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REVIEW

The Double Burden of the COVID-19 Pandemic and Polypharmacy on Geriatric Population – Public Health Implications

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Abstract: COVID-19 pandemic is inducing acute respiratory distress syndrome, multi-organ failure, and eventual death. Respiratory failure is the leading cause of mortality in the elderly population with pre-existing medical conditions. This group is particularly vulnerable to infections due to a declined immune system, comorbidities, geriatric syndrome, and potentially inappropriate polypharmacy. These conditions make the elderly population more susceptible to the harmful effects of medications and the deleterious consequences of infections, including MERS-CoV, SARS-CoV, and SARS-CoV-2. Chronic diseases among elderlies, including respiratory diseases, hypertension, diabetes, and coronary heart diseases, present a significant challenge for healthcare professionals. To comply with the clinical guidelines, the practitioner may prescribe a complex medication regimen that adds up to the burden of pre-existing treatment, potentially inducing adverse drug reactions and leading to harmful side-effects. Consequently, the geriatric population is at increased risk of falls, frailty, and dependence that enhances their susceptibility to morbidity and mortality due to SARS-CoV-2 respiratory syndrome, particularly interstitial pneumonia. The major challenge resides in the detection of infection that may present as atypical manifestations in this age group. Healthy aging can be possible with adequate preventive measures and appropriate medication regimen and follow-up. Adherence to the guidelines and recommendations of WHO, CDC, and other national/regional/international agencies can reduce the risks of SARS-CoV-2 infection. Better training programs are needed to enhance the skill of health care professionals and patient's caregivers. This review explains the public health implications associated with polypharmacy on the geriatric population with pre-existing co-morbidities during the COVID-19 pandemic.

Keywords: elderly, COVID-19, pandemic, viral infection, polypharmacy, co-morbidity, public health

Introduction

According to the World Health Organization (WHO), the world's population of individuals over 60 years will nearly double from 12% to 22% between the years 2015 and 2050. All countries will struggle to ensure adequate health and social care to meet the needs of this age group.[1] Older age is associated with a high incidence of comorbidities, including diabetes mellitus, hypertension, arthritis, chronic heart disease, renal diseases, and Alzheimer's disease.[2–8] Treating communicable and non-communicable diseases in the elderly requires multiple medication regimens known as polypharmacy.[9,10] There is an ambiguity that remains in defining

polypharmacy.[11,12] Polypharmacy as a word in medical science is quite an old terminology related to the consumption of multiple medicines often without any scientific basis or evidence-based practice. It is over one hundred fifty years before first-ever the term polypharmacy has been described in the medical journal.[13–16] Nevertheless, the majority of researchers' most frequently stated definition of polypharmacy based on mathematical calculation, ie, five or more medicine prescribed per day. However, some researchers defined the range as low as two or more to eleven or more medicines per day.[12]

Polypharmacy and Quality of Life

The prevalence of polypharmacy is increasing,[4,6,] mainly in patients above sixty-five years.[17–21] Multinational studies conducted showed that adults with advanced age are taking an average of 2–9 medications/day.[22] Aronson of the University of Oxford has reported that polypharmacy often advantageous and itself is not a noticeable problematic clinical issue. However, the tricky issue remains in the event the particular medicine has been prescribed improperly or adequately, ie, careful selection or imprudent selection of drugs. Thereby, equally discretely and in the background of the entire prescribing medicines.[23–25] Subsequently, polypharmacy may enhance the quality of life of the patient and improve his health status and functionality,[26,27,] while inappropriate polypharmacy is associated with harmful side effects and the leading cause of frailty and dependence.[28,29]

Polypharmacy and Potentially Inappropriate Prescribing

However, research in the filed demonstrated showed an alarming increase in the prevalence of inappropriate polypharmacy that ranges from 11.5% to 62.5% in this age group.[30] Numerous risk factors (eg, obesity, chronic diseases, tobacco, alcohol use) associated with aging are positively linked with polypharmacy.[31–35] Potentially inappropriate prescribing (PIP) is the leading cause for adverse clinical outcomes and increased healthcare costs,[31,32,34–38] estimated at a total value of US$ 18 billion, which accounts for 0.3% of the global total health expenditure.[39] Inappropriate polypharmacy, particularly among the elderly population, increasers and executes a considerable liability of adverse drug reactions (ADRs). Thereby initiate poor health status, incapacity, hospitalization, and even lead to death. The distinct most imperative prognosticator of inappropriate polypharmacy or irrational prescribing and risk of ADRs among the geriatric community is the numerical issue of prescribed medicines.[40] Polypharmacy has been identified as a prevalent issue among the elderly population, and an increase in the number of medicines was significantly correlated with worse clinical outcomes and prognosis. The risk of worse clinical results was increased considerably as reported; the odds ratios (OR) were 1.21, 1.16, and 1.19 for ADRs, falls, disability, and mortality.[41] Patients of institutional care, typically living at home due to illness or old age, are also at a complex risk of polypharmacy complications with higher cost and hospitalization.[26,42–48] Polypharmacy often leads to unpleasant to dangerous, life-threatening penalties for patients and the community that includes probable drug interactions, drug-disease interactions, ADRs, non-complaisance, drug-associated complications, adversative clinical consequences such as renal failure and falls leading to fractures, lower quality of life, increase healthcare costs both of individuals and society, as well as an increased risk of mortality.[22,26,36,42,49] The complexities of polypharmacy are gravely problematic among geriatric patients as these groups of patients are particularly weak and susceptible.[4,5] The dangerous hazards with life-threatening issues of polypharmacy are higher among these patients in comparison to others, due to the presence of one or more additional comorbidities.[6–8]

Aging is typically accompanied by physiological changes, including a declined immune system, increased susceptibility to infections, deteriorated kidney function, and geriatric syndrome. These conditions, added to the burden of polypharmacy, may enhance the risk of morbidity and mortality, especially in cases of acute infections. The Middle East respiratory syndrome (MERS-CoV), severe acute respiratory syndrome (SARS-CoV), SARS-related coronavirus-2 (SARS-CoV-2), and coronavirus disease (COVID-19) are members of the same family as coronavirus.[50] These viruses may lead to fatal outcomes in humans, including acute respiratory distress syndrome, multiorgan failure, and death, particularly in geriatrics patients with multiple morbidities.[4,22–36,49,53] Various studies reported that COVID-19 has a similar pathogenic potential to cause respiratory complications, disability, and death as SARS-CoV and MERS-CoV.[54,55] A recent Chinese study showed that out of 138 hospitalized COVID-19 patients with pneumonia, 26.1% geriatric patients with multiple co-morbidities were transferred to the intensive care unit (ICU) compared with younger

adults with fewer co-morbidities.[56] This review evaluates the public health implications of the double burden of polypharmacy and COVID-19 pandemic on morbidity and mortality the geriatric population with pre-existing comorbidities.

Materials and Methods

The literature search for this narrative review was performed by searching bibliographic databases (including Google Scholar and PubMed). We principally depend on free downloads as this research did not obtain any financial support. Additionally, the link provided by the Universiti Pertahanan Nasional Malaysia [(UPNM) the National Defence University of Malaysia], Kuala Lumpur, Malaysia. The search terms used were: "Elderly", "Aging Process", "Geriatric Community", "Aged Population", "Treatment Options", "Treatment Difficulty", "COVID-19", "Pandemic", "Viral infection", "Polypharmacy", "Co-morbidity", "Public health", and "Global" followed by snowballing references from high-ranking reputed leading journals around the planet and persuasive highly cited manuscript. Only peer-reviewed articles published in English were included. Articles for which the full text was not available and those not written in English were excluded. The articles retrieved in the first round of search; further references were spotted by a manual search among the cited references. As this is a narrative review, whilst we have included predominantly recent papers, those with historical significance (which are older papers) to the narrative have also been included. There was no attempt to develop a systematic review or meta-analysis.

The Epidemiology of COVID-19 Pandemic in Older Age

The China National Health Commission had already reported that mortality mainly occurred amongst patients of 75 years' age group.[57] The high risk of morbidities in old elders due to the COVID-19 pandemic is also seen in Europe and the UK. The excess mortality data and its comparison between different European countries where the first wave of the global pandemic now seems to be receding.[58] Excess mortality is a count of additional deaths due to all causes in comparison to what is expected under normal circumstances. It is evident from that the percentage of deaths due to the COVID-19 concerning excess death has varied between different European countries. The highest rate of excess deaths was reported in Belgium (110%). The excess more than 100% may suggest that the most excess deaths were due to the COVID-19, and the deaths due to other reasons may have declined. The P-score, which is the ratio or percentage of excess deaths concerning normal average deaths, is very high for many European countries like the UK and Spain. The P-scores reflect the impact of the pandemic over an eleven (11) weeks' time frames with Spain and England's values being almost the same.[58] The cumulative P-scores for "all ages" data show that England and Spain reported a practically similar rate of excesses deaths. Belgium and Italy followed Spain in Europe, whereas in the UK, Scotland and Wales followed England. It is interesting to observe that although variant P-scores followed the cumulative p-score in all the groups but remained little below the cumulative p-score. This is because the variant P-scores provide an assumption for historical data variance that defines the threshold for an average number of deaths. It represents the maximum number of deaths associated with that threshold and calculates a percentage. So, the variance P-score is always slightly below the simple P-score. P-score data for all age groups across the weeks of the COVID-19 pandemic.[58] It is evident from the above figure that the consequences of the peak level occurrence of the pandemic are more severe in Spain in comparison to the rest of the countries in Europe and the UK. However, it is lasted longer in England (which caused the high numbers of deaths) in comparison to all the other countries followed by Belgium and Italy. The age-wise P-scores ratio for the groups of working-age adults (15–64 years) and the group of adults who are more than 85 years.[58] There is a clear trend of more "excess deaths" in old age as compared to a younger generation. The cumulative p-scores for the working adults, those are between 15–64 years was negative in France. This might be due to preventive measures such as social distancing, lockdown, and many more measures locally implemented which might have reduced the number of deaths from other causes such as road accidents for the working population. England and Wales reported the highest mortalities in this age group. The p-score was high for the 85+ age group in all the six countries, and Spain reported the highest cumulative P-score over the pandemic weeks in this category. The geriatric population is severely affected by the COVID-19 pandemic in comparison to working-age adults. This might be due to the presence of other comorbidities, weak immunity, and concurrent administration of

several drugs. The comparison of the p-scores over the weeks for different age groups, ie, 15–65 years and 85+ years adults. The old-age adults who belong to the 85+ age group affected severely throughout Europe and the UK throughout the peak of the pandemic.[44] The similar trend is seen in the USA, where 48.7% to total confirmed deaths due to COVID-19 are reported in old adults (75+ years and over).[59]

Polypharmacy and the Risk of Infections in the Elderly Population

The number of people aged 65 or older is estimated to increase twofold from 524 million in 2010 to nearly 1.5 billion in 2050.[60] Current statistics show that people 80 years of age and above accounts for approximately people in the 80-years age group, comprise approximately 10% of the world's population.[61,62] The aging process is accompanied by physiologic changes that vary among individuals and become more critical with advanced age. Older age may be accompanied by multiple comorbidities, including geriatric syndrome, frailty, and dependence. These conditions are associated with the high economic and clinical burden in a world struggling for cost containments due to increasingly scarce resources.[11,63] Co-morbidities in the aging population can pose unusual challenges Ranging from complex medication regimen, inappropriate polypharmacy, non-compliance, ADRs, drug-drug, and drug-food or herbal remedies interactions. This can potentially contribute to further prescribing cascade and prescribing vortex and to significant complications in the elderly leading to frailty and a weakened immune system.[64,65] The physiologic changes typically occurring with age can affect the pharmacokinetics and pharmacodynamics of medications and alters the bioavailability of the medications and, ultimately, the effectiveness of the treatment. As a result, the geriatric population may be at higher risk of hospitalization, a major contributory factor to low immunity, pneumonia, sarcopenia, depression, fall, and malnutrition. In other terms to geriatric syndrome and potentially irreversible dependence. Other risk factors include age predilection (ie, male gender), living in nursing homes, social factors, and family factors.[66,67] This may constitute a tremendous challenge and puts extra pressure on prescribers that struggle to optimize medication use in geriatrics and avoid dependence. The literature review that the elderly susceptibility to communicable diseases, mainly to viral illnesses, is well documented. Patients are usually immunocompromised and, after that, suffer a lot even from the common cold (rhinovirus) in comparison to younger patients.[68] A study revealed that respiratory syncytial virus (RSV) infection is a significant health issue among elderly and high-risk (chronic heart or lung disease) adults.[69] Furthermore, RSV infection is correlated with hospitalizations for pneumonia, chronic obstructive pulmonary disease, congestive heart failure, and asthma accounting for 10.6%, 11.4%, 5.4%, and 7.2% of hospitalizations, respectively.[69] RSV and influenza virus remain as top respiratory viruses responsible for the highest morbidity and mortality,[70] with influenza being an engrained reason for periodic hospital admissions among the elderly population worldwide,[71–73] and in the USA.[55] Although influenza has been principally classified as one of the predominant clinical complications of elderly patients with co-morbidities, it is often under-assessed and, its diagnosis could be challenging.[74,75] In addition to this, the patient's predominant cause of morbidity obscures the identification of essential symptoms and signs of influenza; furthermore, medical professionals tend to focus more on patients' known pathology.[74,76–79] Outcomes in these patients aging 65 years or over, are usually fatal, some even do not develop pneumonia, and 89% die either because of pneumonia and influenza; pneumonia was equally responsible for high death reports during the Spanish flu of 1918.[80,81] Morbidity increases considerably among survivors, and up to 10–12% of these aged patient groups need a higher level of support for day to day work after discharge from hospital for acute respiratory diseases.[55] In the USA, the average rates of influenza and RSV hospitalizations were 63.5 and 55.3 per 100,000 person-years, respectively, with the highest hospitalization rates among patients aged ≥65.[82] Another research involving sixteen countries of the American continent revealed that the mean pooled rate of influenza-related respiratory issues that needed hospital care was 90/100,000 population among children aged below five years, 21/100,000 population among persons aged 5–64 years, and 141/100,000 population among persons aged 65 years or above. This study appraised the mean per yearly influenza-related respiratory pathologies that needed admissions in hospitals among the Americas to be 772,000.[83]

Aging, Polypharmacy and COVID-19 Pandemic

On December 12, 2019, the first COVID case with apparent pneumonia was identified in Wuhan, China, and on

December 31, 27 cases of severe viral pneumonia were confirmed. Medical history revealed the possibility of a viral outbreak of Novel SARS-COV-2 from wild bats and Gp 2-B-CoVs comprising of severe acute respiratory syndrome-related (SARS-COV).[84] According to recent reports, the elderly population with a higher prevalence of frailty and co-morbidities is at utmost risk from COVID-19,[85] due to a decrease in intrinsic capacity and resilience, which undermines their resistance to any disease/infection.[86] Eight out of 10 deaths among confirmed COVID cases in the USA are reported in elderly persons above 65 years.[85] Pneumonia is the most severe complication of the influenza virus or COVID-19; any infectious disease like COVID-19, especially in the elderly patient with multiple co-morbidities and polypharmacy, has the potential to turn into pneumonia.[87,88] Therefore, it may be possible that in the elderly population, polypharmacy acts as a risk factor for the death procession of COVID-19. It has been observed that COVID-19 and influenza viruses have comparable symptoms and signs of respiratory disease, which often remain asymptomatic or mild to severe illness and death. Equally, both viruses are communicated by contact, droplets, and fomites. Accordingly, the identical non-pharmaceutical public health interventions, for instance, hand hygiene and good respiratory custom, stay at home, restrict visitors are precautionary measures every individual should practice averting infection.[85,89] Not enough time has passed to explore the detailed epidemiology of COVID-19; so far, it is known to be non-comprehensive. Phylogenetic analysis revealed SARS-CoV-2 to have significant sequence similarity to the SARS-like bat virus. Bats could be the possible primary reservoir, intermediate host, and further transfer is unknown, though human to human transmission is confirmed.[90] WHO reports,[91] 95% of COVID-19 deaths occurred in older adults > 60years, more than 50% of all deaths were in people >80years; 8 of 10 deaths had at least one underlying co-morbidity, in particular cardiovascular diseases, hypertension, diabetes, and a range of other chronic conditions.[92,93] Lab confirmed COVID-19 cases presenting with any co-morbidity resulted in poorer clinical outcomes than those without; an increasing number of co-morbidities correlate with poorer clinical outcomes.[94] COVID-19 is highly infectious and can result in fatal co-morbidities, particularly acute respiratory distress syndrome (ARDS),[95] involving bilateral pneumonia (75% cases) complicated by ARDS (17%),[86,96–98] a clear indication of ICU admission and mortality in elderly. Currently, the installation of the mechanical ventilator and extracorporeal membrane oxygenation (ECMO) systems are life-saving measures for COVID-19 patients with severe pneumonia or ARDS.[99–101] A recent study[102] from New York (USA) of COVID −19 cases reported of the mortality rate of 97.2% in ICU patients >65 years of age who received mechanical ventilation compared to a rate of only 26.6% for the same age patients who did not receive mechanical ventilation. Weaning from mechanical ventilation posed a risk of myopathy of critical illness and prolonged ICU stay due to acute lung injury, especially in patients above 70 years of age, which is a subsequent challenge.[103] On some occasions, COVID-19 patients developed sepsis, shock, septic shock, and multiple organ failure.[104–106] Unfortunately, the typical pathological progression in COVID-19 is still not a well-determined fact.[107] Furthermore, among deceased cases, low lymphocyte counts, high C-reactive protein, or D-dimer levels were found, which are linked to poor prognosis.[86] Still, it offers no conclusive evidence about the definite cause of death.[96,108,109] Latest reports highlight differences between the ARDS related to COVID-19 and ARDS that are caused by other factors as defined by Berlin criteria,[110] which are suggestive of difference in treatment. COVID-19 clinical symptoms were not consistent with the laboratory and imaging findings. Nevertheless, these patients may deteriorate rapidly and need close monitoring, which is noteworthy and critical for the elderly.[95]

COVID-19 Pandemic: Comorbidities and Atypical Presentation in Elderly Population

In addition to respiratory diseases, hypertension, diabetes, and coronary heart diseases have rapidly emerged as a significant co-morbidity for COVID-19 infection.[1] Patients suffering from these chronic diseases were also vulnerable, with an increased risk of being infected by the coronavirus and experience severe forms of COVID-19 related complications.[1,36,111–115] Treatment of these chronic disease conditions in COVID-19 patients need careful consideration as these patients have already been treated with multiple drugs. Polypharmacy may aggravate the clinical condition of COVID-19 patients. Hypertensive patients with other associated cardiovascular morbidities are often treated with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). The renin-angiotensin-aldosterone system (RAAS) inhibitors may

cause severe COVID-19 infection by binding to ACE2 in the lung to enter cells and replicate.[116,117] A study demonstrated that ACE2 expression increased further in diabetes due to treatment with ACE inhibitors and ARBs.[23] This increased expression facilitates infection in COVID-19 patients, which hypothesized that ACEI and ARB treatment might enhance the access of SARS-CoV-2 into cells, increase the risk of infection or increase the severity of COVID-19.[1,111,112] Although another study stated that these agents are neither found to have harmful nor beneficial effects over COVID-19; therefore, it was advised to continue treatment.[32] De Abajo et al also demonstrated that the use of RAAS inhibitors neither increased the risk of COVID-19 nor required admission to hospital compared with other antihypertensive drugs.[118] However, patients receiving these medications require additional monitoring.[119]

Patients with diabetes have an increased risk of contracting influenza and pneumonia.[120,121] High death rates among diabetic patients were noted with H1N1 influenza and MERS-CoV viruses.[122,123] It is now well established that diabetes is one of the significant comorbidities associated with COVID-19.[113–115,124] The prevalence of diabetes in patients with COVID-19 was reported 520%, 17%, 28.3% in China, Italy, and the USA.[99–101] A recent French study found that 10.6% of COVID-19 patients with diabetes died within the first seven days of hospitalization, and 20.1% required tracheal intubation for mechanical ventilation.[124] In older adults, patients diagnosed with COVID-19 infections may not present with typical clinical symptoms such as cough, dyspnea, and fever. Studies have shown that only 20–30% of infected elderly may have a fever.[125] Atypical manifestations of COVID-19 infection include generalized weakness, delirium, malaise, dizziness, functional decline, fall, headache, nausea and vomiting, diarrhea, abdominal pain, anorexia, increased sputum production, rhinorrhea, chest pain, hemoptysis, nasal congestion, anosmia.[125–127] These atypical symptoms and signs are quite similar among elderly individuals with co-morbidities and inappropriate polypharmacy. Thereby, increases the possibility of admitted to a general medicine or geriatric care ward.[128] Subsequently, several geriatric groups including WHO raise their voice regarding the need for watchfulness and cognizance to avert delayed diagnosis of COVid-19 among senior members of the community and minimizing both morbidity and mortality.[127,129,130]

Strategies to Reduce and Prevent Polypharmacy in Older Patients

Inappropriate polypharmacy is a significant public health concern in the care of the geriatric population. It is reported that approximately 11% of unplanned hospital admissions attribute to harm from medicines, and over 70% of these were due to elderly patients on polypharmacy.[109] The world can save around 0.3% of the global health budget by appropriate management of polypharmacy with timely and effective interventions.[131] Several assessment instruments have been developed to minimize inappropriate polypharmacy and ADRs.[132] Additionally, Medication review, patient and family interview, searching for signs of frailty, patient fall, malnutrition, and geriatric syndrome may serve as baseline information to optimize medication use in the geriatric population.[132] Dwyer et al reported that proper surveillance of those patients consuming multiple medications and its forfeits improves the quality of life in the elderly population.[133] It is also essential to identify frail older individuals with polypharmacy; a study reported a significant correlation between the Frailty Index (FI) score and both PIP and ADRs in hospitalized elderly patients.[134] Medical interventions are intended to benefit patients. However, medication also possesses the risk of ADRs leading to death, resulting in increased public health burden worldwide. Patient safety culture should be promoted to prevent healthcare-associated harms.[135] The WHO Universal Health Coverage (UHC) plan and the UN Sustainable Development Goals (SDGs) have included patient safety as a significant component of health care delivery.[136] "Medication without Harm 2017", to reduce 50% of avoidable ADRs in the next five years, was launched as WHO is the third Global Patient Safety Challenge.[137] Polypharmacy was included among three priority areas, the other two being medication safety in high-risk situations and transitions of care.[136,137] It is equally critical to reducing medication harms; this could be achieved by considering appropriate pharmacy and reducing polypharmacy. Prescribing error rate increases with the number of drugs prescribed,[138,139,] and the incidence of patient-reported errors increase with the number of medicines consumed.[140] Inappropriate medications can be avoided in older adults utilizing Beers criteria.[132] Adverse Drug Events (ADEs) such as medication errors including suspected errors should be reported to ensure patient safety and promote prudent prescribing.[141] Medication reconciliation is necessary at transitions of care to decrease

medication discrepancies, potential adverse effects, and ADEs in especially the high-risk group of patients receiving polypharmacy.[136] It is reported that nursing homes are at higher risk from polypharmacy (often reported topmost) among elderly individuals and ADRs complications due to inappropriate prescribing.[36,142] Moreover, consumption of non-prescribed medications and traditional and complementary medicines contribute to the polypharmacy burden causing Drug-Drug Interactions (DDIs).[142]

Medication reviews are popularly used to tackle inappropriate polypharmacy by providing a structured evaluation to prevent harm, treatments, and medicine use that can be optimized to improve outcomes for each patient.[136] Ideally, medication reviews should be performed in collaboration with the patient or their caregiver. There are reports suggesting medication reviews can reduce the number of preventable ADEs and averts the number of emergency department contacts; however, there was no improvement in mortality rates.[136] The NO TEARS tool can be used by physicians to make the medication review exercise simpler.[132] A recent article highlights the importance of medication optimization and deprescribing potentially inappropriate medications (PIMs) in elderly individuals; by decreasing the use of PIMs and thereby reducing polypharmacy, this population can be better prepared for inclusion in trials, corroborated by pharmacologic treatment or prevention of COIVD-19.[144] A drug-by-drug elimination trial, using risks versus benefit criteria, should be used for discontinuing any drugs used for the treatment of chronic ailments. Finally, a Good Palliative-Geriatric Practice algorithm can be used to guide cessation of any inappropriate medications in older adults.[130]

ADEs in the elderly need to access the emergency department (ED) urgently; therefore, the emergency physicians must be skilled in detecting any ADRs, DDIs including interactions between prescribed and self-medicated medicines.[145] Currently, a significant trend of management by computerized discharge instructions and prescriptions is followed in ED.[145] McDonald et al,[146] recommended that patients having multidisciplinary comorbidities need multidimensional assessment (MDA) and interdisciplinary strategy in the management of the geriatric population. Clinicians should regularly educate regarding medical errors, prescribed medication, traditional medicines, and polypharmacy to their elderly patients and their caregivers.[85,145] A multidisciplinary collaboration amongst health care providers is an essential need.[104]

As older people are most vulnerable and at highest risk for fatality with COVID-19, screening and triage are crucial for early recognition when suspecting COVID-19 infection, especially in elderly patients with comorbidities who are at risk of severe acute respiratory infection (SARI);[147] polypharmacy can also be detected at this point. WHO recommended that early detection of inappropriate medication prescriptions in elderly patients being treated for COVID-19 to prevent any ADEs and DDIs. All health professionals must be cautious of the correct choice and dosage of the medicine with its' potential ADRs. At the same time, safer alternative drug therapies should be considered.[145] Recently, Smith et al,[148] reported the challenge of reliable clinical advice to guide COVID-19 therapy in individuals with one or more comedications. In many cases, critically ill COVID-19 patients are receiving either single or a combination of drugs which may cause cardiovascular side effects such as torsades de pointes (TdP), prolonged QT interval, or may have other risk factors (eg, hypokalemia, female gender, age >70 years). Although there are websites (eg, www.covid19-druginteractions.org, CredibleMeds) that classify drugs having a known risk, possible risk, and a conditional risk, still appropriate clinical advice must be given about the safe use of one or more comedications in elderly patients.[67]

Elderly persons with probable or suspected COVID-19 infection should be provided person-centered assessment through multidisciplinary collaboration and involvement of caregivers and family members throughout the management.[146] CDC recommends the development of patient care plans for the elderly patients, which can be completed in consultation with the treating physician; this can be updated yearly.[85] Further extra precautions are needed for older adults during COVID-19 at seniors living facilities; long term care facilities ought to limit guests, frequently check care staff and residents for fevers and symptoms of COVID-19, and eventually limit activities at intervals the power to stay residents safe. Unfortunately, DDIs can occur even after discontinuing the drugs due to a very long half-life.[149] At the time of discharge, pharmacists mediate with the medical team/primary care provider to prevent polypharmacy, to strictly avoid excessive dispensing and irrational medication, and prevent any likelihood of ADRs.[150] Moreover, a copy of discharge instructions is also provided for a follow-up visit. Extra care is needed as polypharmacy is almost a reality among elderly patients; primary care physicians must have a better understanding of

aging physiology and pharmacology and provide person-centered assessment because they are the primary prescribers in the community.[104] Newly diagnosed patients should be followed by scheduled visits within a limited period of starting a new medication. Primary care physicians can utilize a non-pharmaceutical approach that includes changes in lifestyle based on scientific evidence in selected cases. It was reported that elderly patients with higher literacy were more informed about their medicament and health condition and were more likely to be involved in self-monitoring and accepting medical interventions to avoid polypharmacy; thus, resulting in fewer medications.[65,151] The critical point to remember is that medicines often cause ADRs beside their therapeutic benefits and effects on the improvement of quality of life; they increase both morbidity and mortality in the elderly.[141]

Deprescribing as One Strategy to Reduce Inappropriate Polypharmacy

The term deprescribing (or de-prescribing) at first described in the English health-related scientific manuscript 2003 in an Australian Hospital Pharmacy journal in an article titled, 'Deprescribing: achieving better health outcomes for older people through reducing medications.[152] Deprescribing is defined as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, the current level of functioning, life expectancy, values, and preferences.[40] Other researchers defined as "deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional to manage polypharmacy and improve outcomes".[153] Multiple studies evidenced that of the ADRs related to polypharmacy among the elderly community, concomitantly ropes the necessity for deprescribing especially in ageing population.[26,154–158]

Several instruments were developed to support the deprescribing process.[134,159] The Beers criteria,[160] STOPP tool,[161] Improved Prescribing in the Elderly Tool,[162] McLeod criteria,[163] Medication Inappropriateness Index,[164] Fit for the Aged Criteria,[165] and the PRISCUS[166] has been registered as the screening instruments to recognize drugs those were imprudently prescribed and causative factor for ADRs. However, the Beers criteria and STOPP tool are extensively utilized because of more suitability and reliability in categorizing possible inappropriate polypharmacy among the elderly community.[167] The Drug Burden Index,[168,] and the Anticholinergic Risk Scale,[169] both were evolved to measure risk scales comprehensively regarding the anticholinergic and sedative problem of all the medications. Both instruments were strongly correlated with anticholinergic effects in declining physical and cognitive function.[170,171] Although, these two scales were not widely used in clinical practice because of their complex nature.[172] Additionally, risk Scores[173,175] or clinical probability assessment[176,179] assessed the hazard of ADEs in specific patients depending on multivariate statistics which include sociodemographic parameters, number of prescribed and consumed medicine, renal physiological status, and other comorbidities. Furthermore, deprescribing guiding principles are principally focused on how safely to stop a particular medicine (or classes) which have been recognizing inappropriate/imprudent selection for particular clinical need. These guidelines are flourishing,[143,180–183] nevertheless, the quality of these guidelines on clinical decision-making and outcome is not appraised as a whole.[172]

Appropriate Polypharmacy' and Medicine Safety During COVID-19 Pandemic

Polypharmacy is one of the most significant prescribing challenges within all health care settings worldwide.[13,184,185] According to WHO: Health care interventions are intended to benefit patients, but they can also cause harm. Every year, a significant number of patients are harmed or die because of unsafe health care, resulting in a high public health burden worldwide. Most of this harm is preventable.[186] Medication safety in polypharmacy needs to be ensured at all levels of healthcare settings. Though polypharmacy intensifies the risk of adverse health events, WHO reported that there are cases where polypharmacy is required and has noticeable advantages.[149] Polypharmacy has beneficial effects in specific clinical conditions, eg, diabetes mellitus, hypertension, and patients with multiple-morbidity.[187] Polypharmacy is also identified as a risk factor for under-prescribing, which may compromise patients' safety and well-being.[187] Healthcare professionals often prescribe many drugs to match the complex needs of their older patients with multi-modalities as per disease-specific clinical practice guidelines.[188] It is sometimes problematic to assess the correct selection of medicine, its' beneficial effect, and ADRs in the clinical need.[12,189]

The treatment of COVID-19 patients with co-morbidities may result in problematic polypharmacy and an increased risk of DDIs.[67] The use of safe medication in older adults during the current COVID-19 pandemic is highly essential to

prevent avoidable drug-related adverse events and facilitate quick recovery of COVID-19 elderly patients, especially during unplanned and emergency hospital admission.[190] However, it has been recommended to use the evidence-based practice to reduce inappropriate polypharmacy and promote "appropriate polypharmacy".[2,12,13,26,27] To promote appropriate polypharmacy, multiple sustainable programs have been implemented worldwide, particularly in high-income countries.[191,192] Evidence-based guidelines should be developed on appropriate pharmacies, and more research is needed on patients with multimorbidity and polypharmacy. Better training programs need to be developed and implemented for healthcare professionals to manage complex multimorbidity and polypharmacy in elderly patients. Though there are no specific recommendations for older adults, COVID-19 should be clinically managed by following the WHO and the Centers for Disease Control and Prevention (CDC) guidelines.[193,194]

Conclusion

The prevalence of polypharmacy is abruptly increasing in the elderly. Frail and comorbid elderly populations are at the utmost risk due to a decrease in intrinsic capacity and resilience, which undermines their resistance to any disease/infection. Majority of COVID-19 patients with pneumonia who require ICU treatment were geriatric patients with multiple co-morbidities. Currently, the detail of the epidemiology of COVID-19 is still emerging, and the typical pathological progression is not well-determined. COVID-19 has similar pathogenic potential to cause respiratory complications, disability, and death as SARS-CoV and MERS-CoV. Pneumonia is the most severe complication of the Influenza virus or COVID-19, and any infection in the elderly patient can turn into fatal pneumonia. Respiratory failure due to ARDs is the leading cause of death in the elderly. Polypharmacy may be required in some cases, and "appropriate polypharmacy" is the key to success. The treatment of COVID-19 patients with co-morbidities may result in problematic polypharmacy. The consequence of polypharmacy among the aged population is often correlated with poor compliance, DDIs, medication errors, and ADRs, which includes falls, skeletal bone fractures, confusion, and delirium. A multidisciplinary approach with pharmacists mediating with the medical team/primary care provider to prevent polypharmacy should be followed; excessive dispensing and irrational medication should be strictly avoided in order to prevent any likelihood of ADRs and reduce health care costs; computerized discharge instructions and prescriptions are essential for follow up. Better Training programs are needed for health care professionals and patient's caregivers. Clinical management should follow the WHO, CDC, and other national/regional/international guidelines and recommendations. Overall, the global pandemic gives us a lesson to overhaul total healthcare based on primary health care all over our planet.[195–198,200,207]

Recommendations

During the COVID-19 crisis, non-pharmaceutical interventions, eg, maintain good personal hygiene and good respiratory practice, maintain regular physical activity, and consume natural immunity boosters, especially of food origins, should be practiced; safer alternative therapies should be explored, when available. Clinicians must avoid over-prescription of needless drugs, use simplified regimens with the lowest possible effective dose to prevent ADRs and cost constraints in elderly patients. Excellent communication amongst health care personals with computerized discharge instructions and medications with reporting of any adverse drug event is needed. The telemedicine system with the service of respective health care workers known adverse consequences of polypharmacy is suggested. All stakeholders play pivotal roles in the management of polypharmacy, including multifaceted decision-making, amalgamated knowledge of physicians, nurses, pharmacists, and other health care workers, along with structured involvement, engagement, and empowerment of the patient. The use of easily accessible, updated databases, and software is imperative. Patient and family education regarding medication usage is recommended. WHO suggests that countries and stakeholders focus on three priority areas for effective management: medication safety in high-risk situations, medication safety in polypharmacy, and medication safety in transitions of care. Above all, the guidelines and recommendations prescribed by WHO, CDC, and other national/regional/international should be strictly followed for treatment and prevention of COVID-19 infection. Guidelines established by WHO, CDC, and other leading health-related institutions should be followed and maintained properly to combat the pandemic.

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