Mental health care for older adults: recent advances and new directions in clinical practice and research

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The world's population is aging, bringing about an ever-greater burden of mental disorders in older adults. Given multimorbidities, the mental health care of these people and their family caregivers is labor-intensive. At the same time, ageism is a big problem for older people, with and without mental disorders. Positive elements of aging, such as resilience, wisdom and prosocial behaviors, need to be highlighted and promoted, both to combat stigma and to help protect and improve mental health in older adults. The positive psychiatry of aging is not an oxymoron, but a scientific construct strongly informed by research evidence. We champion a broader concept of geriatric psychiatry – one that encompasses health as well as illness. In the present paper, we address these issues in the context of four disorders that are the greatest source of years lived with disability: neurocognitive disorders, major depression, schizophrenia, and substance use disorders. We emphasize the need for implementation of multidisciplinary team care, with comprehensive assessment, clinical management, intensive outreach, and coordination of mental, physical and social health services. We also underscore the need for further research into moderators and mediators of treatment response variability. Because optimal care of older adults with mental disorders is both patient-focused and family-centered, we call for further research into enhancing the well-being of family caregivers. To optimize both the safety and efficacy of pharmacotherapy, further attention to metabolic, cardiovascular and neurological tolerability is much needed, together with further development and testing of medications that reduce the risk for suicide. At the same time, we also address positive aging and normal cognitive aging, both as an antidote to ageism and as a catalyst for change in the way we think about aging per se and late-life mental disorders more specifically. It is in this context that we provide directions for future clinical care and research.

Key words: Positive psychiatry of aging, cognitive aging, neurocognitive disorders, major depression, schizophrenia, substance use disorders, comorbidities, collaborative care, measurement-based care, caregivers

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By the year 2050, according to the United Nations (UN), one in six persons will be 65+ years of age[1]. Given this increasing number of people entering the worldwide aging community, coupled with lower birth rates – especially in high-income and some middle-income countries – there is concern about the old-age dependency ratio, that is, the number of people 65+ years of age per 100 persons in the working age group (ages 15-64). That ratio is increasing significantly, especially in countries such as China[2].

A common misconception is that elders are mostly a burden to society. The fact is, instead, that many of them keep on contributing in many ways, such as continued work, childcare, maintenance of the household, and meal preparation. Most live independently. Many contribute several hours a week to volunteer activities or serve in leadership roles in community organizations. Yet, as these elders continue to age, they often face increasing disabilities, perhaps minor initially but gradually leading to significant impairments.

Mental disorders are major contributors to these disabilities. They often coexist with each other, e.g. comorbid depression and cognitive impairment, or with physical diseases, e.g. hearing impairment and paranoid thoughts[3]. In many cases, comorbidity spans multiple mental and physical disorders.

Despite the "aging tsunami" we are currently witnessing, the rise of special care for older adults has been slow to develop. Psychiatry has lagged behind medicine, yet it is increasing its knowledge base as well as recruiting sub-specialists, unfortunately not at a rate which can serve the unique needs of older adults with mental disorders, even in high-income countries. The International Psychogeriatric Association, founded in 1982, has been instrumental in encouraging meetings and programs in many low- and middle-income countries, as well as providing a forum for geriatric psychiatrists from throughout the world. In both clinical practice and research within geriatric psychiatry, interdisciplinary collaboration has been foundational and essential, given the complexity of the problems faced by older adults experiencing mental illness.

Both basic and applied research have appreciably increased the evidence base for the diagnosis, treatment and prevention of late-life mental disorders. For example, although we have no pharmacological agent yet proven to prevent or retard the progression of Alzheimer's disease, evidence has accumulated to support the importance of preventive measures, such as education, physical activity and control of vascular risk factors[4]. In depression of older adults, treatment with a combination of pharmacotherapy and psychotherapy, especially learning-based forms such as cognitive behavioral therapies (CBT), has been shown to be effective[5,6]. Alcohol use disorders among older adults are more common than often realized by clinicians, especially in men, so that careful screening for these disorders is now regarded as essential[7].

While negative views of aging continue to permeate the beliefs of many, more positive views have emerged in recent years, as exemplified in the MacArthur Research Network on Successful Aging[8]. They have defined successful aging, in contrast to usual aging, as low probability of disease, high cognitive and physical function, and active engagement with life. Others have also included wisdom as a characteristic of positive aging[9,10].

In this paper, we provide an overview of the burden of mental

health problems in older adults, with a focus on neurocognitive disorders, major depressive disorder, schizophrenia, and substance use disorders. For each of these disorders – which can be better understood as groups of disorders – we cover the epidemiology, prevention, recent treatment advances, and emerging models of service delivery. Further, for each group of disorders, we touch briefly upon heterogeneity at several levels: etiology, clinical presentation, and variability in response to intervention. In so doing, we describe directions for the future of clinical practice and research.

We begin the overview by contextualizing considerations of neurocognitive disorders, major depression, schizophrenia, and substance use disorders within the sciences of positive aging and cognitive aging, including a summary of the social determinants of well-being in older adults. Our view is that the positive elements of aging need to be highlighted, not only to reduce the triple jeopardies of ageism, mentalism and ableism (i.e., discrimination against people on the basis of their age, mental health problems, and disability), but also to provide hope to patients and family caregivers.

SOCIAL DETERMINANTS OF MENTAL HEALTH IN OLDER ADULTS

Social determinants of health are non-medical factors that influence health outcomes and have a significant effect on health inequalities[11]. Prominent examples of these social determinants include nutrition, education, employment and living environment, and these apply to the entire population.

Older adults with mental disorders are impacted by several types of these determinants[12]: a) social determinants that affect overall health, b) unique social determinants of mental health, such as stigma against mental illnesses, mental health care disparity, flawed criminal justice system, and homelessness[13], and c) aging-related social determinants, such as ageism, workforce shortage, and social isolation/loneliness. There are, however, also some positive social determinants of health relevant to old age, such as wisdom, resilience, meaning in life, and community engagement. Evaluating and addressing these determinants at individual and community levels is critical for prevention of mental disorders and enhancement of well-being in older adults in general[9-11,13-15].

Ageism and stigma

Ageism is defined by stereotypes, prejudice and discrimination directed toward people on the basis of their age[16]. Called "an insidious scourge on society"[17], it can be institutional, interpersonal and/or self-directed. Aging and older adults are often discussed by the general public and the media using negative stereotypes, such as a decline in mental and cognitive function. Unfortunately, this type of pejorative view of later life may be internalized by older individuals themselves and enacted, creating a vicious circle resulting in poor mental health.

Ageism causes inequalities and has detrimental effects on the individual, community and society[17]. Combating ageism is one of the four action areas of the Decade of Healthy Ageing (2021-2030) declared by the UN and the World Health Organization (WHO)[16].

The stigma against mental disorders is even greater in later life. An example is the stigma against agitation in dementia patients, many of whom spend days or weeks in emergency rooms because long-term care facilities would no longer admit them, and the society has not provided alternatives. Equally sadly, there are more people with severe mental disorders (excluding dementia) and substance use disorders who are aging in prisons and jails than in hospitals in the US[11,12].

Workforce shortage

The geriatric mental health workforce is slim, even in the most developed countries[18]. Despite the increased number of older adults, the number of psychiatrists trained in geriatric psychiatry has not increased. We know what to do, but how to recruit professionals across multiple disciplines to improve geriatric care in various cultural contexts is an abiding question that needs to be addressed for the future of clinical care and research in this field.

Also as a consequence of this workforce shortage, with the increase of physical and functional challenges in older patients, the need for a caregiver usually arises. The primary caregiver is often a spouse or adult child of the older patient. The role of the caregiver is wrought with physical, psychological and emotional challenges when caring for someone with dementia and/or serious physical illness. The caregivers themselves often suffer from significant morbidity[19].

Loneliness and social isolation

A recent report from the National Academies of Science, Engineering, and Medicine[20] highlighted the public health significance of loneliness (i.e., subjective distress arising from an imbalance between desired and perceived social relationships) and objectively measurable social isolation. Older adults are at a particularly high risk for both loneliness and social isolation[21]. Aging-related risk factors include widowhood, physical disability, poor health, and caregiving responsibilities.

Loneliness and social isolation are associated with adverse mental and physical health outcomes – including alcohol and drug abuse, suicidality, poor nutrition, sedentary lifestyle, inadequate sleep, and worsening physical functioning[22]. Loneliness and social isolation are as dangerous to health as smoking and obesity[23], and are an important risk factor for Alzheimer's disease, major depression, and generalized anxiety disorder, as well as for cardiovascular and metabolic diseases[24-26]. More Americans die from loneliness- and social isolation-related conditions than from stroke or lung cancer[27].

Loneliness is more common in people with severe mental disorders such as schizophrenia than in the general population[28]. The evidence base for social isolation regarding adverse outcomes is much greater than for loneliness, yet the evidence for adverse effects of loneliness is increasing[21].

The National Academies report[20] urges further research to establish the strength of the predictive association of loneliness and social isolation with mortality, and to clarify how these two entities interact with other facets of social relationships, including social support.

Wisdom

Wisdom is a personality trait comprised of several components: prosocial attitudes and behaviors (empathy and compassion), self-reflection, emotional regulation, acceptance of uncertainty and diversity of perspectives, social decision-making and, possibly, spirituality[29,30]. Commonly used self-report-based scales for assessing wisdom with good psychometric properties include the San Diego Wisdom Scale or Jeste-Thomas Wisdom Index[31], the Three-Dimensional Wisdom Scale[32], and the Self-Assessed Wisdom Scale[33].

Across the lifespan, wisdom is associated with positive outcomes, including better overall physical and mental health, happiness, and lower levels of depression and loneliness[34,35]. Amongst older adults, numerous investigations have demonstrated that wisdom is associated with life satisfaction, subjective well-being, and greater resilience[29,30]. These studies have reported that older adults score higher than younger adults on several components of wisdom, especially prosocial behaviors, self-reflection, and emotional regulation[36]. Some empirical evidence indicates that wisdom has a curvilinear relationship with age, peaking in the 70s or early 80s[34].

Neurobiological investigations show that prefrontal cortex (especially dorsolateral, ventromedial, and anterior cingulate), insula, and limbic striatum (especially amygdala) are involved in the various components of wisdom[29]. Intergenerational activities, such as grandparents' help in raising grandchildren, have been found to benefit both the generations biologically, cognitively and psychosocially[37].

A number of recent clinical and biological studies have reported a strong inverse relationship between loneliness and wisdom, especially its compassion component[38-40]. This evidence suggests potential use of individual- and societal-level interventions to enhance compassion and other components of wisdom in older adults, so as to reduce loneliness and improve well-being[40]. There are indeed reports of psychosocial group interventions in older people producing a significant improvement in wisdom[41].

Resilience

Resilience is a trait or outcome that describes recovery or bounce-back from adverse situations or a process of adapting well in the face of adversity, trauma, threats or other sources of major stress[21]. Commonly used measures of resilience include self-report scales such as the Connor-Davidson Resilience Scale[42] and the Grit Scale[43]. Resilience is highly relevant to healthy aging and well-being, and should be viewed as a public health concept[44]. A framework for resilience to the challenges associated with aging is required to complement ongoing risk reduction policies, programs and interventions[45].

Men experience greater feelings of loneliness and have increased difficulty in adjusting to widowhood compared to women, with the exception of veterans. Male veterans exposed to death while serving in the military show greater resilience and report less loneliness than civilian widowers[23]. Resilience has been shown to be associated with better health and functioning as well as greater longevity in all age groups, but especially in the very old adults[46]. Resilience interventions in older adults include mindfulness training, CBT, well-being therapy, social support, lifestyle and mind-body interventions, and phone coaching. Studies applying valid and reliable measures of resilience have reported positive outcomes with small to medium effect sizes using some of these interventions[47].

The COVID-19 pandemic has been particularly isolating to older adult populations, given their lower familiarity with technologies to facilitate social interactions or virtual visits by family, friends, or even health professionals. However, despite these obstacles, preliminary evidence indicates that older adults have been more resilient, experiencing fewer negative mental health outcomes compared to other age groups. In a recent study of over 5,000 American adults, adverse mental or behavioral health symptoms were much more prevalent among adults aged 18-25 compared to those aged 65 years or older[48].

Meaning in life

Meaning or purpose in life is the value and importance attributed to one's own life and activities, and the core significance of one's personal existence[49]. There are a number of validated instruments to assess meaning in life, such as the Meaning in Life Questionnaire[50].

Multiple research studies have demonstrated a strong link between purpose in life and better physical, psychosocial and overall health outcomes, including social engagement, in older adult populations[51,52]. Meaning in life may also be a protective factor against suicide[53]. A recent study reported that the presence of meaning showed an inverted U-shaped pattern across the life span, peaking around the age of 60 and decreasing subsequently as physical health declines[50].

Life review therapy is an individual or group story-telling intervention with a focus on integrating life stories through different phases in life. A randomized controlled trial found that life review therapy significantly improved the quality of life of older participants[54]. A meta-analysis of randomized controlled trials showed that life review therapy has moderate effects on depressive symptoms in older adults[55].

Community engagement

Community engagement is a key beneficial social determinant of mental health in older adults. There are many communities across the world, including those which are formally part of the WHO's Age-Friendly Communities (AFC) Network, in which older adults are actively involved, valued and supported, with a focus on affordable housing, built environments conducive to active living, inexpensive and convenient transportation options, opportunities for social participation and leadership, intergenerational programs, and accessible health and wellness services[56].

The Compassionate Communities and Cities (CCC) movement seeks to promote the motivation of communities and cities to take greater responsibility for the care of people near the end of life. A systematic review of the studies of CCC programs reported that the evidence for their implementation is still limited[57]. A global model for the development and evaluation of CCC in palliative care is warranted.

POSITIVE PSYCHIATRY AND SUCCESSFUL AGING

Positive psychiatry is the science and practice of psychiatry that seeks to understand and promote well-being through assessment and interventions involving positive psychosocial factors in people with or without mental or physical illnesses[58]. A critical construct in positive psychiatry that relates to older adults is "successful aging".

The definition of successful aging and its determinants remains variable. The original model by Rowe and Kahn[8], derived from the MacArthur Research Network, included three domains: absence of disease and disability, high cognitive and physical functioning, and active engagement with life. This model has been criticized for its overemphasis on physical health, which fails to account for many older individuals with physical morbidity who subjectively rate themselves as aging successfully and report a high degree of satisfaction in later life stages[59], and for ignoring a dynamic lifespan perspective[60].

Qualitative studies of successful aging indicate that older adults consider the ability to adapt to circumstances and the positive attitude toward the future as being more important to their sense of well-being than an absence of physical disease and disability[59]. Investigations have also revealed a paradox of aging: even as physical health declines, self-rated successful aging and other indicators of psychosocial functioning improve in later life[61]. Largely similar findings have also been reported in Eastern cultures[62].

A broad definition of successful aging should have the following components: a) subjective well-being, with low level of perceived stress (the extent to which an individual perceives that current demands or challenges exceed his/her ability to cope with them); b) flourishing, which involves eudemonic well-being, including meaning in life and close social relationships[63]; c) post-traumatic growth; d) sustained remission or recovery in people with severe mental disorders, that typically includes an absence or a marked reduction of symptoms along with functional independence.

Neuroscience research during the past three decades has demonstrated a neurobiological basis for successful aging, despite age-associated degenerative changes. There is strong evidence for neuroplasticity in active older adults – i.e., if there is optimal physical, cognitive and social activity, the development of new synapses, dendrites, blood vessels, and even neurons in specific subcortical regions, such as the dentate gyrus of hippocampus, can and does take place[64,65].

Clinical research supports a model in which positive psychological traits such as wisdom, resilience and social engagement interact with and feed into each individual's evaluation of the degree of well-being and are stronger predictors of outcomes such as self-rated successful aging than physical health. We must add that aging is characterized by notable heterogeneity and, therefore, the proposed model would not apply to all the older adults.

COGNITIVE AGING

Cognitive aging is a process that is ubiquitous with humans and occurs gradually throughout adult life[66]. Clinicians caring for older adults should be aware of this process because it does impact social functioning.

Episodic memory and executive function are crucial domains affected by the aging process, and exhibit on average a gradual decline over many years, accelerating in later life[67]. Even normal changes in cognition, however, are quite variable, within and between individuals[61]. Some functions may improve over time, such as wisdom, altruism, prosocial behaviors and reasoning ability in social conflicts[68,69].

The evaluation of the person with potential cognitive aging cannot be limited to the use of typical screening tools such as the Mini-Mental State Examination (MMSE)[70] or the Montreal Cognitive Assessment (MoCA)[71]. The family is perhaps the best source of information. Queries which can be informative include: "Is __ as sharp as he/she was before?"; "Does __ have greater difficulty managing finances and other business matters than in the past?"; "Has __ become lost for brief periods in familiar places?"; "Does ___ have more difficulty recalling the names of acquaintances of long standing but which he/she has not encountered recently?"; and "Does __ have more problems with cooking and have to refer to recipes more frequently than in the past?". Individuals with cognitive aging may also be more reluctant to participate in social gatherings. Each of these changes in behavior may be barely noticeable, yet close friends and family typically do notice.

These age-related problems do not derive simply from a milder form of neuronal loss or plaque formation which is less extensive than in Alzheimer's disease. Brain changes do occur, however, such as changes in astrocyte and microglial function and synaptic plasticity[72]. Genetic predisposition, traumatic brain injury, adverse environmental childhood exposures, and poor educational and cognitive enrichment experiences may also

contribute[73]. In other words, many external experiences which potentially can be ameliorated render prevention of greater cognitive decline with aging important across the life cycle, though some causative factors are inherent to the aging brain.

Many comorbid conditions can cause or exacerbate cognitive aging, including diabetes mellitus, vascular conditions of the brain and heart, chronic lung and liver conditions, renal failure, sepsis, delirium, chronic obstructive pulmonary disease, multiple sclerosis, vision and hearing loss, and sleep disorders[74]. Successful treatment of these conditions can often mitigate the cognitive dysfunction[74]. Additionally, many mental disorders have been associated with cognitive decrements, such as major depression (especially treatment-resistant forms), bipolar disorder, schizophrenia, various types of substance abuse, and anxiety disorders[75].

A number of non-pharmacological interventions may be effective on cognitive aging. These include exercise, which is perhaps the most important preventive tool. Physical activity has been found in several studies to assist individuals in maintaining both their physical and cognitive function throughout life, as well as preventing some important chronic conditions[76]. The evidence derives from both observational and intervention studies[77,78].

In addition, reduction of cardiovascular and related metabolic risk factors, such as treating hypertension and diabetes as well as cessation of smoking and losing weight, have been demonstrated effective[79]. The mantra "What is good for the heart is good for the brain" appears to hold true[66]. For example, evidence is mounting that diets, such as the Dietary Approaches to Stop Hypertension (DASH) or the Mediterranean Diet, may be useful[80,81].

Many medications, especially diphenhydramine and benzodiazepines, can produce cognitive decline, and clinicians must take care in their prescription to older adults. Long-term effects, namely a persistence of cognitive dysfunction secondary to the drugs, are less substantiated by the literature. Sleep problems, such as chronic insomnia or sleep-related breathing disorder such as obstructive sleep apnea, may also contribute[74]. Lack of education and little cognitive stimulation may also be involved, yet the evidence for these risk factors is not as strong as for those listed above[82].

A number of somatic interventions have been suggested[66]. Yet, none of these has held up under strict empirical clinical trials. These include stimulant drugs, such as caffeinated beverages, brain stimulating computer-based games, and electrical brain stimulation procedures, such as transcranial direct current stimulation[83-85].

Given the lack of clearly effective interventions and the apparent minor impairment secondary to cognitive aging, clinicians may be hesitant to devote time to helping affected people and their families. Yet, cognitive aging can benefit from discussions by these clinicians with older adults and their relatives, as attention to risk and protective factors can have a significant positive impact.

One area where intervention can clearly be important is alerting the family of the potential for fraud perpetrated upon older adults[86]. The frequency of fraud has increased dramatically in high-income countries, and perhaps in low- and middle-income countries as well. When disturbing messages are delivered to these elders coupled with a demand for immediate response, the potential for fraud that can be very harmful is high. For example, in the US, elders may be telephoned with fraudulent alerts that they owe taxes and may be jailed if these are not paid immediately, coupled with a demand for their social security number. Warnings to older adults and their families can be most helpful in mitigating these threats[86].

NEUROCOGNITIVE DISORDERS

The DSM-5[87] has introduced the term "neurocognitive disorders" to describe the group of disorders with cognitive impairment as the salient feature, encompassing major (or dementia) and mild neurocognitive disorders, and delirium[88]. The term dementia, however, remains the most frequently used, and mild neurocognitive disorder is used interchangeably with the expression "mild cognitive impairment".

The DSM-5 has tried to bring coherence to the criteria for the various subtypes of these disorders under one framework, but its widespread adoption has been limited largely to psychiatry and psychology. The National Institute of Aging-Alzheimer's Association (NIA-AA) Criteria for dementia[89] and mild cognitive impairment[90] are widely used in the neurology literature. The DSM-IV criteria for dementia[91] are still in use, with the major distinction from the DSM-5 being that significant impairment in one cognitive domain is sufficient as long as the functional criteria are met.

The distinction between dementia and mild cognitive impairment is based on the severity of the cognitive deficits and, more importantly, on their functional consequences. For mild cognitive impairment, the International Working Group criteria are commonly applied[92]. With the increasing interest in preclinical syndromes, the concept of "subjective cognitive decline" (i.e., subjective report of decline in cognitive abilities from a previous level, unrelated to an acute event, with normal performance on standard cognitive tests, accounting for age, gender and education) has also received much attention in recent years[93].

The DSM-5 describes cognitive dysfunction by delineating six domains: complex attention, executive function, learning and memory, language, perceptual-motor and social cognition. It recognizes that varying degrees of cognitive impairment are present in several mental disorders, but cognitive dysfunction must be the salient and defining feature for a diagnosis of neurocognitive disorder[88]. The formal acknowledgement of social cognition as a specific cognitive domain in the DSM-5 has spurred much research and clinical interest[94].

Dementia and mild neurocognitive disorder

Dementia and mild neurocognitive disorder are discussed together for several reasons. They are syndromes with shared

etiology, with the main difference being the severity of cognitive impairment and its functional consequences[92]. Cognitive impairment should, in fact, be considered to be on a continuum, with mild cognitive impairment and dementia being categorical constructs imposed on that continuum. This is consistent with the understanding that the pathology underlying dementia, in particular that due to Alzheimer's disease[95], can take several decades to build up in the brain, and cognitive impairment is similarly slow to develop and progress[95].

Epidemiology

While there are many challenges in "counting" cases of dementia, partly related to the purpose for which this is being done[96], several systematic efforts have been made. The latest global estimate from the Global Burden of Disease Study 2019 is 57.4 million (95% CI: 50.4-65.1) cases worldwide in 2019, projected to increase to 152.8 million (95% CI: 130.8-175.6) in 2050. This rise in prevalence is attributable to the increase in the elderly population, with the age-standardized prevalence remaining stable[97]. There is much regional variation, with the smallest increases projected for Western Europe and high-income Asia-Pacific, and the largest increases for North Africa, Middle East, and Eastern sub-Saharan Africa.

The incidence of dementia is showing a different trend, with several studies from high-income countries, and one from Nigeria, showing a decline, especially in the last three decades[98,99]. No specific cause for this decline has been found, but changes in education, living conditions and health care are thought to have contributed.

The epidemiology of mild cognitive impairment has been less well studied. The published prevalence estimates vary by the diagnostic criteria being used[92]. Applying uniform criteria in the Cohort Studies of Memory in an International Consortium (COSMIC), the crude prevalence in those over 60 years was 5.9% (95% CI: 5.5-6.3) overall, increasing from 4.5% at age 60-69 to 5.8% at 70-79, and to 7.1% at 80-89 years. This was unaffected by gender and did not differ between White Caucasian and Chinese groups[100].

Risk and protective factors

Twelve potentially modifiable risk/protective factors for dementia have been recently identified, as listed in Table 1[101]. To the previously documented nine risk factors with good supporting evidence (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact), three new ones have been added (excessive alcohol consumption, traumatic brain injury, and air pollution).

Together, these factors account for about 40% of dementia risk worldwide, which can theoretically be prevented[102]. The potential is greater in low-income countries, in which the prevalence of some of the risk factors is higher. An ambitious prevention program in terms of both policies and individual action has been therefore proposed, while recognizing that individual behavioral change, on which much of this depends, is difficult to achieve[102]. There has also been an international consensus on enlarging the vista of dementia to include cerebrovascular disease, with the Berlin manifesto of "preventing dementia by preventing stroke"[103].

Table 1 Modifiable risk factors of all-cause dementia (adapted from Livingston et al[101])

	Relative risk for dementia (95% CI)	Weighted population attributable fraction (%)
Less education	1.6 (1.3-2.0)	7.1
Hearing impairment	1.9 (1.4-2.7)	8.2
Traumatic brain injury	1.8 (1.5-2.2)	3.4
Hypertension	1.6 (1.2-2.2)	1.9
Excessive alcohol consumption (>21 units/week)	1.2 (1.1-1.3)	0.8
Obesity (body mass index ≥30)	1.6 (1.3-1.9)	0.7
Smoking	1.6 (1.2-2.2)	5.2
Depression	1.9 (1.6-2.3)	3.9
Social isolation	1.6 (1.3-1.9)	3.5
Physical inactivity	1.4 (1.2-1.7)	1.6
Diabetes	1.5 (1.3-1.8)	1.1
Air pollution	1.1 (1.1-1.1)	2.3
Total		39.7

Prevention

The evidence that the modification of lifestyle and other risk factors can slow cognitive decline and potentially delay the onset of dementia, or prevent it, is gradually accumulating[102].

For most risk factors, the evidence comes largely from observational studies, although some controlled trials are also available[101]. While individual factors – such as education, physical activity, and control of vascular risk factors – are important to address, it is the lifelong cumulation of risk that appears to be most potent. Multimodal interventions over long periods have therefore been investigated.

The best-known investigation is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER Trial)[104], a 2-year multi-domain randomized controlled trial in which the active arm included dietary counseling, physical exercise, cognitive training, and vascular and metabolic risk monitoring. Over 24 months, the improvement in global cognition was 25% higher in the intervention group compared to the general health advice control group. The improvement was observed regardless of demographic and socioeconomic factors, and was also seen in people with genetic susceptibility (*APOE*4* positive) to Alzheimer's disease[105]. Long-term data from this trial, to explore whether the intervention did indeed prevent de-

mentia, are not yet available.

While the FINGER trial generated much enthusiasm, two other large multi-domain trials, the Multi-domain Alzheimer Preventive Trial (MAPT)[106] from France and the Dementia by Intensive Vascular Care (PreDIVA)[107] from the Netherlands, were negative on their primary outcomes (respectively, cognitive decline and all-cause dementia). Sub-analyses of these trials, however, revealed that there was benefit in people with increased risk of dementia.

This highlighted the need for further research and resulted in the development of an international network of trials called the World-Wide FINGERS (WW-FINGERS)[108], which encompasses 25 countries, including some low- and middle-income countries. Some of the trials, such as the Maintain Your Brain Trial in Australia[109], are completely online. This network, with the stated objective of data sharing and joint analyses, has the potential to provide the evidence base to develop prevention of dementia policies across communities and jurisdictions.

While policy change will need to await such evidence, it is reasonable, at an individual level, to advise older people at risk of cognitive decline to implement the measures of controlling vascular risk factors, optimizing their physical, mental and social activities, reducing stress, treating depression if present, and following a balanced Mediterranean-like diet[110]. Indeed, it would be reasonable to argue that dementia prevention is a life-long endeavor, the seeds of which are sown in childhood with good education and a nurturing environment.

Neuropsychiatric symptoms of dementia

Neuropsychiatric symptoms are a common reason for referral of a dementia patient to a psychiatric service. They also lead to much distress, both for the patient and his/her caregivers, and contribute to hospitalization and early admission to residential care[111].

Several approaches have been used for the categorization of these symptoms, with none being completely satisfactory. They include agitation and aggression, psychotic symptoms (delusions, hallucinations), mood symptoms (depression, anxiety, elation, apathy), sleep and appetite disturbances, and ruminative, repetitive and somatoform behaviors[112]. Apathy has been reported to be the most common symptom, followed by depression and agitation/aggression[113].

The Neuropsychiatric Inventory (NPI)[114] is the most commonly used instrument for the assessment of these symptoms in clinical trials, but it does not include all of them and is based on informant report. Other commonly used measures are the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[115] and the Cohen-Mansfield Agitation Inventory[116].

Recent work has shown that neuropsychiatric symptoms may occur early in the course of dementia, at the stage of mild cognitive impairment or even before that. This has resulted in the concept of "mild behavioral impairment"[117]. There is some evidence that individuals with mild cognitive impairment who also have neuropsychiatric symptoms are at risk of faster progression to dementia[118].

The treatment of neuropsychiatric symptoms remains a challenge. The current evidence suggests that the role of drug treatment is limited, and non-pharmacological strategies are first line[119], in particular some behavioral management techniques, especially those involving caregiver- and staff-oriented interventions[120]. However, drug treatment is still common, with frequent adverse effects. Antipsychotics such as risperidone, aripiprazole and quetiapine have evidence supporting short-term use for agitation or psychotic symptoms, but with increased risk of stroke and confusion or cognitive decline, along with extrapyramidal and metabolic adverse effects[121]. Other drugs used in some patients include antidepressants (e.g., citalopram, sertraline, mirtazapine), cholinesterase inhibitors, memantine, benzodiazepines and analgesics, all with limited evidence[112].

A number of small drug trials have also been conducted to treat neuropsychiatric symptoms in frontotemporal dementia[122] and dementia with Lewy bodies[123], but with limited evidence of success. A narrative review[124] and a Delphi consensus group[125] supported the use of donepezil and rivastigmine for neuropsychiatric symptoms of dementia with Lewy bodies, although a network meta-analysis found that these drugs improved neuropsychiatric symptoms in Parkinson's disease dementia, but not in dementia with Lewy bodies[123]. Among antipsychotics, aripiprazole was reported in a small study to be effective and well tolerated for the treatment of psychotic symptoms in patients with dementia with Lewy bodies[126].

There is an ongoing attempt to better understand the neurobiology of neuropsychiatric symptoms of dementia, so that rational therapeutics can be developed[112].

Organization of services

The journey of a person with dementia is long and arduous, and often begins with a delay in diagnosis or its lack altogether. A pooled analysis reported that rates of undiagnosed dementia are as high as 70.7% in Canada, 43.1% in UK, 58.2% in Europe, and 61.7% worldwide[127]. The WHO Global Dementia Action Plan[128] aims to reduce this to 50% in 50% of countries by the year 2025.

The communication of the diagnosis to the patient and/or his/her family, once it is made, is often poor, with only 34% of primary care physicians and 48% of specialists routinely informing the individual about the diagnosis[129]. A negative reaction to the diagnosis is common, which is understandable considering the prevalent anti-dementia stigma in society[130,131].

The diagnosis of dementia should be followed by a management plan for the short and long term, to maintain optimal function and quality of life as long as possible. Too often, the diagnosis is followed instead by advice for disengagement from society[132], which may set up the path to more rapid decline.

There are several worldwide challenges to providing high-quality care to persons with dementia and their families. Both the direct and indirect costs of care are high, and public investment in

this area has been inadequate, even in high-income countries, although dementia was declared a public health priority by the WHO in 2015[133].

The capacity to provide care at home is often insufficient, and systems to ensure the safety and quality of care are not commonly implemented. Institutional care is frequently of poor quality, because of lack of resources and adequately trained staff. People with young-onset dementia and those from ethnic or other cultural minorities are often poorly catered for.

As the world faces a growing dementia population, the health services, and society in general, need a concerted and coordinated response underpinned by high quality. Several international examples of good practices are available for adoption in diverse settings[134,135]. The Global Dementia Observatory of the WHO monitors the public response to dementia in all countries on 35 key indicators, with the objective of achieving the global targets of the Global Dementia Action Plan by 2025[136].

Directions for future clinical practice and research in dementia are provided in Table 2.

Specific dementias

There have been major advances in the last two decades in our understanding of the pathophysiology and biomarkers of specific dementias, in particular Alzheimer's disease. There have also been significant developments in the knowledge about pathology of dementia, including the description of a potentially new form, limbic-predominant age-related TDP-43 encephalopathy (LATE).

Table 2 Directions for future clinical practice and research in dementia

1. Neurocognitive disorders should remain categorized as mental disorders in the DSM and ICD, and psychiatry should play a major role in comprehensively assessing and treating these conditions.
2. A global effort should be made to better understand the origins and disease mechanisms of the various dementia subtypes.
3. An international effort should be promoted to improve epidemiology research on dementia in low- and middle-income countries and to develop global platforms for data sharing.
4. A global effort should be made to develop prevention strategies which are tailored to different populations based on differential risk factor profiles and behavioral repertoires.
5. Clinical services and diagnostic pathways should be improved, so that patients with dementia and mild cognitive impairment can receive an early and accurate diagnosis.
6. Better models of collaborative care for dementia should be developed that are accessible to all, both in the immediate period after a diagnosis and in the longer term.
7. The neuropsychiatric symptoms of dementia should be better understood, so that neurobiologically informed treatments can be developed.
8. The newly developed biomarkers of Alzheimer's disease should be made affordable and clinically available, and biomarkers should be developed for the other dementia subtypes.
9. Drug development for dementia should become a global effort, with the objective that new treatments are tested in all populations, and when brought to the market are affordable and accessible to all.
10. All societies should develop policies and procedures to address ageism and stigma against dementia.

Alzheimer's disease

While the hallmark features of plaques and tangles in Alzheimer's disease have been known for over a century, the understanding of the detailed pathologies involved is more recent. The pathogenesis of the protein abnormalities, the β-amyloid (Aβ) peptides that aggregate to form the amyloid fibrils of the neuritic plaque, and the hyperphosphorylated tau that forms the neurofibrillary tangles, is now much better understood[137].

This is associated with other processes such as neuroinflammation, oxidative stress, autophagy, dysfunction of the glymphatic system, alteration in blood vessels, leakage of the blood-brain barrier, and abnormality in the gut microbiome, all contributing to the cellular pathology underlying Alzheimer's disease[138].

There has long been a controversy on the relative importance of amyloid and tau in the pathogenesis of Alzheimer's disease. The most popular model is the "amyloid hypothesis", which posits that Aβ, most likely in its soluble oligomeric form, initiates a pathophysiological cascade which leads to the hyperphosphorylation and misfolding of tau[139]. The misfolded tau is then propagated through the cortex in a prion-like fashion, leading to cellular failure and the development of cognitive deficits[140]. The complex Aβ-tau interactions are incompletely understood, and it seems likely that both pathologies are important and have a synergistic effect[139].

Diagnosis and biomarkers

Alzheimer's disease accounts for 55-60% of all cases of dementia. The clinical features are well described, with salience of disturbance of episodic memory in the early stages. The clinical criteria used most commonly are the NIA-AA criteria for dementia[89] and mild cognitive impairment[90] due to Alzheimer's disease.

With the recent development of biomarkers for amyloid (A), tau (T) and neurodegeneration (N), Alzheimer's disease has also been described using the AT(N) framework, with a diagnosis requiring the presence of both A and T[141]. This approach distinguishes the pathological process of the disease from the clinical syndrome, recognizing that pathology precedes the development of neurodegeneration and clinical features by several years, if not decades.

A hypothetical model of dynamic biomarkers has been proposed to explain the pathophysiological process of Alzheimer's disease[142], in which Aβ deposition occurs independently and accelerates tauopathy, which then leads to neurodegeneration detectable on magnetic resonance imaging (MRI) and positron

emission tomography (PET) before cognitive symptoms become manifest.

There have been updates of the AT(N) classification to accommodate vascular pathology[143] and other pathologies such as neuroimmune dysregulation, synaptic disruption and blood-brain barrier breakdown[144].

One of the most significant recent advances in Alzheimer's disease has been the development of biomarkers, as listed in Table 3. PET imaging was first established for amyloid[145] and later for tau[146], and both are now in clinical use. It is now possible to assess amyloid and tau status with high specificity and sensitivity by the cerebrospinal fluid measurement of Aβ42 level, Aβ42/Aβ40 ratio and phospho-tau (pTau) levels, for which standardized procedures have been developed[144].

More recently, the development of blood biomarkers for Alzheimer's disease has raised the prospect of affordable and readily accessible tests. While Aβ42/Aβ40 ratio shows promise, more work is needed to standardize its measurement before clinical use[147]. Some pTau fragments (pTau181, pTau217 and pTau231) in the blood have been shown to accurately reflect brain pathology and are rapidly emerging as biomarkers[148]. Blood levels of neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) may accurately reflect neurodegeneration and neuroinflammation, respectively[148].

Genetics

The genetics of Alzheimer's disease has seen major advances in recent years. The fully penetrant mutations in three genes (amyloid precursor protein, presenilin 1 and presenilin 2), that cause disease of early onset, have been known for some time[149]. The main risk gene for sporadic disease is the ε4 allele of the apolipoprotein E gene (*APOE*4*), which increases risk by 2-3 fold in the heterozygous state and 10-12 fold in the homozygous condition.

Genome-wide association studies and next generation sequencing have led to the discovery of an additional >40 genes with small effect (odds ratios of 1.05 to 1.20). Collectively, the polygenic risk score for Alzheimer's disease can distinguish patients from controls with 75-85% accuracy[150].

Treatment

The recent approval by the US Federal Drug Administration (FDA) of a disease-modifying drug, aducanumab[151], has been seen as a major milestone[152]. This is a human monoclonal antibody that targets the amyloid protein and is administered by monthly intravenous infusions.

However, its approval has generated considerable controversy. Phase 3 studies were initially terminated after a futility analysis, but a *post-hoc* analysis led to "accelerated" approval by the FDA because it showed reduction of brain amyloid as a surrogate marker, even though the clinical benefit criterion was not met[153], and the drug showed significant adverse effects in the form of cerebral edema and hemorrhage. This approval occurred despite the advice of the independent advisory committee of the FDA, and came with a price tag of US$ 56,000 per year for the drug.

The validity of reduced amyloid in the brain as a surrogate marker for clinical benefit has been questioned[154]. Nevertheless, many clinicians are preparing for the rollout of the drug in the US, and approval in other countries is being sought. The manufacturers of aducanumab have been given 6-year approval by the FDA to provide evidence of clinical benefit. Guidelines for its appropriate use are beginning to be published[155]. Aducanumab may be the first of several disease-modifying drugs coming to the clinic, and has generated renewed interest in drug treatment of Alzheimer's disease and other dementias.

Other dementias

Advances in other dementias – such as vascular dementia, dementia with Lewy bodies, and frontotemporal dementia – have

Table 3 Biomarkers in the diagnosis of common dementing disorders

	Biomarker class	Imaging	Cerebrospinal fluid	Blood
Alzheimer's disease	Amyloid (A)	PET (Pittsburgh compound-B, ^{18}F ligands)	Aβ42 level; Aβ42/Aβ40 ratio	Aβ42 level; Aβ42/Aβ40 ratio
	Tau (T)	PET	pTau	pTau181; pTau217; pTau231
	Neurodegeneration (N)	MRI, FDG PET	tTau; NfL	NfL
	Synaptic loss	FDG PET	Neurogranin	
	Neuroinflammation	TSPO PET	GFAP; TREM2	GFAP
Dementia with Lewy bodies	Neurodegeneration	MRI, FDG PET		
	Parkinsonism	DAT imaging, MIBG heart scintigraphy		
Frontotemporal dementia	Neurodegeneration	MRI, FDG PET	NfL	NfL

PET – positron emission tomography, FDG – fluorodeoxyglucose, MRI – magnetic resonance imaging, Aβ – amyloid beta, pTau – phosphorylated tau, tTau – total tau, NfL – neurofilament light chain, GFAP – glial fibrillary acidic protein, TREM2 – triggering receptor expressed on myeloid cells-2, TSPO – translocator protein (18 kDa), DAT – dopamine transporter, MIBG – ^{123}I-metaiodobenzylguanidine

been significant, but not as striking as those in Alzheimer's disease.

Vascular cognitive impairment and dementia

Vascular dementia has seen a broadening of the concept to vascular cognitive impairment and dementia[156], and new diagnostic criteria[157,158] have been proposed.

Vascular dementia is the second most common form of dementia, accounting for about 15-20% of all cases[159]. Vascular contributions to dementia are, however, much more common in autopsy studies, with up to 75% having some vascular pathology[160] and about one-third having significant vascular pathology[161].

Recently, international collaborations, such as the Stroke and Cognition Consortium (STROKOG)[162] and the METACOHORTS Consortium[163], have been formed to expedite the development of new treatments and prevention efforts. A framework for research priorities in the cerebrovascular biology of cognitive decline has been proposed[164]. The priorities include the development and validation of imaging and biospecimen-based biomarkers, better experimental models, and increased understanding of the underlying molecular and physiological mechanisms – white matter disease, infarction, microhemorrhage, vascular autoregulation, glymphatic flow, metabolic processes – and the interaction between vascular and Alzheimer pathologies[164].

Dementia with Lewy bodies

Dementia with Lewy bodies has seen the publication of the fourth consensus report on its diagnosis and management[165], which has clearly distinguished between clinical features and diagnostic biomarkers. The report gave more weighting to rapid eye movement (REM) sleep disorder, that involves recurrent dream enactment behavior, in the clinical criteria. The disproportionate deficits in the cognitive domains of attention, executive function and visual processing relative to memory and naming were highlighted.

While there are still no direct biomarkers to establish dementia with Lewy bodies, indicative biomarkers include reduced dopamine transporter (DAT) uptake in the basal ganglia on single photon emission computerized tomography (SPECT) or PET imaging[165,166], reduced iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy uptake[165], and polysomnographic confirmation of REM sleep without atonia[167].

While the genetic architecture of this form of dementia is poorly understood, genome sequencing has identified new loci, and genetic risk scores suggest that it shares risk profiles with Alzheimer's and Parkinson's diseases[168].

There is evidence for the beneficial effects of cholinesterase inhibitors, but not memantine, on cognition[169], but parkinsonism is less likely to respond to dopaminergic drugs compared to Parkinson's disease, with an increased risk of psychosis[170].

Frontotemporal dementia

Frontotemporal dementia is an umbrella term for a diverse group of neurodegenerative disorders characterized by atrophy in the frontal and temporal lobes, with a clinical picture dominated by a behavioral-executive dysfunction (behavioral variant) or a language disturbance (semantic and progressive non-fluent aphasia variants)[171].

Because of the psychiatric features of the behavioral variant, psychiatrists are often the first professionals to see such patients[172], and the condition may be misdiagnosed as obsessive-compulsive disorder, schizophrenia, bipolar disorder or depression, because of some shared features[172]. Personality change is often an early feature of this behavioral variant; there may be features of borderline, antisocial, schizoid or schizotypal personality. Substance abuse may be present[172]. About 50% of patients with frontotemporal dementia initially receive one of the abovementioned psychiatric diagnoses, leading to a delay in the correct diagnosis of up to 5-6 years[171].

Frontotemporal dementia is usually a young-onset disorder, being the second or third most common cause of dementia of young onset, accounting for 3-26% of such cases in various studies[173]. About a third of cases are familial, with three autosomal dominant genes commonly implicated: progranulin (GRN), chromosome 9 open reading frame 72 (C9orf72), and microtubule-associated protein tau (MAPT). However, several other genes have been involved. Rare mutations include TAR DNA-binding protein 43 (TDP-43), fused-in sarcoma (FUS), valosin-containing protein (VCP), and the CHMP2B genes. The C9orf72 mutations are the most common genetic form and may initially present as a late-onset psychosis. These mutations have also been rarely reported in patients with schizophrenia and bipolar disorder[174,175].

The inclusions in frontotemporal dementia contain tau, TDP-43 or FUS proteins. There is increasing research in developing fluid biomarkers for this form of dementia, with NfL showing promise as marker of neurodegeneration[176], but without specificity.

Differential diagnosis from psychiatric disorders and other neurodegenerative diseases is often aided by neuroimaging, using MRI and PET. There is predominant atrophy of frontal and temporal lobes, which is asymmetrical in the early stages, and this is associated with hypometabolism and hypoperfusion in these regions. Differential diagnosis from the frontal variant of Alzheimer's disease is assisted by amyloid imaging[177].

There is currently no approved drug treatment for frontotemporal dementia. The focus of treatment is on the management of neuropsychiatric symptoms. The symptoms targeted have been apathy, disinhibition, obsessive-compulsive and hoarding behaviors, loss of empathy and prosocial behavior, loss of insight, and psychosis, but results thus far have not been conclusive for the various interventions investigated[122]. Drugs to modulate the serotonergic and dopaminergic systems are used off-label to treat these symptoms, but with modest success[122].

Limbic-predominant age-related TDP-43 encephalopathy (LATE)

LATE is a recently described entity which affects older people and presents with an amnestic picture resembling Alzheimer's disease[178]. Its pathology – which typically involves the amygdala, hippocampus and middle frontal gyrus – is common in older brains, seen in nearly 25% of brains at autopsy in a community cohort[179].

The pathogenesis and clinical picture of this condition, and its status in relation to Alzheimer's disease and frontotemporal dementia, are only beginning to be understood.

Delirium

The DSM-5 recognizes delirium as a cognitive disorder with a disturbance of attention (i.e., reduced ability to direct, focus, sustain and shift attention) and awareness (i.e., reduced orientation to the environment). This often leads to what has been referred to as a confusional state or reduced level of consciousness[180].

The presentation is multifaceted, with several cognitive domains being affected, along with altered sleep-wake cycle, emotional lability, delusions, agitation, and other motor and behavioral disturbances. Two forms of delirium – hyperactive and hypoactive – have been described, with the hypoactive form being more common in older people and having a worse prognosis[181].

Delirium remains a clinical diagnosis, with no validated biomarkers. Various inflammatory, metabolic and neurotransmitter-based markers have been investigated, but their clinical application is limited[182]. The electroencephalogram (EEG) may be used as a supportive test, but it has low specificity and sensitivity, and its application is mainly to distinguish delirium from a primary mental disorder or a non-convulsive status epilepticus[183].

The lack of biomarkers and the diverse and sometimes subtle clinical features of delirium often result in its under-recognition. In one study[184], conducted in the context of palliative care, 60% of patients with delirium had not been diagnosed by the treating physician. A high index of suspicion, especially in older individuals in settings where delirium is most likely, is important, preferably complemented by a delirium screening tool[185]. One of the most widely used is the Confusion Assessment Method (CAM)[186], which can alert the clinician to the likelihood of delirium in an individual case.

The pathophysiology of delirium is incompletely understood. Older age is an independent risk factor, and this has been attributed to several changes associated with brain aging, which include reduced blood flow and vascular density, neuronal loss, and changes in neurotransmitters and intracellular signal transduction systems[187]. Numerous predisposing and precipitating factors for delirium have been identified, resulting in its characterization as a state of acute brain failure through multiple pathways. Several hypotheses for its development have been proposed, such as the oxidative stress hypothesis[188], the neuroinflammatory hypothesis[189], the neuroendocrine hypothesis including the role of aberrant stress[190], and the circadian rhythm dysregulation hypothesis[190].

Since the various pathways do not occur in isolation, and do not lead to distinct consequences, delirium is best understood as a large-scale neural network disruption[182], with several processes (i.e., neuroinflammation, neurotransmitter dysregulation, oxidative stress, neuroendocrine disturbance, and circadian rhythm dysregulation) contributing to varying degrees in different situations.

Several clinical management guidelines for delirium have been published[191], which include those from the UK National Institute for Health and Care Excellence (NICE)[192] and the American Geriatrics Society[193]. The emphasis is on prevention, with the use of multicomponent non-pharmacological approaches. The various components are attention to the environment, encouraging ambulation and exercise, early mobilization following surgery, maintaining a fluid balance, attention to adequate nutrition, improving vision and hearing, sleep enhancement, infection prevention, pain management, hypoxia control, and optimization of medications[180]. A non-pharmacological approach based on the above-mentioned components is also the mainstay of treatment. Drug treatment is generally avoided, except for benzodiazepines in delirium from alcohol or benzodiazepine withdrawal.

While antipsychotics such as risperidone, haloperidol, ziprasidone and olanzapine are sometimes used to manage agitation or psychotic symptoms in delirium, there is a lack of strong evidence to support their use[194].

LATE-LIFE MAJOR DEPRESSION

The recognition of major depression is of great clinical importance across the life cycle, and no less so in older adults[195]. This condition presents increasing public health challenges to both high-income and low- and middle-income countries, reflecting demographic shifts to older populations and scarcity of treatment resources[195,196]. It is the second leading cause of disability worldwide, up from the third as of 1990[197].

The hallmark of major depression in old age is its co-occurrence with physical disorders and frailty, mild cognitive impairment, social determinants of health (e.g., major role transitions, bereavement, loneliness and social isolation), exposure to polypharmacy, and heightened risk for suicide. Late-life major depression is also a significant source of caregiver burden for family members.

Approximately 6.7% to 7.5% of older adults report an episode of major depression within one year, among those attending primary care clinics[195]. Rates are still higher among medical inpatients and residents in long-term care, rising with increasing disability and frailty. Women experience 1.7 times the risk as men. Prevalence rates are likely to be higher in marginalized groups, such as those of lower socioeconomic status. The life-

time suicide rate is 25 times greater in major depression than in the general population, with highest rates amongst older adults[196-198].

Major depressive disorder and depressive symptoms not only bring suffering to those afflicted, but also produce amplification of disability from co-occurring physical disorders, poor adherence to co-prescribed treatments, failure to make healthy lifestyle choices, and increased risk for frailty, dementia, and early death. On the other hand, evidence-based treatments work, if delivered appropriately, and may both prolong life and enhance its quality[199].

In essence, the global public health and clinical burden of depression in old age has three dimensions: it is a mirror of brain aging, a mediator of bad outcomes, and a murderer that leads to dementia and to suicide. It is also an unwanted co-traveler with the ills of aging: cancer, cardiovascular disease, and neurodegenerative disorders[195-197].

Major depression in older adults is characterized by variability at multiple levels: etiopathogenesis, clinical presentation, and response to prevention and treatment. A staging-model perspective, analogous to oncology, is useful[200,201]. Some older adults may present with mild or subsyndromal symptoms; some with new-onset major depression; some with recurrent episodes which began earlier in life and show in later years shortening inter-episode intervals and increasing treatment resistance; and still others are ravaged by chronic depression and its sequelae.

Staging has implications for differential diagnosis, intervention and prognosis[202]. Subsyndromal pictures represent opportunities for the indicated prevention of major depression. First episodes, while treatable, may also be prodromal expressions of dementia. Recurrent depressive episodes and chronic depression pose challenges of increasing treatment resistance and heightened risk for dementia. As in oncology, early intervention to prevent the transition to incident episodes and to recurrence may be life-saving and life-enhancing, by taking advantage of neuroprotective mechanisms early in the course of illness, while reversibility may still be attainable[200,201].

In this context, the relationship of insomnia disorder to depression is clinically relevant, because insomnia is not only a symptomatic manifestation of major depression, but also a risk factor for incident and recurrent depressive episodes. Persistent insomnia (insomnia disorder) heightens the risk for a chronic relapsing course and thus warrants independent clinical attention to optimize outcomes[203].

Insomnia may partially mediate depression risk for Alzheimer's and related dementias via beta-amyloid accumulation, tau protein aggregation, inflammation and blood-brain-barrier disruption[204-206]. It is also a driver of suicidal ideation and behavior, and may be a modifiable risk factor for suicide[203,207].

A long-term view of late-life depression is necessary clinically: getting well is not enough, it is staying well that counts, given the propensity of depression to relapse, recurrence, chronicity, and treatment resistance, not to mention heightened risk for dementia and suicide.

Prevention

Major depression can be prevented across the life cycle[196,208]. The case for its prevention in the later years of life is important from both public health and clinical perspectives. Major depression is prevalent, persistent and burdensome in respect to both morbidity and mortality. Treatment is only partially effective in reducing years lived with disability. There is, moreover, limited access to treatment, related to both mental health workforce issues and barriers confronting socially disadvantaged older adults and those from racial/ethnic minorities. The social inequalities of risk widen with age, generating disparities of access, utilization and response. This treatment gap reinforces the need for the development and implementation of pragmatic prevention programs[208].

A meta-analysis[209] estimated a reduction of about 20% in the incidence of major depressive episodes over 1-2 years, compared with care as usual or waitlist, through the use of brief behavioral or learning-based psychotherapies (such as CBT, interpersonal psychotherapy, problem-solving therapy, and behavioral activation). The 38 randomized controlled trials included in the meta-analysis enrolled mixed aged (adult and geriatric) participants, receiving care in high-income countries. Studies investigated either indicated prevention (in persons already living with mild or subsyndromal symptoms) or selective prevention (in those with physical or psychosocial risk factors for depression, such as stroke or age-dependent macular degeneration).

Only one randomized controlled trial of depression prevention specifically focused on older adults with mild symptoms (indicated prevention) has been conducted in a low- or middle-income country[210]. The "DIL" intervention (meaning "Depression in Later Life" and also representing the local Konkani word for "heart") was delivered by lay counselors to older adults at rural and urban primary care clinics in Goa, India. The intervention model was multi-pronged, grounded in the strategies of behavioral activation[211], but also including brief behavioral treatment for insomnia[212], education in better self-care for common physical disorders such as diabetes and osteoarthritis, and assistance in accessing medical and social services.

Over one year, DIL led to a reduction in the incidence of major depressive episodes compared to care as usual (4.4% versus 14.4%, log rank p=0.04) and in the burden of depressive and anxiety symptoms (group x time interaction: p<0.001). Participants randomly assigned to DIL reported to more frequently engage in pleasurable social and physical activities – a countermeasure to the "tension" and worry that plagued their daily lives. They took a more active hand in managing their health, coming to feel more in control and less helpless[210]. If these findings are replicated, the DIL intervention may be scalable to other low- or middle-income countries.

More recently, the VITAL-DEP randomized clinical trials examined the efficacy of two nutraceuticals, vitamin D and fish oils, in preventing incident and recurrent major depressive episodes in over 23,000 older adults, with an over-sampling of African Americans[213,214]. The scope of the trials was wide, examining

universal, selective and indicated prevention of depression. The trials did not, however, detect evidence for efficacy, relative to placebo, with either nutraceutical, despite a cogent neurobiological rationale for positing the prophylactic effect of each, singly and in combination. For example, vitamin D and/or fish oils could lower depression risk via reduction in inflammation and oxidative stress, and improvement in vascular/metabolic health and neuroprotection. These processes represent senescence-associated secretory phenotypes (SASPs), i.e., molecular signatures of aging[215].

Studies such as DIL and VITAL-DEP highlight the importance of addressing the interplay between behavioral and biological factors involved in aging processes. Moreover, attention to workforce issues (via the use of task sharing or shifting to lay counsellors) and to the streamlining of evidence-based behavioral interventions and psychotherapies, with sensitivity to differing cultural contexts, may help to optimize cost-utility of prevention interventions. Identifying biomarkers of risk that may mediate or moderate response to preventive interventions remains a vital part of the research agenda in late-life depression.

Treatment

Treatment goals for major depressive disorder in older adults should include not only symptomatic remission, but also functional recovery; reduction of risk for relapse, recurrence and chronicity; and protection and maintenance of brain health and cognitive fitness[216]. Combined treatment (antidepressant medication plus depression-specific psychotherapy) may be more effective than either alone in some populations, but side effect risks and patient demands/burdens may be greater[5,6,195,217].

Psychotherapies may have a greater impact than antidepressant medication in the long run[216,217]. Moderators of outcome include individual patient-level differences such as those concerning gender, ethnicity, disability status, neurocognitive performance, and physical comorbidity. Therapist competence (including ability to tailor treatment to the individual), therapeutic alliance, and patient preferences all influence the strength of response to treatment[6].

The limitations of the available evidence include little comparative research, together with a need for greater attention to long-term effects, comorbidity, and diverse populations. With respect to antidepressant pharmacotherapy, response rates in older adults are greater in trials lasting 10-12 weeks than in those lasting 6-8 weeks. Antidepressants are moderately effective in bringing about remission relative to pill placebo, with numbers needed to treat in the range of 8-13[218]. Learning-based psychotherapies (CBT, interpersonal psychotherapy, problem-solving therapy, behavioral activation) are also moderately effective in bringing about remission[216].

Continuing antidepressant medication in those who have initially done well appears to be effective in preventing relapse during 6-12 months of continuation therapy, and in preventing recurrence for up to three years during longer-term maintenance treatment, with reported numbers needed to treat of about 4[219]. Going forward, pharmacogenomics-informed clinical decision making is likely to continue emerging as a useful strategy in probing treatment response variability (both efficacy and tolerability/safety) and contributing to better outcomes[220,221].

Failure to achieve symptomatic remission after two or more trials of antidepressant pharmacotherapy is common in older adults with major depression. The largest published randomized controlled trial to date amongst older adults ("IRL GREY") – a multi-site, double-blind, placebo-controlled trial of aripiprazole augmentation of primary pharmacotherapy with venlafaxine – demonstrated efficacy for augmentation, yielding a 44% remission rate versus 29% with placebo (number needed to treat: 6.6)[222]. Aripiprazole was well tolerated in analyses of both cardiometabolic and neurological outcomes, and led to a reduction in the prevalence and severity of suicidal ideation.

A randomized pragmatic trial comparing augmentation versus switching class of antidepressant medications for treatment-resistant late-life major depression has recently been completed[223]. Preliminary analyses suggest that pharmacotherapy augmentation strategies (e.g., with bupropion or aripiprazole) are superior to switching strategies (to another monotherapy) in bringing about remission, and are no less safe with respect to such adverse events as falls.

A psychotherapy called "Engage", rooted in a neurobiological framework addressing the reward system network, and streamlined for effective administration by community-based psychotherapists, has been shown to be non-inferior to problem-solving therapy in late-life depression[224], and proposed for combination with pharmacotherapy in patients with persistent symptoms.

Prolonged grief disorder (PGD) is an important but often unrecognized factor in late-life treatment-resistant depression. The ICD-11 and the DSM-5-TR have provided clinical guidelines and diagnostic criteria, respectively, for its diagnosis[225]. In PGD, acute grief becomes chronic, with intense yearning for the deceased, and accompanying symptoms of anguish, loneliness, suicidal ideation and pervasive functional impairment. PGD represents a failure to adapt to loss and to restore meaning in life without the lost loved one. This condition, which frequently coexists with major depression in older adults, responds well to grief-specific psychotherapy, but not to antidepressant pharmacotherapy or to interpersonal psychotherapy for depression[226].

We do not know if treating depression in older adults reduces the risk for dementia[101]. However, slowing cognitive decline in elderly with treatment-resistant depression is now recognized as an important front in the fight against dementia, and a vital aspect in the staging of late-life major depression[101,201].

Progression of late-life depression to Alzheimer's and related dementias is likely to be a multi-mechanism process. Data-driven proteomic analyses have revealed several biological pathways and molecular functions associated with cognitive impairment in late-life major depression, related to neuro-inflammatory control, neurotrophic support, cell survival/apoptosis, endothelial function, and lipid/protein metabolism[204-206]. Experimental studies of dementia prevention in late-life major depression will need to monitor accumulation of tau and beta amyloid, and

white matter disease, provide measures of cognitive and brain health, and document course of depressive illness.

The central question, as yet unanswered, is whether the modulation of biologic cascades related to the pathogenesis of cognitive impairment in late-life major depression can also retard cognitive decline and reduce dementia incidence, particularly in more treatment-resistant depression.

Organization of services

What do we know about the integration of primary care and behavioral health care for the treatment and prevention of major depression in older adults? How do we translate intervention science to real-world care and management of suicide risk?

Collaborative care models integrate behavioral health care and primary care[227,228]. They are the best-known real-world enactments of measurement-based care in older adults. Measurement-based care includes standardized assessment of depressive symptoms, medication side effects, and patient adherence. It uses a multi-step decision tree (algorithm) in treatment planning and patient follow-up. While it provides feedback to assist in the management of patients, it is not a substitute for clinical judgment.

A Cochrane database systematic review has shown that collaborative care models (in mixed-age samples) yield significant improvement in depression and anxiety outcomes compared with usual care. Improvement is evident over the short, medium and long term, with standardized mean differences of 0.25-0.35[227]. Examples of successful models of collaborative care for midlife and older adults in high-, middle- and low-income countries include Improving Mood Promoting Access to Collaborative Care Treatment (IMPACT)[228], Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT)[229], Friendship Bench in Zimbabwe[230], and MANAS[231] and DIL[210] in India.

IMPACT and PROSPECT addressed population- and patient-centered care in older adults with major depression. These studies, showcasing the principal characteristics of collaborative care, embodied evidence-, team-, measurement-, and algorithmic-based strategies to achieve and sustain remission in older adults attending rural and urban primary care clinics. These models facilitate a personalized approach to treating depression in older adults, starting with interventions requiring fewer specialized resources and moving to more elaborate interventions as needed.

In IMPACT[228], over half of the participants in collaborative care reported at least a 50% reduction in depressive symptoms at 12 months, as compared with only 19% of participants in usual care. The benefits persisted for at least one year, when IMPACT resources were no longer available. IMPACT participants experienced more than 100 additional depression-free days over a two-year period.

In PROSPECT[229], resolution of suicidal ideation was faster among intervention participants as compared with usual care; differences peaked at 8 months (70.7% vs. 43.9%). In addition, follow-up after a median interval of 98 months found a 24% reduction in all-cause mortality relative to care-as-usual participants[198]. *Post-hoc* analysis showed that the decline in mortality reflected fewer deaths from cancer. The mechanism of this protective effect could involve an interplay between behavioral factors (e.g., better self-care) and cellular or molecular processes of aging. Thus, a key question for research going forward is whether treating depression effectively modifies the risk architecture for cancer at either or both behavioral and molecular levels.

Further enhancements of collaborative care occur through the use of lay counsellors or community health workers, especially to reach under-served racial/ethnic minorities. The MANAS[231] and the DIL[210] trials, deploying lay counsellors for the treatment and prevention of depression, respectively, in primary care patients (adults and older adults), provide compelling examples of task sharing/shifting to confront workforce issues that impede access to care in under-resourced areas of the world.

Similarly, Chibanda et al[230] have shown that the use of lay health workers for delivering problem-solving therapy ("Friendship Bench") in a resource-poor setting such as Zimbabwe may be effective in the primary care of common mental disorders. Community health workers and lay counselors perform a number of tasks, including screening for depression, relaying results to supervising clinicians, educating persons with depression and their caregivers about the illness and its treatment, facilitating identification of local resources for social and economic support, encouraging self-care and cooperation with primary care for co-occurring physical problems, and delivering depression-specific psychotherapies, such as interpersonal therapy, behavioral activation, and problem-solving therapy, in one-on-one or group formats.

Collaborative care models also facilitate re-engineering care delivery to improve management of suicidal risk in depressed patients. In most countries, suicide rates are highest among older adults, and suicide attempts by older adults are frequently serious, with high lethality potential. Collaborative care promotes an explicit focus on factors that contribute to distress and to suicidal urges versus those that contribute to constraint and resistance[232]. It also integrates counseling with patients and family caregivers to reduce access to lethal means for suicide, together with safety planning and attention to family discord, victimization, and the need for social support. These and other elements of re-engineering practice have been shown in the UK to yield suicide reductions of 22-29%[233].

Going forward, the use of machine learning to identify relevant data in electronic health records[234] and the use of adaptive screening tools[235] may improve our ability to match the intensity of services to level of suicide risk – thereby enacting a fundamental principle of collaborative, stepped-based care. In addition, more research into both the short-term and long-term (maintenance) efficacy and safety of ketamine for the rapid reduction of suicidal ideation in older adults with major depression is warranted[236]. Finally, addressing depression-related reductions in top-down cognitive control should be a goal of psychotherapy in suicide attempters. Deficits in cognitive control result in disadvantageous decision-making and limited problem-solving, contributing to feelings of entrapment and hopelessness[237].

Access to mental health services by older adults with major depression is driven by a shortage and skewed geographical distribution of providers. User-facing apps coupled with assistance from coaches, and other telepsychiatry tools, can help address the treatment gap, but barriers related to culture, policy and funding issues remain[195,238]. Collaborative care models of service delivery should invest in supporting telepsychiatry.

In summary, the scalability of collaborative care is promising, not only because of its demonstrated effectiveness and, increasingly, the use of community health workers and lay counselors, but also because of its potential for cost-offsetting impact. The evidence for cost-effectiveness remains inconclusive, but certain policies do promote its implementation and uptake. For example, the Center for Medicare and Medicaid Services in the US now allows the use of current procedural terminology codes (so-called CPT codes) to facilitate reimbursement of mental health specialists for work in primary care settings, including consultation on clinical management even when the psychiatrists may not have personally examined the patient.

Directions for future clinical practice and research in late-life major depression are provided in Table 4.

Table 4 Directions for future clinical practice and research in late-life depression

1.	Pragmatic intervention programs (e.g., collaborative, stepped-care models) should be further developed and implemented, using both pharmacotherapy and depression-specific psychotherapies (e.g., problem-solving therapy, cognitive behavioral therapy, and interpersonal psychotherapy), amenable for use also in low- and middle-income countries.
2.	Further comparative effectiveness/safety/tolerability research should be conducted to develop staged algorithms of care for use in both primary and specialty mental health settings, that will match needs of patients with intensity of intervention.
3.	Measurement-based care should be promoted to optimize efficacy, tolerability, safety, and treatment adherence.
4.	The implications of staging models of depression for assessment, prevention and treatment should be further investigated.
5.	Indirect, less-stigmatized approaches to depression prevention in older adults, such as treatment of insomnia disorder, should be further investigated.
6.	The use of lay counsellors, community health workers, and peer-support specialists should be expanded through task sharing/shifting, to address the dearth of mental health specialists in low-, middle- and high-income countries.
7.	The use of telepsychiatry, especially to better reach under-served and rural older adults, should be further integrated.
8.	There should be a focus on health-span, not only on lifespan, in clinical care and in cost-benefit analyses.
9.	A focus of research should be whether preventing and treating depression effectively modifies the risk for the major scourges of old age: cardiovascular disease, dementia and cancer.
10.	Further research should be conducted into suicide prevention in older adults, especially addressing high-risk periods such as transitions from more to less intensive care settings.
11.	Research on ketamine should be expanded to include older adults, in order to further address the clinical care of those with treatment-resistant depression, suicidal ideation, and cognitive impairment.
12.	Research in psychedelic-assisted psychotherapy (e.g., psilocybin) for treatment-resistant depression in older adults should be expanded.
13.	Pharmacogenomically-informed clinical decision-making for the care to older adults with major depression should be further explored.

SCHIZOPHRENIA

The disorders that feature prominently in the differential diagnosis of an older adult with psychotic symptoms include schizophrenia, delusional disorder, substance/medication-induced psychotic disorder, psychotic disorder due to another medical condition, and major or minor neurocognitive disorder with behavioral disturbance in the form of psychotic symptoms. Here we focus mainly on schizophrenia, as the prototypical psychotic disorder which has generated more research than most other mental disorders over the past 150 years.

A number of studies of schizophrenia in older adults have challenged the Kraepelinian concept of dementia praecox. While Eugen Bleuler also believed in worsening of this mental illness with age, his son Manfred disagreed, as he found that the course was highly heterogeneous. Half of the patients had an undulating course with remissions, and 12-15% recovered fully[239]. Manfred Bleuler also reported that schizophrenia could have its onset in later life.

Although the Epidemiologic Catchment Area study found prevalence rates of schizophrenia of only 0.3% among persons aged 65 and over, it seemed to under-sample in areas where persons with mental illness may be concentrated[240]. The actual prevalence rate is probably around 1%, and about 85% are living in the community[241]. A systematic review of literature published between 1960 and 2016 found that the pooled incidence of schizophrenia in those over 65 was 7.5 per 100,000 person-years at risk, with an increased risk in women (OR=1.6, 95% CI: 1.0-2.5)[242].

Schizophrenia is associated with accelerated biological aging. Yet, it does not follow the course of known neurodegenerative disorders such as Alzheimer's disease, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia, which are all accompanied by major atrophic changes in specific regions of the brain. There are no specific and observable degenerative changes that can be seen on an MRI or in neuropathological examinations of the brains of people with schizophrenia who die at older age[243].

While there is aging-associated cognitive decline, studies have found no significant difference in the rate of change in cognition in adults with versus without chronic schizophrenia[244]. However, cognitive trajectories differ significantly between institutionalized patients and outpatients with schizophrenia. The deterioration observed in the former patients seems to be related to greater illness severity, heavier medication load, vascular risk factors, and lack of stimulation[245].

Several longitudinal investigations have shown that the clinical course of schizophrenia in late stages is often relatively stable

and non-deteriorating[246-248]. With aging, there is frequently an improvement in psychotic symptoms[246]. Most hospitalizations in older persons with schizophrenia are due to physical rather than psychological problems.

Studies have found that, relative to their younger counterparts, middle-aged and older adults with schizophrenia tend to have better psychosocial functioning, including better adherence to medications and self-rated mental health, and lower prevalence of substance use and psychotic relapse. A common explanation offered for this observation is the so-called survivor bias – i.e., the sickest people died young from serious psychopathology, including suicide or drug use-related events, so those who survive into older age are less sick. However, longitudinal studies show that, when people with schizophrenia are followed for many years, a sizable proportion do show progressive improvement in their functioning with age[248]. This improvement may reflect better ability to handle stress and engage in healthful behavior.

Both schizophrenia and aging are characterized by heterogeneity. It is not surprising, therefore, that the course of schizophrenia in later life is highly variable, ranging from complete remission to a dementia-like state[241]. Reported predictors of sustained remission include greater social support, being (or having been) married, higher level of cognitive/personality reserve, and early initiation of treatment. Patients with very chronic illness, severe symptoms including disorganized thinking and behavior, resistance to treatment, and brain abnormalities are at higher risk of poor prognosis[247,248].

It is important to recognize that some people with schizophrenia can and do have positive traits and states such as resilience and happiness. One study using a validated scale of happiness found that, although the mean level was lower in patients with schizophrenia than in healthy comparison subjects, 38% of the patients had happiness ratings in the highest range, despite worse physical health and objectively more stressors[249]. Associations of greater happiness include higher levels of resilience, optimism, and personal mastery, and healthier levels of biomarkers of stress[250].

There are possible neurobiological explanations for improvement in mental function with aging in general, including in patients with schizophrenia. These include aging-associated reductions in dopaminergic, noradrenergic and serotonergic activity leading to decreased severity of positive symptoms and decreased impulsivity; reduced stimulation of reward circuitry resulting in decreased illicit substance use; and reduced amygdala activation with negative emotional stimuli contributing to decreased emotional negativity. Several studies have reported posterior-to-anterior shift with aging (PASA), resulting in better executive functioning[251]. Obviously, these are largely speculative hypotheses in terms of inferring causality.

Compared to the general population, persons with schizophrenia have an 8.5-fold greater risk of suicide. However, much less is known regarding suicidal behavior in older patients with schizophrenia[252]. The literature mostly consists of mixed samples of middle-aged and older individuals. It suggests that depressive symptoms, hopelessness, previous attempts, low quality of life, and history of trauma are likely risk factors[252-254]. While depression is a well-known risk factor for suicide in schizophrenia, a qualitative study found that delusions and hallucinations were central to suicidal behavior in some patients[255].

Patients with schizophrenia require thorough assessment for the presence and nature of suicidal ideation or behavior, suicide risk, and factors contributing to suicidality. An integrated approach incorporating different psychosocial modalities relevant to the individual is recommended. CBT helps persons with schizophrenia having suicidal ideation or behavior[256]. Second-generation antipsychotics may be more effective than first-generation ones in reducing suicide risk, although few studies have examined their impact on suicidality in older patients with schizophrenia[257]. While clozapine has been reported to be particularly effective in reducing suicidal behavior, its use in older patients is restricted due to its strong anticholinergic side effects as well as granulocytopenia. While there is some evidence for a possible antisuicidal role of selective serotonin reuptake inhibitors in patients with schizophrenia, there is a dearth of such studies in older patients[258].

Late-onset schizophrenia and very late-onset schizophrenia-like psychosis

The term "late-onset schizophrenia" was coined by Manfred Bleuler in 1943 to describe a form of schizophrenia with an onset between the ages of 40 and 60[259]. He found that 15% of his patients with schizophrenia met this definition, with only a small number of cases presenting later. These patients' symptoms were fundamentally similar to those in persons with earlier onset, and there were no cognitive or physical signs suggesting a degenerative brain disease.

Roth and Kay[260] described "late paraphrenia", characterized by a well-organized system of paranoid delusions with onset after age 45, with or without hallucinations, in the setting of a well-preserved personality and affective response. They did not consider this to be a subtype of schizophrenia.

The DSM has changed its stance on distinguishing late-onset from earlier-onset schizophrenia over the past four editions. The DSM-III did not allow a diagnosis of schizophrenia if symptoms emerged after the age of 45[261]. The DSM-III-R removed this restriction and introduced a "late-onset" specifier for onset after age 44 years[262]. That specifier was removed in the DSM-IV[91].

In 2000, the International Late-Onset Schizophrenia Group proposed the term "late-onset schizophrenia" for cases with onset between 40 and 60 years, and "very late-onset schizophrenia-like psychosis" for those presenting first after age 60[263]. This distinction was supported by empirical evidence, although the threshold of 40 years for the diagnosis of the former condition was somewhat arbitrary. The group felt that both conditions had clinical usefulness and that their identification could promote research in the field. Late-onset schizophrenia appeared to be as stable a diagnosis as early-onset schizophrenia; both diagnoses remained unchanged in up to 93% of cases in a follow-up, and only rarely were they reclassified as mood disorders[263,264]. How-

ever, few studies have focused on the diagnosis of very late-onset schizophrenia-like psychosis. The DSM-5[88] does not use an age cutoff in the diagnostic criteria for schizophrenia, nor does the ICD-11[265].

Studies have shown similarity between late-onset and early-onset schizophrenia in terms of family history of the illness, presence of minor physical anomalies, brain abnormalities such as slightly enlarged ventricles on MRI, nature of psychopathology, and type of cognitive impairment[266]. However, there are also differences between the two conditions. A noteworthy difference is related to gender. Early-onset schizophrenia is more common in men, whereas late-onset schizophrenia is much more common in post-menopausal women than in age-comparable men, suggesting a possible protective effect of estrogen in pre-menopausal women. The finding does not seem to arise from gender differences in care-seeking and societal role expectations or in delay between symptom emergence and service contact[263].

The higher frequency of late-onset schizophrenia in women has led to trials of estrogen therapy. In a recent 8-week, double-blind, randomized, placebo-controlled parallel-group study of 200 women with schizophrenia randomized to a 200 μg estradiol patch or placebo added to antipsychotics, participants receiving estradiol had significant improvement in positive and negative symptoms as well as general psychopathology[267]. Obviously, further clinical trials of this type are needed to establish the value of estrogen in women with late-onset schizophrenia.

The severity of psychopathology as well as that of cognitive impairment tends to be lower in late-onset than early-onset schizophrenia[263], and patients with the former condition may require lower dosages of antipsychotics than age-comparable persons with the latter[259]. Thus, late-onset schizophrenia may be a distinct subtype of the illness.

Aging-associated psychosocial factors such as retirement, financial difficulties, bereavement, deaths of peers, or physical disability may contribute to the precipitation of the symptoms of schizophrenia in later life[263]. However, the role of these factors has not been studied systematically. Sensory deficits, especially long-standing conductive deafness, are common in the late-onset form[264], but may primarily reflect the patients' reluctance to seek corrective measures or their inability to get correction of these deficits because of poor access to quality health care. Premorbid educational, occupational and psychosocial functioning is less impaired in the late-onset than in the early-onset form[268]. The relatives of patients with very late-onset schizophrenic-like psychosis have a lower morbid risk for schizophrenia than the relatives of those with the early-onset form[266].

Late-onset schizophrenia does not appear to be a prodrome of Alzheimer's disease, as patients do not demonstrate faster decline in memory beyond age-associated loss[244,266]. Individuals with schizophrenia are known to have reduced cognitive reserve that puts them at increased risk of a dementia diagnosis as they age. However, there is no evidence of higher rates of Alzheimer's disease in patients with schizophrenia[268]. A post-mortem study found that Alzheimer's disease pathology was rare among cognitively impaired persons with very chronic psychosis[243].

Treatment: pharmacotherapy

Antipsychotics constitute the backbone of treatment of schizophrenia at all ages, including older patients. During the last three decades, first-generation antipsychotics have been largely replaced in older persons by second-generation ones, because of the side effects of the former, such as tardive dyskinesia. However, the newer drugs have proven to be far from optimal in terms of both efficacy and safety. While they control the positive symptoms and prevent relapses similarly to first-generation medications, they are no more efficacious than the older drugs.

One study compared the longer-term safety and effectiveness of the four most commonly used second-generation antipsychotics (aripiprazole, olanzapine, quetiapine and risperidone) in 332 patients, aged >40 years, having psychosis associated with schizophrenia, mood disorders, post-traumatic stress disorder, or dementia[269]. The overall results suggested a high discontinuation rate (median duration 26 weeks prior to discontinuation), lack of significant improvement in psychopathology, and high cumulative incidence of metabolic syndrome (37% in one year) and of serious (24%) and non-serious (51%) adverse events with all the four antipsychotics[269].

Pharmacokinetic and pharmacodynamic changes that occur with age lead to an increased sensitivity to antipsychotics in older individuals, and increase the risk of side effects, especially parkinsonism, tardive dyskinesia, sedation, hypotension and falls[270]. Given the improvement in psychotic symptoms with age in a number of patients with schizophrenia, a progressive reduction in daily dose over a period of weeks or months may be attempted. A watchful eye should be kept on signs of early relapse, so that the dose can be increased as and when needed. In a minority of aging patients with schizophrenia, eventual discontinuation of antipsychotics is feasible, but the patients should be followed carefully[271].

Modifiable risk factors for tardive dyskinesia should be identified, to minimize its incidence and severity. These include diabetes mellitus, smoking, substance abuse including alcohol and cocaine, and anticholinergic co-treatment[272]. Two novel vesicular monoamine transporter type 2 (VMAT2) function inhibitors, valbenazine and deutetrabenazine, have been approved in the US as add-on therapy for persons with tardive dyskinesia[273]. VMAT2 inhibitors may be used to address tardive dyskinesia-associated impairments and impact on psychosocial functioning[274].

Treatment: psychosocial interventions

Clinicians should combine pharmacotherapy with appropriate psychosocial interventions in older patients with schizophrenia. There are three skills training programs specifically designed for older adults with severe mental illness and shown to be effective in randomized clinical trials: cognitive-behavioral social skills training (CBSST), functional adaptation skills training (FAST), and Helping Older People Experience Success (HOPES).

They are all group-based; provide accommodations for persons with physical or cognitive disabilities; help develop skills in incremental steps; and use age-appropriate psychosocial training techniques to meet the needs of older persons[275].

The CBSST[276,277] is a manualized group intervention, within the framework of the biopsychosocial stress-vulnerability model of schizophrenia, consisting of three modules, each with four-weekly sessions, to be repeated, for a total of 24 sessions. The modules focus on thought challenging, seeking social support, and solving problems, with homework assignment after each session. Skills include promoting cognitive behavioral strategies, recognition of early warning signs of relapse, improved communication with health care professionals and social interactions in everyday activities, treatment adherence, and behavioral strategies for coping with psychiatric symptoms.

Randomized controlled trials of CBSST in older adults with schizophrenia have shown a high rate of adherence and low dropout rates[276]. While there was no significant change in psychopathology in pharmacologically stabilized patients, there was significant improvement in social activities, cognitive insight and mastery of problem-solving skills, as well as a reduction in defeatist attitudes, at the end of the intervention. Some improvement was sustained 6 months post-treatment[277].

The FAST[278] focuses on communication, transportation, medication management, social skills, organization and planning, and financial management in 24 semi-weekly two-hour group sessions. Active learning approaches include in-session skills practice, behavioral modeling, role-playing and reinforcement, and homework practice assignments.

A randomized controlled trial including 240 older adults with schizophrenia showed that FAST participants, compared to a time-equivalent attention-control group, had significant improvement in everyday functional skills as well as social and communication skills at the end of treatment and three months later[278]. A pilot study of an adapted version of the FAST program showed improved functioning and well-being in middle-aged and older Latinos with severe mental illness[279].

The HOPES[280] integrates psychosocial skills training and preventive health care management. The skills training component includes classes, role-play exercises, and community-based homework assignments in social skills, community living skills, and healthy living. The weekly skills class curriculum provided over 12 months consists of seven modules: communicating effectively, making and keeping friends, making the most of leisure time, healthy living, using medications effectively, and making the most of a health care visit.

A randomized controlled trial of HOPES including 183 older adults with severe mental illness showed significantly greater improvement in skills performance, psychosocial functioning, self-efficacy, and psychopathology at one-year and three-year follow-up compared to usual care[281]. A greater proportion of HOPES participants received flu shots, hearing tests, eye exams, mammograms, PAP smears, and completed advanced directives than the usual care recipients.

Randomized controlled trials have also shown significant improvement with other manualized psychosocial interventions in older patients with schizophrenia, such as supported employment without and with compensatory cognitive training to help them obtain and retain paid jobs[282,283].

Recent advances in technology along with the COVID-19-associated social distancing have hastened a rapid growth of psychosocial interventions administered remotely. For example, computer-initiated text messaging three times per day for 12 weeks, or live telephone interaction two times per week, can be used to promote self-management in people with severe mental illness. Following initial training in the use of the necessary technology, people with schizophrenia have minimal dropout rates, few broken devices, and high patient satisfaction[284]. There is a need for more research in this area among older adults with schizophrenia.

Organization of services

In the past few decades, there has been a dramatic decline in the number of persons with schizophrenia living in mental institutions, and an increase in the number of older outpatients[241]. Thus, there is an increasing pressure for community programs to provide services to older persons. As mentioned above, older persons with schizophrenia have higher frequency and severity of physical diseases than people without severe mental illness, and yet receive much less than adequate health care. Also, for schizophrenia patients of all ages, the Epidemiologic Catchment Area Study reported a lifetime prevalence of 33% and 28% for alcoholism and drug abuse disorders, respectively[285].

Structural barriers in the health care system as well as physician attitudes create impediments to care. A Scottish study reported that primary care doctors were less willing to have persons with schizophrenia on their practice list, and more likely to believe that such persons were apt to be violent[286]. In the US, there are considerable racial inequalities in health status due to diminished access to health care, poorer health practices, and lower socioeconomic status among marginalized ethnic groups compared to non-Latino Whites[287].

The excess risk of early mortality, physical comorbidity, early institutionalization, and high costs among older adults with schizophrenia require the development and dissemination of effective and sustainable integrated care models that simultaneously address both mental and physical health care needs. Current evidence-based integrated care models primarily adopt three approaches: psychosocial skills training, integrated illness self-management, and collaborative care and behavioral health homes. The next step should be the development of innovative models that build on these approaches by incorporating novel uses of telehealth, mobile health technology, and peer support, and strategies implemented successfully in developing economies[275].

An optimal mental health care system for older persons with schizophrenia should have a full multidisciplinary range of clinical, rehabilitative, preventive and supportive services[288]. These

include comprehensive assessment; case management; intensive outreach; smooth coordination of mental health, physical health, and social services; appropriate community and inpatient mix; and provisions for maintenance of family caregivers' mental and physical health. Unfortunately, such a system does not exist, and services remain fragmented and under-utilized by this highly disenfranchised population[289].

Successful aging with schizophrenia

Despite the above-mentioned biological and societal issues, successful aging is not an oxymoron even among aging adults with schizophrenia. The clinical practice of positive psychiatry discussed above applies to these people too. The strategies necessary for seeking this goal include appropriate pharmacotherapy and psychosocial interventions, along with healthful diet, physical exercise, non-toxic environment (e.g., cessation of smoking), and positive attitude on everyone's part. It is never too early nor too late to start on this path.

Positive psychiatric care of people with schizophrenia should include assessment not just of psychopathology but also of well-being, strengths, perceived stressors, and lifestyle. This can be done by completing validated brief questionnaires in waiting room or online at home. Using these data, the clinician can identify treatment targets such as lifestyle (e.g., sedentary behavior) or social network, and implement appropriate interventions[290].

A prescription given to a person with schizophrenia must go beyond an antipsychotic drug. It must include enhancement of personal psychosocial strengths, appropriately individualized behavioral interventions, and healthy lifestyle strategies such as physical, cognitive and social activities, adequate sleep, and nutritious diet. In the coming years, there will be an increasing use of digital technologies to disseminate evidence-based interventions to large numbers of patients. Directions for future clinical practice and research in older adults with schizophrenia are provided in Table 5.

All this must be accompanied by community support. Just as it takes a village to raise a child, it takes a community, which does not carry stigma against mental illnesses and their treatments, to provide optimal care to older people with schizophrenia.

Table 5 Directions for future clinical practice and research in older people with schizophrenia

1.	A full multidisciplinary range of clinical, rehabilitative, preventive and supportive services – including comprehensive assessment, case management, intensive outreach, and smooth coordination of mental health, physical health, social services and peer support – should be implemented.
2.	Efficacious antipsychotics without metabolic side effects should be investigated.
3.	Well-designed randomized controlled trials of psychotherapeutic interventions incorporating principles of cognitive behavioral therapy and socialization training should be conducted.
4.	Individual or group interventions, such as cognitive training, to promote brain fitness in older patients should be used.
5.	Treatment targets such as lifestyle (e.g., sedentary behavior) should be identified, and appropriate interventions (e.g., regular physical activities) should be implemented.
6.	"Wellness within illness" should be assessed and promoted: well-being, resilience, optimism, personal mastery, wisdom, social engagement, and social support.
7.	Social determinants of mental health in aging, such as loneliness and social isolation, should be evaluated, and interventions targeting these features in individual patients – e.g., psychosocial skills training – should be used.
8.	Mobile interventions, including use of smartphones to deliver psychosocial interventions, should be implemented to promote self-management of illness, using user-friendly technologies.
9.	Collaborative care and behavioral health homes should be further established and evaluated.
10.	Medications and non-pharmacological treatments for cognitive impairment in older patients with schizophrenia should be investigated.
11.	Pragmatic trials of hormone therapies such as estrogen derivatives in post-menopausal women with schizophrenia should be conducted.
12.	Anti-suicidal medications useful for older patients with schizophrenia should be investigated.
13.	Effectiveness and safety of anti-inflammatory and other medications to slow down accelerated aging in schizophrenia should be explored.
14.	Digital phenotyping at the level of sensors, data science and health care should be investigated, to help in relapse prediction and prevention in old age schizophrenia, possibly using machine learning and other relevant technologies.
15.	Further research on caregivers of older people with schizophrenia should be conducted, and further appropriate interventions should be developed.

SUBSTANCE USE DISORDERS

Substance use disorders are often overlooked worldwide as causes of problems for older adults, overshadowed by emergencies such as the opioid crisis among young and middle-aged adults in high-income countries. The extant literature reflects this deficit. Empirical studies of substance use among older adults are sparse to non-existent from virtually all low- and middle-income countries, and infrequent even in high-income countries. Yet, these disorders are more frequent than many mental health workers believe, and their adverse consequences can be highly impairing.

In addition, interventions directed to these disorders in the elderly have been sparsely studied. Usually, however, diagnoses and interventions for younger adults can be applied to these elders, with judicious implementation which considers the biological, psychological and social factors unique to the elderly[291,292].

Among the older adults, there are many challenges which may be exacerbated by alcohol and drug misuse, including functional and cognitive decline, compromised immune function, falls, other household injuries and depression. This reinforces the need for psychiatrists and all physicians to be more alert to and screen for substance use disorders, despite the many competing

health concerns with which older adults present to them[293].

Epidemiological studies from the US and many parts of Europe have found that the number of older persons in treatment for drug use problems has increased in recent years, most likely due to the aging of the baby-boom generation who were born between 1946 and 1964. As birth rates in high-income countries have now declined, the baby boomers have contributed to the "squaring of the age pyramid" leading to major increases in persons 65+ years who bring with them higher levels of illicit drug use and prescription drug misuse than previous age cohorts[294,295].

In the US, nearly 1 million adults aged 65 and older live with a substance use disorder, as reported in 2018 data[296]. While the total number of admissions due to substance use disorders between 2000 and 2012 differed slightly, the proportion of admissions of older adults increased from 3.4% to 7.0% during this time[297]. In a study from Germany among subjects aged 60-79 years, 69% consumed alcohol regularly and 17% consumed it at some risk[295]. From 2007 to 2016, prevalence rates of drug use among those in the 50-59 and 60 and older age groups in Australia increased by 60-70%[295].

Yet another factor requires physicians, especially those who treat many older adults, to be more vigilant. Older adults in high-income countries take a plethora of prescribed and over-the-counter medications[298]. Over a seven-year period, non-medical use or misuse of pain relievers doubled (from 0.8% in 2012 to 1.7% in 2019) among people aged 65 or older in the US, while among the total population there was a slight decrease (from 4.8% in 2012 to 3.5% in 2019)[296]. Combinations of acetaminophen and hydrocodone or propoxyphene were the most commonly used drugs[299].

Social factors are the most important risks for substance use in older adults. For example, being divorced, separated or single is associated with increased or unhealthy drinking in late life in the US, though this may differ across genders[300,301]. Another factor is having drugs available in the house or from friends. Risk factors for drug use in late life further include physical problems, especially uncontrolled pain following surgery. Pain from back or shoulder strain may also be involved.

Mental health problems also contribute to increased drug use, especially depression and anxiety. Men are more like to have a long history of alcohol intake which extends into late life, and they tend to drink greater quantities. Overall decline in physical health may contribute as well[292].

Screening and diagnosis

The first step by the clinician in addressing potential drug use is screening. Many tools have been demonstrated effective in eliciting the problem among older adults. These include the Alcohol Use Disorders Identification Test-Concise (AUDIT-C)[302] and the CAGE Questionnaire Adapted to Include Drugs (CAGE-AID)[303]. The AUDIT-C questions specific amounts of alcohol a person consumes[302]. The CAGE-AID focuses upon the symptoms that derive from substance use disorder. Both the AUDIT and CAGE screening scales are used internationally.

The CAGE-AID tool contains the following four questions, which can be used for both alcohol and other substance use[303]: 1. Have you ever felt that you should *Cut* down on your drinking or drug use?; 2. Have people *Annoyed* you by criticizing your drinking or drug use?; 3. Have you ever felt bad or *Guilty* about your drinking or drug use?; 4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (*Eye-opener*)?

This screening should be part of the usual evaluation of the older adult, for all too often the clinician may wrongly assume that the elder has no problem with substances. Substance use may be overlooked by family members or not considered important. Clinicians may also believe that problems from substance use are not critical or that little can be done to decrease use[292].

The DSM-5 criteria capture a wider proportion of older adults with substance use disorders compared to DSM-IV ones. Even so, many elders will likely remain unidentified[304]. Age-associated physiological changes that increase the effects of alcohol and other substances cause older adults to experience a reduction of tolerance to these substances, thus interfering with one of the hallmarks of substance use disorder, namely increased tolerance[291]. Furthermore, interruption in social and vocational activities or other social consequences of drinking or drug use may be less likely to occur or less noticeable in old age.

Using item response theory with the 2009 National Survey on Drug Use and Health data, one study explored whether there were age-related biases among the DSM-5 criteria for alcohol use disorder[304]. The findings revealed that there were differential responses among older versus middle-aged adults, such that older adults were half as likely to endorse the criteria related to tolerance, activities to obtain alcohol, social/interpersonal problems, and physically hazardous situations. The criteria that were most effective in identifying alcohol use disorder among older adults were unsuccessful efforts to cut back, withdrawal, and social and interpersonal problems.

Treatment and organization of services

Some assume that older adults who abuse substances experience such a chronic condition that they will not respond to treatment. On the contrary, they have demonstrated treatment outcomes that are as good, or even better, than those seen in younger groups[291].

Nevertheless, access to specialized services tailored for older adults is limited[305]. Brief interventions by health care professionals are the first and one of the most important steps in a treatment plan. The older adult who is gently alerted about the problems with substances may take heed when the health care professional warns of the danger, yet otherwise ignoring warnings coming from friends and family.

A common thread of most brief interventions is the use of elements of motivational interviewing[306]. Such interventions pro-

vide education about the substance and how it might be harmful, thereby enhancing motivation for change. One approach is "normative feedback", in which a patient's drinking is compared with his/her peers. This feedback is then combined with brief advice about how to cut down or eliminate substance use[306].

This approach on the surface is appealing to clinicians working with older adults and the elders themselves[306]. Unfortunately, little high-quality evidence of the effectiveness of standardized brief interventions, such as motivational interviewing, is available, although naturalistic studies are promising[292]. Older persons are more likely to complete treatment than younger persons.

Medication use is essential for withdrawal from alcohol and other substances. Symptoms associated with alcohol withdrawal include increased pulse rate, blood pressure and temperature, as well as restlessness, disturbed sleep, anxiety and, when severe, delirium, seizures and hallucinations[292]. Medications used to alleviate alcohol withdrawal syndromes are usually benzodiazepines, which are tapered over a few days, primarily to prevent delirium and seizures. They should only be used on a short-term basis.

Only two medications have been used extensively for the treatment of alcohol use disorder in older adults. Disulfiram was the first, yet the data on its use in preventing alcohol abuse among older adults are unclear. Furthermore, clinicians have been reluctant to use the medication, given its side effects if alcohol is ingested. Nevertheless, at a usual dose of 250 mg daily, the drug is considered safe for older adults who are otherwise in good health[307]. Of interest, limited data indicate some efficacy for naltrexone in the treatment of alcohol use disorder among older adults[308].

Buprenorphine is the preferred treatment for opioid dependence, and appears to be safer than methadone. Nevertheless, to prescribe buprenorphine in the US requires special training. Drugs approved by the US FDA for the treatment of opioid dependence include sublingual buprenorphine and buprenorphine/naloxone tablets or strips. Because of safety issues, buprenorphine/naloxone is the preferred formulation[309,310]. Treatment with buprenorphine is safe and effective. Many patients can manage the induction period on their own at home.

Naltrexone is the most well-studied medication used for substance use disorder treatment among older adults, and it has demonstrated effectiveness with this population. Naltrexone is an opioid receptor antagonist and is thought to reduce craving for opioids as well as alcohol by blocking dopamine release in the brain. Its major limitation in older adult people, many of whom have chronic pain, is that it blocks the effect of opiate-based pain medications, often used following surgery. It can also potentiate the symptoms of a preexisting major depression. Patients with histories of comorbid depression should therefore be closely monitored[311]. Naltrexone is usually accepted by older adults, and its effectiveness is about equivalent of what is found in younger adults[308].

Overall, group support for abuse and addiction is the most valuable long-term intervention. Groups such as Alcoholics or Narcotics Anonymous (AA) can help older adults with a substance use disorder by reducing isolation, shame and stigma, though there have been no systematic studies on their effects.

Table 6 Directions for future clinical practice and research in late-life substance use disorders

1.	Clinicians and lay persons should be educated about the importance of substance use disorders in older adults, including their medical sequelae such as falls, cognitive decline, and worsening of co-occurring physical and mental disorders.
2.	Screening for substance use disorders should be integrated in both primary care and specialty mental health services for older adults.
3.	The most important risk factors for substance use disorders in older adults – particularly social isolation, loneliness, bereavement, and felt loss of purpose and meaning in life – should be better known, evaluated and addressed.
4.	Self-help groups should be adapted for older adults, e.g., by slowing the pace to accommodate cognitive impairment, and/or by addressing issues related to social support.
5.	The silos of mental health and substance abuse services should be broken down.
6.	Possible adaptations of diagnostic criteria/guidelines for substance use disorders should be considered to improve their performance in older adults.
7.	Further research should be conducted into the effectiveness of standardized brief interventions, such as motivational interviewing, in older adults.
8.	Further research should be carried out into the effectiveness and safety of using medications such as buprenorphine and naltrexone in older adults with substance use disorders.
9.	Factors in midlife which predispose to the development of substance use disorders in late life should be explored.
10.	Differences in substance use disorders by ethnicity, gender and geography should be investigated, and risks associated with disruptions in the lives of older adults that might lead to these disorders should be explored.

Elders use AA frequently worldwide in over 180 countries[312]. Yet they may face the same barriers to participation in self-help groups as they do with formal treatment: stigma and shame of needing to attend to these issues in late life. If their primary substance use problem is alcohol, they often experience discomfort in attending meetings that include younger poly-substance users. Such discomfort may not be as acute for baby boomers.

Traditional self-help groups can be modified for older adults. For example, slowing the pace of the meeting to reflect cognitive changes in aging, and devoting attention to handling losses and extending social support, could be critical for recovery[291,313].

Despite decades of research and clinical trials, the treatment and prevention of substance use disorders in older adults has been of marginal success. This is frustrating to patients as well as clinicians. The need for improved treatments tailored for older adults is critical (see Table 6).

CONCLUSIONS

Mental disorders in older adults are a leading cause of suffering and disability in the world, much of it avoidable. These dis-

orders are common, impairing social functioning and economic productivity, undermining adherence to co-prescribed medical treatments, and increasing the risk for loss of independence and early mortality from suicide and physical illness. Prevention, timely recognition and treatment are global public health and moral priorities.

Within the broader context of a positive psychiatry of aging, and as a countermeasure to ageism and stigma, it is essential to champion the assessment and promotion of wellness within illness, in order to enhance well-being, resilience, optimism, and self-efficacy/personal mastery. Moreover, it is important to evaluate the social determinants of mental illness in older adults, particularly loneliness and social isolation, and to use interventions that target these issues in individual patients and the family caregivers.

Because older adults with mental illness often engage in unhealthy lifestyles, particularly lack of physical activity, it is important to identify and implement appropriate interventions that will repay both mental and physical health benefits. Interventions to promote brain and cognitive fitness may be offered in individual and in group formats that provide rewards and reinforcement for adopting healthier behaviors in physical activity, diet and sleep.

Recent technological developments now allow the use of mobile interventions, including "just-in-time" interventions such as the use of smartphones for computer-initiated text-messaging or live telephone interactions to promote and enhance self-management of illness. In addition, further use and investigation of digital phenotyping at the levels of sensors, data science and health care may prove useful in relapse prevention – given the frequently relapsing and chronic course of mental disorders in old age.

Future practice and research need to combat the fragmentation of clinical care through the establishment and evaluation of collaborative care and behavioral health homes. Such models should build on comprehensive approaches incorporating novel use of telehealth, mobile health technology, and peer support, capitalizing on strategies implemented successfully in low- and middle-income countries. Team-based care needs to become increasingly measurement-based and interdisciplinary, incorporating and enacting a range of clinical, rehabilitative, preventive and supportive services. These services should include comprehensive assessment, clinical management, intensive outreach, and coordination of mental health, physical health and social services.

We also underscore the importance of care that is not only patient-focused but also family-centered. The caregivers of older persons with mental disorders are themselves burdened and in need of information and support. Including them as informal members of the caregiving team repays benefits to the identified patient and to caregivers alike and facilitates accurate clinical assessment and targeted interventions to promote wellness and to prevent serious adverse events (including suicide).

Cutting across all of the diagnostic entities considered in this paper is the need for further investigations of medications that can ameliorate cognitive impairment and slow down its progression. Medications that may reduce risk for suicide are also sorely needed, together with research on how best to use them within clinical care and systems of care. Further development and evaluation of medications without metabolic, cardiovascular and neurological side effects is needed to optimize safety and tolerability as well as efficacy and effectiveness.

Mental disorders of old age are heterogeneous at multiple levels: etiopathogenesis, clinical presentation, and response to intervention. They reflect genetic, environmental, social and developmental vulnerabilities as well as resilience. Taking these dimensions into account is critical to implementing personalized and effective treatment approaches and to doing meaningful research.

Because response variability to medications and other psychosocial and psychotherapeutic interventions is great among older adults, further investigation of moderators and mediators of response variability during acute, continuation and maintenance treatment is needed. This may allow clinicians to better personalize treatment, by understanding what works for whom, when and how. Finally, in the translational and clinical neuroscience space, further investigation of anti-inflammatory medications to slow down accelerated aging is highly relevant to advances in clinical care.

Fortunately, science in the service of promoting healthy brain aging and cognitive fitness in the later years of life has become increasingly compelling. We believe that strategies for health promotion and care for older adults living with mental disorders are deeply linked.

Drawing upon the lessons learned in cardiovascular medicine and oncology, we suggest that detecting and diagnosing later-life mental disorders early in their course is crucial to preventing their complications (such as treatment resistance, cognitive impairment, and mortality). Early detection and diagnosis facilitate care that is both evidence-based and proportionate to the needs of the individual patient and family caregivers. Staging approaches that take into account where a patient is in the trajectory of his/her illness have clear clinical relevance, power and utility across the life cycle into old age.

Given the complexity of mental disorders in older adults, team-based collaborative care models provide an evidence-based and scalable way for health systems to implement prevention and personalized care. Furthermore, the use of telemedicine and the integration of peer-support specialists, lay counselors and community health workers are helping to bridge the gap created by the worldwide paucity of geriatric mental health clinicians. They are also powerful antidotes to the barriers posed by fear and stigma.

In essence, addressing the rights and needs of older people and their families living with mental disorders remains a global public health and – no less – a moral imperative born of progress in discovery and applied sciences.

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