicine” AND “Anxiety” AND “Elderly” OR “Geriatric” OR “old age”. The inclusion criteria comprised articles published in either English or Indonesian that were available as free full-text, published within the last 10 years (from 2015 to 2025). Eligible studies included various types of quantitative and qualitative research, as well as review articles. Authors then reviewed and discussed each publication that met the criteria.

RESULT

Psychological distress such as anxiety shares a complex, multifactorial and bidirectional relationship with polypharmacy. The association between these two have not yet been fully explained. Polypharmacy may cause adverse reactions and drug interactions that can induce psychological distress, while the burden of managing numerous prescriptions can further contribute to stress. Psychological distress may necessitate the use of multiple medications to manage symptoms, leading to polypharmacy (Awad et al., 2020; Cheng et al., 2025). Polypharmacy can also trigger anticipatory anxiety due to concerns about the medication safety, drug interactions, adverse reactions, or dietary restrictions (Leventhal et al., 2016).

Multiple studies show significant association between polypharmacy and psychological distress such as depression and anxiety in older adults. A study conducted by Assari, *et al* reported a significant association for African American adults who are prescribed ten or more medications, experience worse psychological distress such as anxiety and depression compared to those who take less medications. Higher age tends to be a risk factor for polypharmacy, because aging is associated with multimorbidity that need pharmacological treatment and leads to psychological distress (Assari & Bazargan, 2019). Other study done in Peru reported that polypharmacy strongly associated with anxiety. Individuals experiencing polypharmacy often have multimorbidity and tend to feel more anxious, particularly about death. This relationship might be bidirectional, as polypharmacy can occur alongside anxiety, worsening symptoms and resulting in an increased number of medications (Mutepfa et al., 2021).

DISCUSSION

Mechanism of Polypharmacy and Multi-Morbidity in Elderly

Aging typically lower physiological and biological function, the decline in aging process is associated with DNA damage, oxidative stress, free radical, apoptosis, telomere shortening, and altered gene expression causing damage to mitochondrial and DNA hence decreased organ function (Drenth-van Maanen et al., 2020; Fauziyah et al., 2017). Aging results from these underlying changes rather than being the cause of them. This decline results in increasing comorbidities and polypharmacy on older population. Managing multiple medicines in elderly

is often challenging for physicians due to altered pharmacokinetics and pharmacodynamics (Drenth-van Maanen et al., 2020);(Ngcobo, 2025a).

One of the explanations for the increased polypharmacy in elderly is that preventative interventions is raising to reduce the risk of mortality, especially with cardiovascular disease. Multiple preventative medicines are likely to increase the risk of harm than the benefits. However, not all polypharmacy is harmful or inappropriate. Multiple medicines may be indicated in patients with complex medical conditions and need optimized therapies according to evidence, such as heart disease or diabetes mellitus. Inappropriate medicines occurs when there is multiple medicines and the potential risk of adverse reaction outweighs benefits and leads to lower adherence, adverse drug reactions or potentially harmful effects.(P. Aggarwal et al., 2020; Halli-Tierney et al., n.d.)

Multi-Morbidity is defined as the presence of two or more concurrent chronic disease at in one individual. Individuals with multi-morbidity are more likely to worsen pre-existing mental health issues, hospital admission, higher rates of polypharmacy and adverse drug reactions, and reduced quality of life raising mortality rates (P. Aggarwal et al., 2020). A study of multimorbidity reported the most common diseases are cardiovascular and metabolic diseases, followed by mental health disorders and musculoskeletal disorders. In a Study conducted in Germany with elderly population, anxiety/depression disorders were among the most comorbidity patterns found (Chowdhury et al., 2023). Aging is one of the most significant risk factor for having multimorbidity (Fabbri et al., 2015). According to general practice databases, nearly 25% of the population is affected by multimorbidity and this prevalence significantly rising as the age is older, so most people over 65 years old have multimorbidity. Most chronic diseases such as cardiovascular disease, Alzheimer's disease, arthritis, diabetes mellitus, metabolic syndrome, renal disease and lung diseases appear to be influenced by Aging process. Patients affected by multimorbidity are more likely to receive multiple drugs, face difficulties with medications adherence, and suffer more physiological distress and depression (Barnes, 2015).

Pathogenesis of Anxiety in Elderly

The aging process involves wide range of physiological changes, aging is a relative, intrinsic, psychological, and social phenomenon. Aging can significantly impair psychological function, predisposing elderly to various psychological distress, such as depression, anxiety, and stress. Anxiety is an unpleasant and vague feeling associated with a sense of uncertainty about an unknown factor, can impair functional capabilities and overall quality of life (Jalali et al., 2024). Mental healthcare in the elderly can increase the burden of the individual's well-being and health system. One out of five elderly are reported to have mental or neurological disorders. Nearly 7.0% has depression, 4% suffered from anxiety disorders. A meta-analysis in 2024 reported that the estimated prevalence for anxiety among elderly globally is 25% (Shafiee et al., 2024). Depression and anxiety often unnoticed and under-diagnosed both by the individuals and the healthcare provider due to misconception that these are normal process of aging (Cho et al., 2021).

New onset of anxiety in elderly can be associated with medical causes such as Cardiopulmonary illnesses such as heart failure and arrythmias, endocrine disorder including diabetes mellitus and thyroid disease, or medications including albuterol, caffeine and steroids can precipitate anxiety. Anxiety in elderly can be classified into General Anxiety Disorders (GADs) occurring in 1.2% to 4.6% in elderly, Panic Disorder occurring in 0.4% to 2.8% of elderly, Social Anxiety Disorder (Social Phobia), Specific Phobia occurring from 4.0% to 9.9% in older population, Fear of Falling with prevalence ranged from 20.8% to 85% , Anxiety in Neurocognitive Disorders with estimates prevalence ranged from 17% to 52%, Anxiety with

Co-Occurring General Medical Illnesses, and Substance/Medication-Induced Anxiety (R. Aggarwal et al., 2017).

The pathogenesis of anxiety disorders in general is a complex interaction involving biological, environmental, and psychological mechanisms. Genetics have an important role in the pathogenesis of anxiety disorders, APOE ε4 allele carriage among amyloid-β-positive older adults was associated with the severity of anxiety, and this found to be prominent in the female (Holmes et al., 2016). Neural Networks as measured by using magnetic resonance imaging (MRI) shows a lower cortical thickness and gray matter changes in the orbitofrontal cortex (OFC), the inferior frontal gyrus, and the anterior cingulate cortex (ACC) (Andreescu et al., 2017). Report also shows that GAD in older subjects failed to activate prefrontal cortical (PFC) regions involved in the downregulation of negative emotions (Hellwig & Domschke, 2019).

Changes in hypothalamic-pituitary-adrenal (HPA) axis function in elderly is significantly associated with stress regulation and leads to anxiety disorders. The Study of Women's Health Across the Nation (SWAN) suggests a role of changes in hormonal levels across the menopausal women increased anxiety symptoms since estradiol modulates fear learning and fear extinction. Panic attacks also shown to be rising and worsen with menopause. Some study reported oral estrogens over 4-year treatment showed improvement in depressive and anxiety symptoms (Hellwig & Domschke, 2019). Cluster A and B personality disorders such as schizotypal, borderline, and narcissistic were recognized as risk factors for panic disorder, social phobia, and GAD. Cognitive impairment or dementia have been found to worsen anxiety and linked to poorer outcomes (Hellwig & Domschke, 2019).

Anxiety has been associated with psychosocial aspects such as loss, loneliness and social isolation. Loneliness can be described as the subjective sense of lacking companionship, occurring when there is discrepancy between perceived and desired quality and/or quantity of social relationships. As the age increases, the likelihood of experiencing losses increases, this leads to a higher prevalence of loneliness. A prospective cohort study shows that loneliness was an independent rsik factor of poorer prognosis for anxiety and depression (Hellwig & Domschke, 2019; Svensson et al., 2024).

Anxiety in Elderly with Polypharmacy

Psychological distress such as anxiety shares a complex, multifactorial and bidirectional relationship with polypharmacy. The association between these two have not yet been fully explained. Polypharmacy may cause adverse reactions and drug interactions that can induce psychological distress, while the burden of managing numerous prescriptions can further contribute to stress. Psychological distress may necessitate the use of multiple medications to manage symptoms, leading to polypharmacy (Awad et al., 2020; Cheng et al., 2025). Polypharmacy can also trigger anticipatory anxiety due to concerns about the medication safety, drug interactions, adverse reactions, or dietary restrictions (Leventhal et al., 2016).

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anxiety and other psychological disorders in the old age population is challenging because elderly tends to minimize anxiety symptoms and attribute them to physical illness and cognitive decline, another factor is anxiety is often seen together with depression, hence the diagnosis might be overlooked (Aktaş & Sarıaslan, 2025; Puşuroğlu et al., 2023).

CONCLUSION

The rising numbers of polypharmacy among elderly is concerning because of its negative impacts. Psychological distress such as Anxiety is associated with elderly that takes multiple medicines. Relationship between anxiety and polypharmacy in elderly demonstrates a complex, multifactorial, and bidirectional, which can worsen the quality of life, overall outcomes and increase healthcare burden. This review highlights the necessity to evaluate and developing strategies such as structured deprescribing and prevention of inappropriate prescribing to minimize impact of polypharmacy and anxiety in elderly population.

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