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DEAR COLLEAGUES,

I am delighted to introduce to you the first Consortium Psychiatricum issue of 2022. We open this year with the thematic issue on old-age psychiatry, which was prepared in collaboration with Dr. Debanjan Banerjee, a specialist in geriatric psychiatry from India, as a guest editor.

In this issue, our aim was to highlight topics that have been somewhat overshadowed in the traditional professional discussions in the field of geriatric psychiatry — the human rights of older adults, policy in providing medical care for a diverse old-age population, and sexual health in later life. Thus, we focused mostly on the humanistic aspects of old-age psychiatry. We do hope that the positions, statements, and voices of both professionals and professional associations, like the World Psychiatric Association, International Psychogeriatric Association, and SAARC Psychiatric Federation that we publish in this issue, will be heard by mental health specialists, policymakers, and other stakeholders, and will add to improvements in the mental health of older people worldwide.

Present-day challenges were reflected in the research paper devoted to the changes in the brain tissue of older people with histories of COVID-19 and a review on loneliness among the elderly, while opportunities are presented in the reviews about technology-based neurocognitive assessment in the elderly and novel therapeutic options in the treatment of Alzheimer disease. Experiences of sexuality and sexual health in older persons have been explored by Dr. Debanjan Banerjee in his research.

We continue our traditional rubric on community psychiatry around the world and publish papers on the organization of community mental care in the Kyrgyz Republic and Azerbaijan.

I would like to thank Professor Afzal Javed and Professor Svetlana Gavrilova for writing editorial papers for this issue. I would also like to express special gratitude to Dr. Debanjan Banerjee, whose enthusiasm, creativity, and professional devotion helped this issue to happen.

I wish you pleasant reading.

George Kostyuk,
Editor-in-Chief, Consortium Psychiatricum

DEAR ALL,

Greetings from India!

It is my pleasure to present to you this special issue of the Consortium Psychiatricum, themed on Old Age Psychiatry. This issue reflects months of work by both the authors and editorial team, which has resulted in a rich academic collection.

The world is facing rapid population aging. Older persons face unique biopsychosocial challenges in terms of their mental health and wellbeing, which have further surfaced during the ongoing COVID-19 pandemic. A significant mental health burden exists amongst older adults that is, unfortunately, compounded by the social problems of ageism, marginalization, stigma, loneliness, and elder abuse. Hence, research needs to be tailored to the needs of this vulnerable part of the population that can lead to evidence-based mental health and policy interventions.

This issue comprises research works from leading experts in geriatric psychiatry from across the world, with special notes from Dr. Afzal Javed (President, World Psychiatric Association) and Dr. Carlos Augusto Mendonca de Lima (Chair, WPA — Section of Old Age Psychiatry). The content is multi-dimensional in nature, covering loneliness, rights of older persons, policy changes and risk-reduction strategies, the special needs of sexual minorities, psychosexual health, technology-based assessments in old age mental health, neurocognitive disorders, and the neurobiological effects of COVID-19. Another highlight of this issue is a special SAARC meeting report of International Psychogeriatric Association (IPA) Old Age Mental Health Awareness Week 2021.

I hope this thematic issue will serve as a sound reference framework for mental health professionals, physicians, social workers, and policymakers alike working in the field of geriatric mental health. We welcome feedback from readers to improve on our work and look forward to further issues in this relevant yet somewhat neglected field.

Dr. Debanjan Banerjee,
Guest Editor

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Mental Health of Older Adults: an Agenda for Action

Психическое здоровье пожилых людей: программа действий

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Editorial

Afzal Javed
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Афзал Джавед
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The world's population is ageing rapidly. Estimates by the United Nations (UN) and World Health Organization (WHO) suggest that between 2015 and 2050, the proportion of the world's older adults will almost double from about 12% to 22% [1]. In absolute terms, this is an expected increase from 900 million to 2 billion people over the age of 60. Older people face unique physical and mental health challenges that need to be recognized. Mental health and well-being are particularly important in older age. While most have good mental health, many older adults are at high risk of developing mental and neurological disorders, as well as other medical conditions. Similarly, as people age, they are more likely to experience a number of conditions at the same time [2]. Besides, there are numerous social, psychological, and ecological factors that can impact the mental wellbeing of older people.

There are multiple prejudices about the meaning of mental illness in old age. Many older adults today still see mental illness as a sign of weakness and are unlikely to admit their difficulties. In addition, symptoms of dementia and depression are too often considered a part of normal aging. Older people may be vulnerable to multiple risk factors for mental health problems and, like adults, older people may experience life stressors common to all people in addition to the challenges that are more common in later life, like a significant ongoing loss in capacities and a decline in functional ability. Additionally, older people are more likely to experience events such as bereavement, or a drop in finances with retirement. Limitations in mobility, frailty, and other medical health problems may require additional and long-term care. All these factors can result in isolation, loneliness, or psychological distress amongst older people, for which they may require specialized care. Likewise, mental health conditions can have a significant impact on an older adults' ability to carry out the basic activities of everyday life, leading to reductions in their independence, autonomy, and quality of life. Unfortunately, mental health conditions are not often diagnosed and treated. Many older adults struggle without proper help, or simply without any help at all. Besides, ageism and age-based discrimination, which are prevalent globally, threaten the human rights and dignity of older people, enhancing the risks of elder abuse, limited help-seeking, and loneliness. The ongoing Coronavirus Disease 2019 (COVID-19) pandemic has further widened the gaps inherent to later-life health inequalities, leading to marginalization and human rights crises in this age group [3]. Hence, additional focus on research related to the mental health conditions of older people is warranted to improve service and policy interventions.

The World Psychiatric Association (WPA) recognizes old age mental health problems as a public health challenge and calls for global action to ensure a better understanding of care for elderly people [4, 5]. The WPA's Section of Old Age Psychiatry (WPA-SOAP) has been extremely active in improving the knowledge in this area and in advocating a better mental health for older adults around the world. The WPA thus strongly supports the International Psychogeriatric Association (IPA) and joins their efforts to ensure that older persons with mental health conditions and psychosocial disabilities are not discriminated against on the basis of their age, their mental health, or psychosocial disability status, and are treated as full citizens enjoying all rights on an equal basis with other citizens. The Joint Statement of WPA-IPA is a step forward in empowering our psychogeriatric colleagues' efforts to raise awareness among mental health professionals regarding the human rights of older persons [6]. Collaborating on dialog- and evidence-based practices on mental health challenges among older adults thus represents an urgent need.

Mental health care has undergone a paradigm shift in recent years to a rights-based approach and the same applies to all ages. The UN Decade of Healthy Ageing (2021–2030) calls for advocacy, an age-friendly environment, combatting ageism, and integrated care among older people [7]. It is a global collaboration in line with the last decade of Sustainable Developmental Goals (SDG) that serve as a framework for professionals, academics, civil societies, governments, and international agencies to *"improve the lives of older people, their families, and the communities they live in"*. A vital decade-enabler of this global initiative is *"strengthening research, data, and innovation."*

Against this backdrop, the publication of a thematic issue on old age psychiatry by Consortium Psychiatricum is indeed a great initiative and I hope this issue will generate increased attention amongst the scientific community to the problem of delivering mental health care for the old age population. This issue caters to various dimensions related to mental health care among older adults: human rights advocacy, psychosexual health, loneliness, technology-based interventions, and COVID-19-related neurobiological changes, to name but a few.

This thematic issue may have the potential to sensitize mental health professionals across the globe towards the mental health needs of, and challenges faced by older people. It may also serve as a resource for researchers and academicians in the field of geriatric psychiatry.

Best Wishes,
Afzal Javed
President, World Psychiatric Association

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The Evolution of Diagnostic Boundaries of Alzheimer's Disease and Novel Therapeutic Options

Эволюция диагностических границ болезни Альцгеймера и новые терапевтические возможности

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Review

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ABSTRACT

Over the past three decades, the definition and diagnostic boundaries of Alzheimer's disease (AD) have been repeatedly revised due to significant progress in understanding of the pathogenesis of neurodegeneration associated with Alzheimer's disease and in the development of high-tech diagnostic methods. The current approach to AD diagnostics relies on the detection of biomarkers that reflect two main neuropathological processes involved in the primary neurodegeneration that underlies AD: abnormal amyloidogenesis, and neuronal degeneration. The currently available diagnostic tools are limited to the detection of cerebrospinal biomarkers and/or assessment of the abnormal amyloid and tau protein burden in the brain via amyloid and tau positron emission tomography (PET) ligands. Practical implementation (mostly in the research field) of the biological model of AD diagnosis has led to a significant expansion of its diagnostic boundaries with the inclusion of predementia AD stages: asymptomatic and symptomatic, the latter is clinically corresponding to amnestic mild cognitive impairment (aMCI-amnestic mild cognitive impairment). On the one hand, this approach significantly expands the possibilities to study and use preventive technologies aiming to avert or delay the progression of predementia cognitive impairment to dementia but, on the other, it is associated with a number of negative implications from both the clinical and ethical points of view. A significant limitation of purely biological diagnosis of AD based on biomarker levels is due to the low prognostic value of biomarkers, which can cause diagnostic confusion in certain circumstances. Moreover, since the future evolution of the asymptomatic stage is not yet clear and there are still no reliable ways to prevent the cognitive and behavioral symptoms associated with AD, disclosure of stressful information about this "terrifying" diagnosis to patients can cause irreversible damage by triggering depressive disorder, which is a risk factor of AD itself.

The current knowledge about AD prognosis in amyloid-positive cognitively unimpaired patients is insufficient.The most adequate approach to early AD diagnostics appears to be the clinical and biological model, as recommended by the International Working Group (IWG 2021), which requires a combination of the clinical AD phenotype and the detection of biomarkers specific to this disease.

The article discusses the potential directions for the development of biological diagnostic methods, including those based on the so-called peripheral (serum) biomarker technologies and promising directions for the development of biological methods of secondary AD prevention.

АННОТАЦИЯ

За последние три десятилетия дефиниция и диагностические границы болезни Альцгеймера (БА) неоднократно пересматривались, что было связано с существенным прогрессом в понимании патогенетических механизмов альцгеймеровской нейродегенерации и в разработке высокотехнологичной диагностической техники. Современный подход к диагностике БА опирается на открытие биомаркеров,отражающих два главных нейропатологических процесса, вовлеченных в развитие первичной нейродегенерации, лежащей в основе БА, — аномального амилоидогенеза и нейрональной дегенерации. Существующие сегодня диагностические технологии ограничиваются выявлением ликворных сбиомаркеров и/или оценкой распространенности в структурах головного мозга амилоидной и тау-патологии с помощью позитронно-эмиссионной томографии (ПЭТ) с лигандами бета-амилоида и тау протеина. Внедрение в практику (в большей мере — исследовательскую) биологической модели диагностики БА привело к значительному расширению ее диагностических границ за счет включения додементных стадий заболевания — асимптоматической (бессимптомной) и симптоматической, клинически соответствующей синдрому мягкого когнитивного ухудшения амнестического типа (aMCI-amnestic mild cognitive impairment). Такой подход, с одной стороны, существенно расширяет возможности изучения и применения превентивных технологий, направленных на предотвращение или замедление перехода в деменцию додементных когнитивных расстройств, но с другой стороны сопряжен с рядом негативных последствий клинического и этического плана. Существенным ограничением чисто биологической диагностики БА на основе определения биомаркеров является низкая прогностическая ценность биомаркерных критериев, которая может в определенных случаях создавать диагностическую путаницу. Кроме того, раскрытие стрессогенной информации о «страшном» диагнозе пациенту при том, что траектория развития асимптоматической стадии еще надежно не определена и все еще нет надежного способа предотвратить развитие когнитивных и поведенческих симптомов, связанных с БА, может нанести непоправимый вред пациенту, спровоцировав депрессивного расстройства, которое само по себе является одним из факторов риска БА.

На современном этапе неполных знаний о прогнозе развития БА у амилоид-позитивных когнитивно сохранных пациентов, наиболее адекватным подходом к ранней диагностике БА представляется клинико-биологическая диагностическая модель, рекомендуемая рабочей группой IWG 2021,которая требует сочетания клинического фенотипа БА и выявления биомаркеров,характерных для этого заболевания.

В работе обсуждаются возможные направления развития биологических методов диагностики,в том числе, в области так называемых периферических (сывороточных) биомаркерных технологий и перспективные направления в разработке биологических методов вторичной профилактики БА.

Keywords: *Alzheimer's disease; diagnostic boundaries; biomarkers; treatment; secondary prevention*
Ключевые слова: *болезнь Альцгеймера; диагностические границы; биомаркеры; лечение; вторичная профилактика*

INTRODUCTION

A global issue of the 21st century is combating socially significant diseases, including neurodegenerative diseases accompanied by dementia, primarily Alzheimer's disease (AD). AD currently affects more than 50 million people worldwide and, based on the prognosis of the World Health Organization (WHO) and Alzheimer's Disease International (worldwide federation of Alzheimer's disease associations), this number is expected to reach 150 million by 2050. The medical, social, and economic consequences of AD are expected to show a trend of exponential growth over the next few years as a result of the demographic changes currently underway in both developed and developing countries, and will almost certainly lead to an increasing proportion of elderly and senile individuals in the population and to an inevitable increase in the number of individuals with dementia among them. Over the next 30–40 years, almost every currently living person will presumably be affected by dementia either as a patient or as a caregiver. The highest growth in morbidity is expected in low- and middle-income countries, Russia being one of the latter. The proportion of patients with dementia in these countries is predicted to increase from 58 to 71% of the global dementia population. Dementia caused by AD places a huge economic burden on a country and society in general. In the USA alone, medical care and long-term care expenditures associated with dementia (in more than 60% of cases associated with AD) are estimated to be 355 billion dollars [1].

Despite massive investments, primarily in the global market of drugs used for the treatment of this disease, AD still inevitably leads to severe disability and death. After more than thirty years of highly active research in neurobiology and neuropharmacology, and tremendous financial expenses comparable to the annual budget of an average European country, there are still no drugs that can not only reduce the clinical severity of the disease symptoms but also reliably modify its course, i.e., stop or significantly delay its progression.

EVOLUTION OF THE VIEWS OF ALZHEIMER'S DISEASE DIAGNOSTICS

Experts in this area believe that one of the main reasons for such poor outcomes of AD treatment is the late start of therapeutic intervention. In clinical practice, AD is generally first diagnosed only at the stage of clinically apparent dementia, i.e., at the stage of advanced neurodegeneration. Therefore, there is an urgent need to develop routine methods for the diagnosis of AD at an early, predementia — or even pre-symptomatic — stage of neurodegeneration, i.e., when neuropathological abnormalities specific to Alzheimer's disease are present, but no clinical symptoms are yet manifesting. Experts estimate that this asymptomatic stage may last for at least 20 years. According to some researchers, at this earliest stage of the pathological process the maximum therapeutic effect, focused on preventing the transition from predementia cognitive impairment to dementia, can be expected. In the last decade, important progress has been made in the development of in vivo biomarkers of AD, which significantly help in both understanding the pathogenesis of this disease and determining its diagnostic boundaries. The NINCDS-ADRDA [2] diagnostic criteria were first revised in 2007. The International Working Group (IWG) led by Professor B. Dubois [3] proposed to consider AD a clinical-biological entity based on a combination of in vivo biomarkers (cerebrospinal fluid biomarkers or MRI signs of atrophy together with FDG PET hypometabolisms in certain brain areas or autosomal dominant mutations) and a specific clinical phenotype. Consequently, the definition of AD applies not only to dementia but also to the predementia stage. In 2010, the same working group proposed the inclusion of two predementia stages, the asymptomatic and the symptomatic, within the diagnostic boundaries of AD. The asymptomatic stage applies to people with AD biomarkers in the absence of clinical manifestations. The diagnosis of symptomatic stage applies to patients who clinically meet the criteria of mild cognitive impairment (MCI) or mild neurocognitive disorder (DSM-5 terminology), and in whom AD biomarkers have been detected [4]. The diagnostic criteria were further improved in 2011. Under the auspices of the US National Institute on Aging (NIA) and the Alzheimer's Association (AA), the working group developed guidelines on the diagnosis of AD comprising two sections: the first includes a set of clinical criteria that can be used in the healthcare practice since they do not require high-technology neuroimaging studies or cerebrospinal fluid tests; the second includes a set of exploratory criteria to be used for research purposes and in clinical trials of novel drugs [5]. These exploratory criteria require mandatory detection of biomarkers using either high-technology neuroimaging methods (amyloid PET or tau PET) or cerebrospinal fluid tests in the diagnosis of AD. Depending on the presence and nature of detected biomarkers, AD criteria are divided into four levels of diagnostic certainty based on the presence of biomarkers reflecting amyloid pathology only, neuronal degeneration only, or both.

According to these new NIA-AA criteria, the diagnostic boundaries of AD encompass not only dementia and symptomatic AD but also the asymptomatic stage. Thus, the diagnosis of AD can be established before the onset of cognitive symptoms [6]. The diagnosis is based on the detection of specific biomarkers reflecting the localization and nature of Alzheimer's neurodegeneration. These include biomarkers indicating the accumulation of amyloid-β (low cerebrospinal fluid amyloid-β 42 and/or high tracer retention in amyloid PET) and biomarkers confirming neuronal degeneration (high cerebrospinal fluid tau, both total and phosphorylated) and FDG PET hypometabolism in the temporo-parietal cortex, along with signs of brain matter atrophy via structural MRI. An important limitation of these diagnostic criteria is the lack of standardized values for each biomarker. The researchers admit that some aspects of AD diagnostic criteria based on biomarker validation may require revision in the future. Presumably, such revisions will be regularly made as new information becomes available.

Although the diagnostic criteria above were intended for research purposes only, they raised controversy due to their potential extension to clinical practice, for example, if positive biomarkers are detected in cognitively unimpaired elderly and senile individuals who never develop clinical symptoms of AD throughout their lives. Problems also arise when AD biomarkers are detected in patients with a clinical presentation of another neurodegenerative disease (e.g., Parkinson's disease or Lewy body dementia), i.e., when Alzheimer's neuropathology is some form of comorbidity. The implementation of a diagnostic approach based on Alzheimer's biomarkers in practice is also problematic due to the lack of consistent biomarker thresholds. The delimitation between positive and negative patients for any given biomarker significantly varies between studies. At the same time, any changes in biomarker thresholds, e.g., as diagnostic technologies improve, will have a significant impact on both the diagnostic boundaries of AD and disease staging.

Moreover, a significant limitation of the purely biological definition and, respectively, diagnostic boundaries for AD solely based on biomarker levels is the low predictive value of biomarker-based criteria. Several longitudinal studies showed that positive AD markers in asymptomatic individuals are not sufficient to predict symptoms typical for clinical AD phenotypes, i.e., aMCI or Alzheimer's dementia.

In particular, in the INSIGHT study [7, 8], no clinical signs, either cognitive, behavioral, or neuroimaging, were observed during 5 years in 83% of amyloid-positive elderly patients (mean age at the study entry: 77 years) compared with the baseline characteristics of these patients or with a cohort of amyloid-negative individuals of the same age. The results of another prospective study (ALBA) confirmed the data above: 81% of elderly patients from a cohort of amyloid-positive individuals (mean age at the beginning of the prospective study: 75 years) also showed no cognitive decline after 6 years.

Moreover, in a large cohort of cognitively unimpaired elderly individuals (576 subjects with a mean age of 71 years), amyloid and diffuse tau pathologies were found in a quarter (24%) of subjects [9].

Other studies [10, 11] showed that similar amyloid and tau pathologies were detected via PET imaging using appropriate tracers in both cognitively unimpaired elderly individuals and subjects with mild cognitive impairment.

Moreover, biomarker-based diagnosis of AD in cognitively unimpaired elderly and senile individuals has negative ethical aspect. Telling cognitively sound individuals that they have an irreversible disease associated in public opinion exclusively with inevitable severe disability, dependency, and death will negatively affect their treatment compliance and patient-doctor interactions, aside from the potential negative psychological reaction to this "terrifying" diagnosis. Given that the future evolution of the asymptomatic stage is not yet clear and there are still no reliable ways to stop the progression of cognitive and behavioral symptoms associated with AD, disclosure of this stressful information to a patient can cause irreversible damage by triggering depressive disorder, which is a risk factor of AD itself. When Alzheimer's biomarkers are detected in cognitively unimpaired individuals, they can only be informed that they are at risk of progressive cognitive impairment rather than being diagnosed with a preclinical stage of AD. This will cause no psychological damage and can even help in discussing the strategy of preventive measures with the patient with the aim of eliminating the potentially modifiable risk factors or in discussing the benefit-to-risk ratio of the preventive treatment that is offered to the patient.

It should also be noted that AD diagnosis based on biomarker detection rather than clinical phenotype can potentially create diagnostic confusion. This is particularly true for cognitively unimpaired individuals of very old age (85 years and older), almost all of whom have subjective complaints of memory-related problems and a few signs of AD based on PET biomarker and cerebrospinal fluid testing. According to IWG-2021 [12], detection of AD biomarkers is not sufficient to reliably predict the progression of asymptomatic stage to clinical AD symptoms. The author shares this view.

According to experts, the relationship between the presence of amyloid beta and tau pathology on the one hand, and progressive cognitive decline on the other is still uncertain at the individual level [13].

However, a pressing issue in improving the AD diagnostics and a prerequisite for future use of preventive antidementia strategies in neurodegenerative diseases is finding so-called peripheral AD biomarkers, i.e., markers that can be measured in blood serum or other body fluids (urine, saliva). In contrast to those currently used, such markers do not require traumatic invasive methods (e.g., spinal puncture) or high technology that are extremely costly and thus unavailable in general medical practice (such as amyloid or tau PET, FDG PET, etc.). It must be emphasized that the aforementioned limitations of biomarker use in routine clinical practice must equally apply to peripheral biomarkers.

A certain degree of progress in the detection of serum biomarkers has been achieved in recent years. Modern approaches (proteomics, metabolomics, mass spectrometry) have helped to discover a number of proteins, their metabolites, or combinations of several protein molecules that are assumed to be potential peripheral markers of AD [14–16]. However, to confirm the diagnostic significance and to determine the thresholds of these new biomarkers, they must be validated, including in prospective or follow-up studies. Candidates currently evaluated as possible early diagnostic markers of AD include P-glycoprotein (P-gp); microRNAs (miRNAs), and free copper ions [17].

Russian researchers have proposed the following possible diagnostic serum AD markers: low expression of amyloid degradation enzyme neprilysin [18]; changes in ratio of sphingolipids sphingomyelin and ceramide [19], anti-p75 receptor antibody levels [20], etc. Studies are currently being developed to evaluate the sensitivity, specificity, and reliability of these biomarkers for the diagnosis of AD at the predementia stage.

From our point of view, considering the multifactorial nature of the neurodegeneration associated with Alzheimer's and its heterogenous phenotypes, developing a multimodal panel of biomarkers appears to be more reasonable than expecting that a single biomarker that can reliably confirm the Alzheimer-related nature of cognitive decline will be discovered. AD is known to develop as a result of a combination of multiple pathogenic factors, including genetic, environmental, constitutional, somatic, and temporal factors. Heterogenous combinations of such factors result in various AD phenotypes: familial and sporadic, presenile (early-onset) and senile (late-onset), pure and mixed, i.e., combined with other types of brain disease. Thus, a multimodal panel of biomarkers should, in theory, better reflect the complex nature of this disease, although the assessment of such data would entail a number of additional challenges and the algorithm for the analysis of their diagnostic value is yet to be developed.

In this regard, new data on the pathogenetic role of neuroinflammation in the development of AD are of particular interest [21–23]. A correlation has been established between increased inflammatory marker levels and the severity of cognitive disorders in AD patients, as well as the progression of cognitive decline in older age. A prospective three-year study in a cohort of 252 elderly patients with aMCI showed that a low-grade systemic inflammatory response detected based on the levels of certain cytokines, tumor necrosis factor, and CRP in peripheral blood serum predicts a significant increase in cognitive decline or progression to dementia within the next three years [24]. It was also shown that such an integrative parameter as the ratio of leukocyte elastase (LE) enzymatic activity and alpha1-proteinase inhibitor (alpha1-PI) functional activity has a statistically significant correlation with the probability of AD in patients with aMCI [23]. These data served as the basis for developing the Alzheimer's disease immune test [25]. Thus, the results of recent clinical and immunological studies create new opportunities to develop a novel pathogenetic model of AD and new diagnostic approaches based on this model. However, further significant efforts are needed to validate the peripheral biomarker-based criteria and to standardize the biomarker tests before they can be used as part of patient care.

NEW APPROACHES TO DRUG THERAPY FOR ALZHEIMER'S DISEASE

An equally pressing task at present is to find effective methods of pharmacological intervention able to stop or substantially delay neurodegeneration that has already started and thus prevent or delay the onset of dementia for several years. If this issue is not solved, the ultra-early diagnosis of AD or another progressive neurodegenerative disorder leading to dementia becomes a purely scholastic activity which is not only useless to the patients but can even subject them to significant harm by causing chronic psychological stress and depression, which is in itself a risk factor of dementia in elderly individuals.

Over the last several decades, multiple — and increasingly well-designed — clinical trials have been conducted to evaluate various drugs (nonsteroidal anti-inflammatory drugs, Ginkgo Biloba, statins, estrogens, progesterone, vitamins E and C, betacarotene, folic acid, selenium, etc.) presumed to exert disease-modifying effects. Unfortunately, none of the investigated agents demonstrated reliable preventive effects, i.e., the ability to prevent or delay dementia. The anti-amyloid strategies for AD therapy extensively investigated over the last few years in international programs using various amyloid targeting drugs have also failed to yield significant clinical results. A clear breakthrough in this regard, however, was the FDA approval of aducanumab, which is an anti-amyloid drug. It was approved for AD predementia and mild dementia stages. Although it has a rather narrow therapeutic window, this drug opens new opportunities in the prevention or delaying dementia associated with AD, provided that treatment is initiated at the symptomatic stage, i.e., in amyloid-positive individuals with aMCI.

The analysis of previously used methods of prevention and treatment showed that in the vast majority of cases, treatment goals were aimed at blocking certain pathogenetic links of AD or mitigating the consequences of long-term neurodegeneration. However, attempts to influence the existing compensatory mechanisms in the human brain, i.e., the so-called endogenous system of brain defense and recovery were only made as part of small pilot studies. The endogenous brain defense system consists of a number of natural neurobiological processes, including neuroprotection, neurotrophic regulation, neuroplasticity, and neurogenesis, which ensure the survival of neurons exposed to certain damaging factors.

Under natural circumstances, these components of the endogenous brain defense system are regulated by natural neurotrophins such as NGF, BDNF, etc. In the last decade, neurotrophins, in particular NGF, became very promising candidates for the treatment of AD, as it was shown that low neurotrophic support plays an important role in the pathogenesis of Alzheimer's neurodegeneration. NGF prevented cholinergic neurons degeneration after experimental damage of basal forebrain septo-hippocampal nuclei and averted the progression of cognitive disorders in experimental animals. Unfortunately, natural neurotrophins cannot cross the blood-brain barrier due to the large size of the molecules, whereas low-molecular-weight synthetic neurotrophins are not yet available. Thus, studies of already approved neurometabolic drugs with demonstrated neurotrophin-like properties became a new area of clinical research. In particular, the researchers turned their attention to the long-known-about drug Cerebrolysin, which was used in the treatment of cerebrovascular diseases about half a century ago. New data are available on its biological and clinical effects due to the biologically active low-molecular-weight peptides present in its composition, part of which are similar in structure and chemical properties to natural neurotrophins [26]. Experimental data suggest that Cerebrolysin has sustained effects on neuropathological manifestations of AD: it reduces the formation of amyloid plaques and synaptic deficit in experimental animals, increases survival and structural integrity of neurons following exposure to pathophysiological stressors [27, 28], and can prevent the degeneration of cholinergic neurons [29].

A meta-analysis of six randomized, placebo-controlled studies demonstrated significant therapeutic effects of this drug based on the assessment of cognitive functions and its overall clinical effectiveness in the treatment of mild to moderate AD [28]. The results of a relatively small (110 patients) three-year comparative, prospective, parallel group study which showed significant effects in preventing the conversion of aMCI to the dementia associated with AD in elderly patients treated with two yearly courses of Cerebrolysin therapy are of particular interest in investigating the possible preventive anti-dementia effects of this drug [30].

Moreover, a recent clinical and immunological study conducted as part of the development of a strategy of preventive therapy for dementia in elderly patients with aMCI identified immunological markers of long-term therapeutic effects of Cerebrolysin [31].

Overall, the data above regarding the role of neuroinflammation and immune response in the development of AD create new opportunities to develop methods to correct the immune response as a promising direction of secondary dementia prevention in patients with early predementia manifestations of AD.

CONCLUSIONS

One-fifth of people aged 65 years and older are reported to have mild cognitive impairment (MCI), and the number of such patients in developed countries is steadily increasing. About one half of elderly individuals with aMCI are diagnosed as MCI associated with AD (or the predementia stage of AD) based on biomarker measurements. This implies the progressive nature of cognitive decline and its probable conversion to dementia within the next three years. This particular category of elderly individuals can be viewed as the most accessible "window" for interventions aimed at preventing the dementia associated with AD. The results of a few longitudinal studies indicate that preventive drug interventions such as antidiabetic or neurotrophin-like agents may reduce the rate of conversion to dementia. Therefore, the assumption that agents potentially increasing brain neuroplasticity along with anti-amyloid drugs should be used as prevention therapy appears to be promising. Experimental data confirm that several drugs, such as Cerebrolysin, citicoline, and acetyl-L-carnitine used in clinical practice for other indications, can influence endogenous brain defense and recovery mechanisms.

Considering the phenotypic and pathogenetic heterogeneity of Alzheimer's neurodegeneration, one can assume that multimodal and multicomponent preventive interventions directed at multiple causes of cognitive decline progression in individuals at risk of AD, in particular elderly people with aMCI, could help to reduce the rate of conversion to dementia. However, only the results of prospective, randomized, placebo-controlled studies in large cohorts of patients with MCI of a biomarker-confirmed Alzheimer-related nature can provide clarity in this regard.

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Towards a WPA Position Document on the Human Rights of Older Adults with Mental Health Conditions

К документу с изложением позиции Всемирной психиатрической ассоциации по вопросу соблюдения прав пожилых людей с психическими расстройствами

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Short communication

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ABSTRACT
The increasing number of older adults in countries across the world is a huge challenge to those that are in charge of promoting, protecting, and implementing their human rights. This task is particularly difficult in the absence of a strong international framework addressing the principles required to guide the actions to combat all human rights violations. The existence of such a specific framework for older adults with mental health conditions is justified in view of the particular vulnerability of this section of the population by virtue of societal ageism, stigmatization, exclusion, as well as the disability and dependency which mental health conditions in old age may confer. The present article is a development of a previous statement by the International Psychogeriatric Association and the World Psychiatric Association Section of Old Age Psychiatry. As there is a call to all organizations to support efforts to combat Human Rights violations among older adults, a text will be submitted to the Executive Committee of the World Psychiatric Association to approve an official position statement on Human Rights of Older Persons with Mental Health Conditions.

АННОТАЦИЯ
Растущее число пожилых людей во всех странах мира является большой проблемой для тех, кто отвечает за продвижение, защиту и реализацию прав этой группы населения. Задача дополнительно усложняется ввиду отсутствия устоявшейся международной системы, определяющей принципы работы организаций, борющихся за права человека. Необходимость создания специфической для пожилых людей с психическими расстройствами системы особенно оправдана ввиду повышенной уязвимости этой группы населения из-за дискриминации по возрастному признаку, стигматизации, изоляции, а также инвалидизации и зависимого положения, с которыми могут столкнуться люди пожилого возраста с психическими расстройствами. В настоящей статье развивается ранее изложенная позиция Международной психогериатрической ассоциации и Секции психиатрии позднего возраста Всемирной психиатрической ассоциации. Поскольку призыв поддержать действия, направленные на борьбу за права пожилых людей, обращен ко всем организациям, текст будет представлен исполнительному комитету Всемирной психиатрической ассоциации для утверждения официальной позиции в отношении соблюдения прав пожилых людей с психическими расстройствами.

Keywords: *old-age mental health; old-age psychiatry; human rights of older adults; convention on the rights of older people*
Ключевые слова: *психическое здоровье в пожилом возрасте; психиатрия позднего возраста; права человека в пожилом возрасте; конвенция по правам пожилых людей*

INTRODUCTION

“There is no older adults’ mental health in absence of respect for the Human Rights principles”. This statement is the leitmotiv of this article, which intends to determine the basis of a World Psychiatric Association position statement on Human Rights of Older Adults with Mental Health Conditions, as proposed by the Section of Old Age Psychiatry.

The rapid ageing of world population will contribute to increase the proportion of persons aged 65 years and more from 9% in 2020 to 16% by 2050, when 1.5 billion people will be over 65 years. This growth is not restricted purely to developed countries [1]. It is estimated that approximately 20% of these persons will have mental health conditions such as dementia, depression, anxiety, and substance abuse, often complicated by physical and psychosocial comorbidities culminating in disability.

According to the Global Burden of Diseases 2019 [2], mental disorders remained among the top ten leading causes of burden worldwide. In people aged 50 and over, depressive and anxiety disorders are the leading causes of disability-adjusted life-years (DALYS) and years lived with disability (YLDs), with all ages included (and this without the inclusion of neurological disorders, such as dementia, and substance abuse disorders).

One must recognize that in a world of limited resources and with the majority of mental health systems around the globe in crisis, the gap between older people’s needs in terms of health and well-being and the offer of support is increasing sharply, accompanied by several violations of basic human rights. Healthy ageing implies much more than just the satisfaction of older persons’ needs: it also includes support for the ageing process throughout their lifetimes. In this sense, the refusal to invest in mental health may contribute to a reduction in economic outcomes. 17% of the global workforce is aged 55 or over, so supporting the mental health of these older workers may help to sustain the economies of families and nations alike, and reduce the burden of diseases [3, 4].

Older adults may experience multiple jeopardies of discrimination and stigma conferred by age itself (ageism) and by having mental disorders (“mentalism”) [5]. Older adults with mental health conditions are often segregated in institutions where they have to live far from other members of the community, their voices being ‘invisible’, with no support to protect themselves against abuse, neglect, or violence. These victims of ageism and mentalism are often sidelined and disproportionately excluded from all kinds of protection, including those sustaining life: this was particularly observed during the COVID-19 pandemic [6]. This “grossly unmet need” for rights-based mental health and psychosocial care is the result of a combination of factors, including the failure to incorporate the voices of those most affected in health and government policy and inadequate environmental, social, home, and family support [7]. The voices of older people themselves are often missing in health and policy interventions that are, ironically, intended for them.

A global organization able to articulate the needs of older adults experiencing the highest disease burden remains absent. The non-existence of an institution with the capacity to ensure the protection of that rights of older adults may be understood as being a consequence of the fact that when the United Nations and the WHO were created in 1945 and 1948, respectively, demography was not in favor of older adults. The global life expectancy at that time was still quite low, and the number of older adults worldwide was not particularly significant. This has dramatically increased due to improved life-expectancy: if in 1950 there were seven children aged less than 15 for per older adult, by 2050 this ratio will be in the region of 1:1. In terms of sheer numbers, this appears concerning as the population which is vulnerable and needs human rights protection is massive, and indeed is continuing to grow.

TOWARD A WPA POSITION STATEMENT

It is now necessary more than ever that all organizations able to advocate and act to protect the Human Rights of Older Adults with Mental Health Conditions take a clear position on this matter. The International Psychogeriatric Association (IPA) with the World Psychiatric Association Section of Old Age Psychiatry (WPA-SOAP) have already published a joint statement [7]. The challenge now is to invite the WPA to publish a position statement on this same matter.

Key to the WPA’s mission and work is ensuring the ethical treatment and care of those people around the world suffering from mental health conditions and, thus, the ethical responsibilities of those providing treatment. Although there may be cultural, social, and national differences, the need for ethical conduct and continual review of ethical standards is universal. WPA has developed ethical guidelines for psychiatric practice and position statements on topics relevant to psychiatric practice and the role of psychiatrists. The position statements are prepared by the WPA Executive Committee. These would present the views of the WPA on public health and social matters relevant to mental health, as well as the functioning of the WPA itself. The WPA is a global association representing 145 psychiatric societies in 121 countries, bringing together more than 250,000 psychiatrists. The association has formal links with the WHO. According to the Journal Citation Reports, the WPA's official journal, World Psychiatry, is the Number 1-ranked journal in psychiatry and in the Social Science Citation Index.

Two position statements have already been published in October 2017 by WPA related to the theme of Human Rights. The first concerns the WPA Bill of Rights for Persons with Mental Illness [8]. In this statement, the WPA urges ALL Governments to ensure that persons with mental health conditions are not discriminated against based on their mental health status, and are treated as full citizens enjoying all rights with equality and respect. With this statement, the WPA supported the efforts of the international community as expressed through various international human rights Covenants and Conventions and, more particularly, the United Nations Convention on the Rights of Persons with Disabilities (CRPD). The WPA still reiterates that persons with mental health conditions have the capacity to hold rights and exercise their rights and should, therefore, be treated with dignity, equality, and respect.

The second position statement is the WPA Position Statement on the Rights of Persons with Disabilities [9]. The UN Committee on the Rights of Persons with Disabilities indicated its belief that the CRPD precludes any non-consensual hospitalization or treatment, or the appointment of a substitute decision maker for an incapable person, under any circumstances whatsoever. It bases this belief on the view that "the existence of an impairment…must never be grounds for denying legal capacity." The WPA has found the interpretation of the CRPD to be unconvincing and potentially extremely harmful to persons with disabilities themselves.

Throughout the position statement, the WPA sustains the strong belief that non-consensual hospitalization and treatment and the use of substitute decision making have appropriate roles to play in protecting the interests of persons with severe mental disorders, when used in appropriate cases, with careful oversight and rigorous procedural protections. The WPA strongly supports efforts to assist persons with decisional impairment to recover capacity, so that they can make their own decisions with autonomy. Hence, the WPA requested that the UN Committee reconsider its interpretation of the CRPD, and recommended that subsequent amendments to the CRPD clarify the importance and legitimacy of protecting people with severe mental disorders when they lack the capacity to defend their interests or protect themselves.

The CRPD, which is celebrating 10 years of operation, was a crucial step towards protecting the Human Rights of People with Disabilities. It is regretful that the authors of this Convention thought it unnecessary to introduce a specific article on older adults with disabilities. There is one on Women with Disabilities (Article 6) based on the recognition that women and girls with disabilities are subject to multiple forms of discrimination, and in this regard shall take measures to ensure the full and equal enjoyment by them of all human rights and fundamental freedoms. There is another article concerning Children with Disabilities (Article 7) that ensures the full enjoyment by children with disabilities of all human rights and fundamental freedoms on an equal basis with other children. This absence of a specific article protecting the interests of older adults is another argument to advocate the establishment of a specific convention on the rights of older people [10, 11].

GENERAL PRINCIPLES OF HUMAN RIGHTS OF OLDER ADULTS WITH MENTAL HEALTH CONDITIONS

In a previous consensus statement [5], the WPA Section of Old Age Psychiatry (WPA-SOAP) has recognized that there are existing frameworks outlining Human Rights Principles for Older People [12, 13] and for people with mental illnesses [14]. It was also considered in a previous WPA-SOAP consensus statement [5] that several health professional organizations have developed codes of practice that embody ethical principles and human rights. However, the rights of older people under these documents have not been actualized due to ageism, systemic inertia, mentalism, and failure to recognize the specific needs of older adults with mental health conditions. The existence of such a specific framework for older adults with mental health conditions is justified in view of the particular vulnerability of this section of the population by virtue of societal ageism, stigmatization, exclusion, as well as the disability and dependency which mental health conditions in old age may confer. An international convention could potentially provide a legal framework for the recognition, protection, and implementation of human rights among older people. It is a collective responsibility of all related organizations/bodies to support and call for such a convention.

The WPA-SOAP consensus statement [5] proposed the following general principles, which should underpin any such framework:

- *Independence*. Older adults with mental conditions have the right to contribute usefully to society and to make their own decisions on matters affecting their lives and deaths;
- *Safety and dignity*. With this principle, it was recognized that older people with mental health conditions have the right to live safely, with adequate food and housing, free of violence, abuse, neglect, and exploitation
- *Care and treatment*. This principle affirms the right of older people with mental health conditions to benefit from family and community care and protection and to be given access to healthcare to help them maintain or regain their optimum level of function and well-being and prevent or delay deterioration.

PROPOSAL FOR A WPA POSITION STATEMENT ON HUMAN RIGHTS OF OLDER ADULTS WITH MENTAL HEALTH CONDITIONS

The following text is a draft that will be submitted to the WPA Executive Committee to propose a final WPA position statement on Human Rights of Older Adults with Mental Health Conditions.

The World Psychiatric Association (WPA), a global organization representing nearly 250.000 psychiatrists, urges ALL Governments and Intergovernmental agencies to ensure that older persons with mental health conditions are not discriminated against based on their age and on their mental health status and are treated as full citizens enjoying all rights on an equal basis with other citizens. The respect of basic Human Rights is essential to ageing with dignity. Human Rights sustain the ethical and the legal framework to support healthy ageing and to protect those whose autonomy and self-determination may be compromised by the presence of mental health conditions.

The WPA supports the efforts of the international community as expressed through various international rights covenants and conventions, but recognizes the limitations of these documents in actualizing the rights of older people due to ageism, systemic inertia, and failure to recognize the specific needs of older adults with mental health conditions. Critical health perspectives and social considerations tailored to the needs of older people are warranted to safeguard their human rights and promote health equity.

The WPA reiterates that older adults with mental health conditions are owed exercise of these rights and to be treated with respect and dignity on an equal basis with other citizens. Human Rights most relevant to older persons' mental health include, but are not limited to, the rights to (not in any hierarchical order) [7]*:*

1. *enjoyment of the highest attainable standards of affordable mental and physical health, including at the end of life* [15]*, and respecting specific needs that arise on account of disability* [16]*;*
2. *autonomy with equal recognition before the law, including the right to equal legal capacity, expression of will and preferences, with support for decision-making when required* [5, 17]*;*
3. *dignity and quality of life* [18, 19]*;*
4. *an ageism-free world* [20]*;*
5. *the absence of any distinction based on gender* [21]
6. *safeguarding against undue influence and abuse, freedom from cruel, inhumane, degrading treatment, and punishment* [5, 17]*;*
7. *living independently and being included in the community, participating in the cultural and social life of the community* [22]*;*
8. *making contributions to the community through work or other activities, and to be protected during these activities as any other citizens* [4]*;*
9. *provision of adequate income to meet basic needs for food, housing, clothing, and other necessities* [4, 22]*;*
10. *accessible, integrated, affordable housing, the right to which is protected even when legal capacity is compromised* [22]*;*
11. *living in a safe environment, including protection against climate negative consequences on mental health* [23]*;*
12. *accessible leisure and education as available to other citizens;*
13. *respect for family, relationships, sexual health, and the right to intimacy* [24]*;*
14. *confidentiality and privacy; and*
15. *to practice a spiritual life of one's choosing* [25].

WPA has identified key strategies to promote, sustain and protect these rights including 8, 9:

- *the publication of a United Nations convention on the rights of older persons that could provide a framework for limiting social and economic inequities, insecurities and vulnerabilities; to promote opportunities to improve older persons quality of life and to articulate further developments in the future;*
- *the creation of an international agency with capacity and resources to lead and coordinate UN activities related to human rights of older persons, to propose guidance to promote physical, mental, social wellbeing and related political and economic aspects. This agency could offer support to national governments, collaborate with the efforts of civil organizations working in the field and implement policies, programmes and services;*
- *active collaboration and joint advocacy by all national and international organizations working for the rights of older people, especially with respect to sensitizing the Governments for action.*

WPA strongly recommends integration of future generations of older persons in all such developments related to the Human Rights of older persons in coordination with other agencies to support the humanity-enhancing need to age well. An international convention will go a long way in providing a legal and systemic framework for protecting the human rights of older adults and thus facilitate healthy ageing. *WPA has identified key strategies to promote, sustain and protect these rights including:*

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WPA strongly recommends integration of future generations of older persons in all such developments related to the Human Rights of older persons in coordination with other agencies to support the humanity-enhancing need to age well. An international convention will go a long way in providing a legal and systemic framework for protecting the human rights of older adults and thus facilitate healthy ageing.

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Mental Health Promotion and Risk Reduction Strategies for Mental Disorders in Older Persons: Why Should Governments and Policymakers Care?

Стратегии улучшения психического здоровья и снижения риска развития психических расстройств у пожилых людей: почему об этом должно позаботиться государство?

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Commentary

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ABSTRACT

There is no health without mental health. These are both indispensable human rights and are prerequisite to living one's life with dignity. Unfortunately, mental health systems have been in crisis, with burden of mental illness being among the ten leading healthcare-related issues worldwide, with no measurable reduction in such for over 30 years. Concurrently, the demographic clock continues to tick. Toady's 703 million people aged 65 or older are projected to reach 1.5 billion by the year 2050. Of these, 20% will suffer with serious mental health conditions. At the heart of the global crisis for older people is ageism, frequently intersecting with ableism, mentalism, sexism, and racism.

These biases result in the violation of older peoples' human rights every day, with the resultant poor quality of life and premature death. They are compounded by major gaps in legislation, policies, and practices, rendering the central transformative promise of the UN's 2030 Agenda to "Leave No One Behind" a very elusive goal. Evidence-based interventions designed to prevent or reduce the risk of common mental health conditions and psychosocial disability are already available. All governments and policymakers have a major role to play in the promotion of good mental health and the prevention of mental illness by integrating these into public health and general social policy.

This requires adopting, implementing, and scaling up of evidence-based, cost-effective interventions to reduce the risk of the development of mental disorders and providing access to adequate treatment when needed for older persons. All governments and policymakers also have a pivotal role to play in leading and supporting a UN convention on the human rights of older people. A UN convention would help combat ageism at the national and international levels by ensuring integration of monitoring and enforcement mechanisms to effectively implement policies and laws that could address discrimination, inequity, and the protection of human rights of older people, including their mental health.

АННОТАЦИЯ

Психическое здоровье не менее важно, чем физическое. Возможность заботиться о своем психическом и физическом состоянии — неотъемлемое право каждого человека и обязательное условие сохранения достоинства. К сожалению, процессы, направленные на сохранение психического здоровья населения, далеки от совершенства. Уже более 30 лет психические заболевания входят в десятку самых проблемных направлений мирового здравоохранения, и предпосылок для улучшения ситуации пока не наблюдается. Население Земли продолжает стареть: если сейчас в мире насчитывается 703 млн людей в возрасте 65 лет и старше, то к 2050 году их количество вырастет до 1,5 млрд. По прогнозам, у 20 % из них будут диагностированы серьезные психические расстройства. Эйджизм — одна из главных причин глобального кризиса в сфере защиты здоровья пожилого населения, наряду с эйблизмом, ментализмом, сексизмом и расизмом.

Все эти формы дискриминации ежедневно приводят к нарушению прав пожилых людей, снижению качества их жизни и преждевременной смерти. В значительной степени этому способствуют многочисленные пробелы в законодательной, политической и практической работе. Именно поэтому одна из основных целей, обозначенных в стратегии развития ООН на 2030 год — Leave No One Behind (Не оставлять никого в стороне) — настолько труднодостижима. Тем не менее уже разработаны научно обоснованные инструменты профилактики и минимизации риска развития распространенных психических заболеваний и психосоциальной дезадаптации населения. Ключевую роль в улучшении психического здоровья и профилактики психических заболеваний играют органы государственной власти: от них зависит, будут ли включены эти вопросы в политику общественного здравоохранения и общего социального развития.

Для этого необходимо разработать, внедрить и распространить программу научно-обоснованных и экономически эффективных мер по снижению риска развития психических заболеваний, а также создать возможности для организации доступной психиатрической помощи пожилым людям. Во всех странах органы государственной власти должны играть ключевую роль в продвижении принципов конвенции ООН по защите прав пожилых людей. Конвенция ООН по борьбе с эйджизмом предусматривает внедрение специальных механизмов мониторинга на национальном и международном уровнях для эффективного исполнения законодательных мер, направленных на противодействие дискриминации и неравенству, а также на защиту прав пожилых людей, в том числе права на психическое здоровье.

Keywords: *ageism; mental health; human rights; older person; United Nations; mental health promotion; government; policymakers*

Ключевые слова: *эйджизм; психическое здоровье; права человека; пожилой человек; Организация Объединенных Наций; улучшение психического здоровья населения; государство; законодательные меры*

WE HAVE NOT COME VERY FAR

Health and mental health are fundamental human rights that are indispensable to the exercise of other human rights. Every individual is entitled to the enjoyment of the highest attainable standard of health conducive to living a life in dignity [1, 2]. “There is no health without mental health”, according to the World Health Organization (WHO) [3]. Sadly, but not surprisingly, mental disorders remain one of the top ten leading healthcare-related burdens worldwide [4]. Despite mental health systems having functioned in crisis mode for decades, no net reduction in the associated burden has been seen in the past 30 years [4, 5]. Mental illnesses account for at least 18% of the global disease burden, with a projected annual global cost of US$6 trillion by the year 2030 [6]. It is therefore critical that governments and policymakers focus on the scarce resources and time available to create a paradigm shift that emphasizes upstream interventions that have the potential to improve mental health systems and the population’s health. The foundation of this transformation must converge on innovative, evidence-based strategies for prevention of mental health conditions, the promotion of mental health maintenance, the reduction of the impact of psychosocial disability, as well as effective and timely treatment programs for persons who live with mental health conditions [4]. The fundamental human right to mental health has been flagrantly violated for decades with dire consequences to global society, health, and the economy — this must be urgently rectified.

THE CLOCK IS TICKING

Today, there are 703 million people aged 65 or older, a number that is projected to reach 1.5 billion by 2050 [7]. Of these, approximately 20% will have mental health conditions such as dementia, depression, anxiety, and suffer other issues such as substance abuse, often complicated by physical and psychosocial comorbidities culminating in disability [8]. These ominous trends have been accelerated by the COVID-19 pandemic with widespread increases in mental health challenges.

Easily accessible, dependable, and reliable community, hospital-based, and residential mental health care is urgently needed for older persons. Timely access to care, in close proximity to the older person’s family, by a team of collaborative healthcare provider services, who have received special education and training in the care of older persons with mental health conditions, is critical. All care and treatment planning must balance the degree of risk posed to self and others by the older person's mental health condition with their personal need for dignity, desire for autonomy and independence [9].

The promotion of the mental and psychosocial wellbeing of the older population is in alignment with the WHO's vision of the Decade of Healthy Ageing (2021–2030) and Sustainable Development Goals (SDGs) [10]. Governments and policymakers must mainstream older persons' mental health and support for their dignity and human rights [1]. This paradigm shift will require health care providers to work collaboratively as team players with members of other societal sectors such as education, labor, justice, transport, environment, housing, welfare, academia, civil society, and the private sector to pave the way improving the lives of older people, their families, and the communities in which they live.

A PERFECT STORM

Ageism is a massive, but nevertheless conquerable barrier that governments and policymakers must also deal with in order to successfully transform mental health care systems. Ageism is highly prevalent, extremely toxic to the health and dignity of older persons, and very costly to society [11, 12]. A shocking one out of every two people in the world are ageist [13]. Ageism has a colossal, albeit stealthy impact on older people's as well as global health and the economy [14]. Ageism is associated with poor health outcomes in 95.5% of studies with a strong association between mental health conditions and ageism, particularly depression, as reported by a comprehensive global review of the health consequences of ageism, a meta-analysis with over 7 million participants [15]. Ageism's staggering annual health care cost in the United States alone is $63 billion; thankfully, health benefits and cost reduction are predicted if ageism's toxic effects are negated by interventions targeting societal, legislative, and policy changes [16]. The WHO's Global Report on Ageism outlines three evidence-based strategies for combating ageism — education, intergenerational contact, and changes to policy and laws, which must be adopted by all governments and policymakers. Complex intersections of ageism include mentalism, ableism, sexism, and racism, and other biases, culminating in poor quality of life and premature death [13, 17].

MONUMENTAL GAPS

Monumental gaps in our society permit deeply rooted ageism to stealthily disregard the human rights of older persons, especially those living with mental health conditions. These include inequity in accessing physical, mental, social, and end of life care, work and justice, transportation, safe and inclusive living options, lifelong learning, protection against elder abuse, financial insecurity, abetting the digital divide and climate change and exclusion from lifesaving and life-enhancing research and the collection of meaningful data. These critical elements are relied upon by governments, institutions, corporations, and others to create the current unfair and unjust ageist policies and laws. Exclusion, inequity, debarring, and blatant abuse of fundamental human rights have seriously eroded older persons' dignity, autonomy, and independence.

IMPACT OF COVID-19

The recent tragedy of the COVID-19 pandemic, superimposed upon decades of deep-rooted ageism, has resulted in a dual pandemic creating a deplorable situation for older people. It has posed a major ethical, moral, and legal challenge to civil society, governments and policymakers, compelling them to examine ways in which they might enhance and protect the basic human rights of older people [18–22]. Abundant cases of older people have been witnessed who were previously functioning well but have struggled to survive and succumbed as a result of the dual pandemic and the ravages of human rights violations. Dreadful and pervasive cases of social isolation, loneliness, insurmountable fear, paralyzing anxiety, and depression have been commonly accompanied by suicidal ideation, suicidal behavior, or requests for medically assisted suicide. This has been frequently compounded by malnutrition, dehydration, deconditioning, and frailty due to sedentariness, resulting in a precipitous decline in the physical and mental health of countless older people, not to mention devastation experienced by their family members and loved ones [11]. Social isolation and physical distancing measures during the COVID-19 pandemic have seriously damaged the cognitive and mental health of people with neurocognitive disorders across the world. Out of 15 studies describing the effects of COVID-19 isolation measures on the health of 6442 patients living with dementia, 60% reported changes in cognition, 93% reported worsening or new onset of behavioral and psychological symptoms, and

46% reporting functional decline in daily activities. Urgent guidance is needed that balances infection control measures with necessary mental health care during pandemic times for this population [23].

Rates of elder abuse have increased during the COVID-19 pandemic [24]. Elder abuse can lead to serious physical injuries and long-term psychological consequences. Approximately one in six people aged 60 years and older have experienced some form of abuse in community settings, with much higher rates in institutions, e.g., long-term care settings, where two in three staff report committing abuse in the past year.

Social isolation, namely the number of relationships and frequency of contact a person has with others, is a risk factor for loneliness, that is, a subjective perception of a lack of meaningful relationships [25, 26]. Social isolation affects 24% of older people living in the community and is considered a major public health priority. It is considered to be as toxic to health as smoking fifteen cigarettes per day, and is causally linked to multiple cardiovascular diseases, anxiety, and depression. Loneliness, which has been reported by 43% of community-dwelling older people, can also lead to depression, alcoholism, and suicidal thoughts, and is known to accelerate cognitive decline, especially during the dual pandemic [27, 28]. In 2017, Medicare reported an additional $6.7 billion in costs that could be attributed to social isolation, which was reported by 14% of older adults in the US [29]. Reported rates of loneliness are at least double among long-term care residents than those of older community-dwelling adults [25].

PAUSE AND REFLECT

By 2050, one in six people in the world will be over the age of 65 [30]. While this demographic shift poses significant challenges to the healthcare, workplace, technology, housing, and other sectors, especially in the post-pandemic world, there are also many opportunities to harness the social and economic power of a multigenerational society. We must seek the key opportunities that accompany this demographic shift to realize the vision outlined in the UN Decade of Healthy Ageing and the SDGs [7]. We must pause and reflect: What are most innovative ways in which we can encourage healthy aging around the world? What are the areas of cooperation in which governments, the private sector, and multilateral organizations can collaborate to support this population? In what creative ways can we enhance the quality of life, and mental and physical health to benefit this growing segment of our population [3]?

THE WAY FORWARD

In the current WHO framework, universal, selective, and indicated preventive measures are all included within primary prevention. Primary preventive interventions in mental health are those targeting risk factors and promoting mental health in individuals without a clinically diagnosable mental disorder. Such interventions may be “universal”, targeting the mental health of the general public regardless of individual risk, and can be applied without professional advice or assistance. In contrast, “selective” interventions target a particular subpopulation known to be at increased risk of mental illness, whilst “indicated” interventions target individuals at high risk of mental illness who are showing sub-threshold clinical manifestations [31, 32]. The promotion of mental health and prevention of mental illness in older persons requires an “all hands on deck” approach. Leveraging the combined resources and capacity of health professionals, local volunteers, the private sector, and many others in a given community setting represents a successful and efficient use of human health resources. Using technological devices, especially during the COVID-19 pandemic, could promote positive mental health during a time when older persons are at the greatest health risk. Providing support to older persons willing to navigate technology can enable them to stay connected to their community, serving as a protective factor against adverse health outcomes [33]. Digital interventions are particularly suited to mitigating psychosocial consequences at the population level. In times of physical distancing, quarantine, and restrictions on social contact, decision makers should develop digital strategies for continued mental health care and invest time and efforts into the development and implementation of mental health promotion and mental illness prevention programs [34].

THE IMPERATIVE

Governments and policymakers can and must implement evidence-based, cost-effective public mental health interventions to promote mental wellbeing and resilience, and to reduce the risk of the development of mental disorders amongst older persons. Currently, preventative interventions in this space are virtually absent, where very few individuals with mental illnesses can gain access to adequate treatment when needed. To this end, an excellent and comprehensive Mental Health Policy review by Campion et al. was recently published, outlining the specific actions needed for preventative mental health, with positive health, social, and economic outcomes predicted if implemented appropriately [6]. While Campion's review focuses on strategies focused on the general population, we must remember that people are, on average, living longer, and a more specific focus on realizing better mental illness prevention and promotion of mental health strategies is needed to address the needs of older people [35, 36]. Governments and policymakers must build the capacity for preventative mental health services, utilizing health promotion to encourage successful aging [37].

Although most older persons wish to age at home, as their conditions deteriorate this is not always feasible or desirable for all. Having a mental health condition, such as dementia, is a risk for placement in a residential setting, where the physical, social, organizational, cultural, and the care components impact each resident's daily life and manifestation of neuropsychiatric symptoms and have become particularly prominent during the recent pandemic. Traditional large-scale buildings where residents are segregated and confined within the residence, separated from the community at large and often from other residents with poor outcomes and ineffective in supporting everyday functioning, and may even be harmful. Inactivity, high levels of agitation, depression, and other neuropsychiatric symptoms, use of physical restraint, high levels of psychotropic drugs, loneliness, and stigmatization. There is an urgent need for the development and design of inclusive care environments in which older persons with mental health conditions and psychosocial disabilities can be supported to enjoy their human rights [38].

Older people with dementia, those with serious mental illness, and those with intellectual disability are vulnerable to "bad deaths" due to violations of these rights. An integrated care model that encompasses physical and mental health, palliative care, and social and spiritual support must be on offer, while recognizing that good dying is needs-based and self-determined, i.e., based on what the person needs and wants at the end of life [39].

Governments must be encouraged and supported to adopt policies integrating the promotion of mental health and prevention of mental illness into public health and, indeed, general social policy [40]. The stigma of ageism stealthily harms global health, the economy, violates human rights, creates inequity and injustice, results in a loss of dignity, causes intergenerational conflict, and creates a barrier to policies that promote healthy ageing. Ageism intersects with ableism, mentalism, sexism, and racism, causing poor quality of life and premature death, compounding disadvantages over the course of individuals' lives [11]. Stigma results in a lack of attention from governmental policymakers and the public, which then results in a lack of resources and morale, decaying institutions, lack of leadership, inadequate information systems, and inadequate legislation [40]. The WHO global report on ageism [13] recommends three evidence-based interventions to combat ageism which must be adopted by all governments and policymakers: 1) education, both formal and informal, at various levels during each individual's formative years (primary school to university, formal and informal) to help provide more accurate information and refute stereotypical examples to enhance empathy, dispel misconceptions, and reduce age-based prejudice; 2) intergenerational contact interventions, known to reduce ageism, intergroup prejudice, and stereotypes by nurturing communication between people of different generations; and 3) policies and laws to reduce ageism by strengthening policies and legislation to address age discrimination, inequality, and human rights laws. Older people, especially those with mental health conditions, have largely been ignored in human rights frameworks. This requires governments to adopt modifications of the existing instruments — which currently permit age discrimination — and new instruments at the local, national and international level. There is an urgent need for all governments to support and ratify a UN convention on the rights of older persons [41]. This could guide governments on ways to protect each older person's rights. It could form a basis for policy, programming, public awareness, and education.

LEAVE NO ONE BEHIND

As the world grapples with surviving the COVID-19 pandemic, the emerging mental health crisis is plaguing the world. At the heart of this decades-long mental health crisis are major gaps in legislation, policies, and practices driven by stigma that predominantly target older people. The central transformative promise of the

UN's 2030 Agenda to "Leave No One Behind" remains a very elusive goal [42]. Evidence-based interventions designed to prevent or reduce the risk of common mental health conditions and psychosocial disability are already available and should be scaled up [43, 44]. Governments have a major role to play in joining the campaign to end ageism and the human rights violations of older persons.

A UN convention provides the legally binding protection of older persons' rights under international law, which views them as rights holders. It acts as an anti-discriminatory tool to challenge negative stereotypes and enforces the view of older people as individuals with knowledge, power, wisdom, and experience. A UN convention could guide the Government on ways to protect each older person's rights. This could form a basis for policy, programming, public awareness, and education. Government has a role to play in joining the campaign to end ageism and the human rights violations of older persons, including those with mental health conditions and psychosocial disability.

Currently, strong biases are entrenched in people's hearts and minds as institutional ageism. They are in the form of policies and laws that currently dominate the outlook of, and opinions available to individuals and, indeed, society at large. These biases strongly influence how older people, especially those with mental health conditions, are perceived and treated. "All hands on deck" will be needed to succeed at combatting ageism and mentalism, to help every human being to think, feel, and behave more positively towards older persons. This is in alignment with the UN's Decade of Healthy Ageing (2021–2030), calling for a global collaboration of Sustainable Development Goals that brings together governments, civil society, international agencies, professionals, academia, the media, and the private sector to improve the lives of older people, their families, and the communities in which they live.

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Loneliness Among the Elderly: a Mini Review

Одиночество человека в пожилом возрасте: краткий обзор

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Review

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ABSTRACT

Loneliness is understood as a painful negative emotion. Since its introduction into the psychiatric literature in 1959, the understanding of loneliness has improved considerably, and is now understood to be a distinct entity to such issues as social isolation, solitude, and depression. However, there is still a lack of consensus on the general definition of loneliness. Similarly, different dimensions of loneliness have been described in the literature. It is understood in terms of either transient versus situational versus chronic loneliness; state versus trait loneliness; and the concept of unidimensional versus multidimensional loneliness. The reported prevalence of loneliness varies considerably in the literature, with evidence from metanalysis suggesting the prevalence of moderate loneliness that ranges from 31 to 100% with a mean of 61%, and that of severe loneliness ranging from 9 to 81%, with a mean prevalence of 35% among the elderly. Loneliness among the elderly is associated with significant adverse mental and physical health outcomes in the form of cardiovascular diseases, stroke, diabetes mellitus, arthritis, depression, anxiety, dementia, and even problematic internet use. Over the years, different instruments [University of California Los Angeles Loneliness Scale (UCLA-LS), De Jong Gierveld Loneliness Scale, Single-Item direct measure of loneliness] have been designed to assess loneliness among the elderly. Some of the interventions suggest that persons experiencing loneliness could benefit from improved social skills, enhanced social support, increased opportunities for social contact, and addressing maladaptive social cognition.

АННОТАЦИЯ

Одиночество — болезненное состояние, сопряженное с отрицательными эмоциями. С момента появления термина в психиатрической литературе в 1959 году понимание одиночества значительно улучшилось. На сегодняшний день его считают самостоятельной нозологической единицей и воспринимают отдельно от социальной изоляции, уединения и депрессии, однако согласованного определения одиночества до сих пор нет. В литературе описаны различные параметры одиночества: разделяют временное или ситуативное одиночество и одиночество хроническое; одиночество может расцениваться как самостоятельное состояние или как проявление другого состояния; также одиночество может восприниматься как концепция, характеризующаяся одним или множеством параметров. Распространенность одиночества, по данным литературы, существенно варьирует: результаты метаанализа свидетельствуют о том, что распространенность умеренно выраженного одиночества составляет от 31% до 100% (при среднем значении 61%), а распространенность тяжелого одиночества — от 9% до 81% (при среднем значении 35% среди пожилых людей). Одиночество у пожилых людей сопряжено со значительными неблагоприятными последствиями для психического и физического здоровья, которые выражаются в виде сердечно-сосудистых заболеваний, инсульта, сахарного диабета, артрита, депрессии, тревоги, деменции и проблем с использованием интернета. За последние годы для оценки одиночества среди пожилых людей были разработаны различные инструменты [Шкала оценки одиночества

Калифорнийского университета в Лос-Анджелесе (University of California Los Angeles Loneliness Scale, UCLA-LS), Шкала оценки одиночества де Джонга Гервельда (De Jong Gierveld Loneliness Scale), однокомпонентный инструмент, направленный на непосредственную оценку одиночества]. Некоторые вмешательства, предлагаемые для коррекции состояния лиц, испытывающих одиночество, включают совершенствование социальных навыков, усиление социальной поддержки, расширение возможностей для социальных контактов и устранение дезадаптивного социального познания.

Keywords: *loneliness; consequences; assessment*
Ключевые слова: *одиночество; последствия; оценка*

INTRODUCTION

Today, loneliness appears to be becoming ubiquitous. The importance of loneliness can be understood from the fact that the Government of the United Kingdom appointed a Minister for Loneliness in 2017, followed by a similar move by the Government of Japan in 2021. It is now understood to represent a 'hidden killer' and has been shown to have a significant negative impact on both mental and physical health. It is known to be associated with high morbidity and mortality. Loneliness has been reported across all age groups, although it has been most commonly studied among the elderly.

This brief review discusses the concept of loneliness among the elderly and the suggested interventions to address it.

CONCEPTUAL ISSUES

The word "loneliness", which is understood to be a painful negative emotionality due to the perceived lack of social connectivity, first appeared in the literature in the 1800s [1]. Prior to the use of the term 'loneliness', the closest concept was 'oneliness', which meant being alone though without the negative connotation of lack of emotions [1]. It is said that earlier, God was always with people, who were hence never truly alone. However, with the ongoing modernization of society, the increasing importance ascribed to individualism and the decreasing influence of religion, loneliness has become rampant [1].

Frieda Fromm-Reichmann (1959) [2] was the first to consider loneliness to be a psychiatric condition and acknowledge the challenge in conceptualizing the term. He wrote that *"The writer who wishes to elaborate on the problems of loneliness is faced with a serious terminological handicap. Loneliness seems to be a painful, frightening experience that people will do practically everything to avoid. This avoidance seems to include a strange reluctance on the part of the psychiatrist to seek scientific clarification of the subject … Thus, loneliness is one of the least conceptualized psychological phenomena"* [3]. When Frieda Fromm-Reichmann used the term loneliness in the context of psychiatry, a broad range of experiences, i.e., social isolation and solitude, could not be distinguished from loneliness. Over the years, many researchers have distinguished loneliness from social isolation and solitude [3]. Accordingly, various attempts have been made to define the term: Perlman & Peplau (1982) defined loneliness as an "*unpleasant experience that occurs when a person's network of social relationships is deficient in some important way, either quantitatively or qualitatively*" [4]. De Jong Gierveld, who also designed a scale for the assessment of loneliness, defined it as a *"situation experienced by the individual as one where there is an unpleasant or inadmissible lack of (quality of) certain relationships* [5]." The Hidden Citizens report defines loneliness as *"a negative experience that involves painful feelings of not belonging and disconnectedness from others. It occurs when there is a discrepancy between the quantity and quality of social relationships we want and those we have. Thus, loneliness is a subjective psychological perception* [6]."

In a review of the literature, Heinrich & Gullone (2006) concluded that there are multiple definitions of the concept of loneliness that differ according to their their focus, i.e., definitions with a clinical focus, based on empirical psychological research and the definitions linking loneliness with social relationships and the human need to belong. In terms of factors contributing to developing and maintaining loneliness, Heinrich & Gullone (2006) identified different theoretical perspectives in this regard. These include the social need approach (which is influenced by early life experiences), cognitive discrepancy approach (which considers loneliness to be an outcome of faulty cognitive processes, wishes, and perception), interactionist approach (i.e., character traits interact with situational and cultural factors), deficits in social relationships (i.e., the need to belong), and, finally, a consequence of the universal human need to belong [3, 7]. When one attempts to understand these various definitions in a more holistic manner, it can be said that loneliness can be understood in terms of social relationships, and that when a person's need for social relationships is not met, loneliness ensues.

In terms of various dimensions, researchers have again tried to understand loneliness as a transient (occasional short-lasting feelings of loneliness, encountered from time to time by the majority of people in their day-to-day lives), versus situational (the feelings of loneliness when faced by specific life crises/transitions that adversely affect the relationships in a person who has otherwise had satisfying relationships in the past), versus chronic loneliness (which is understood to be enduring feelings of loneliness and dissatisfaction with social relationships lasting for more than two years) [7]. Other researchers have also tried to distinguish loneliness as a state (current and immediate feelings of loneliness) versus a trait (enduring feelings of loneliness) [7]. The conceptualization of loneliness also differs with regard to whether it is a unidimensional or a multidimensional (three ways in which loneliness can manifest itself, i.e., intimate, relational, and collective) concept. Researchers have also tried to conceptualize it based on a medical model (cause, effect, and management) versus a typical experience (transient experience) [7]. Another conceptualization of loneliness includes collection versus social versus intimate dimensions. This conceptualization is based on the understanding of 'attentional space', as described by Hall (1963, 1966) [8, 9]. Hall categorized attentional space as either *intimate space* (an individual's most closely surrounding space), *social space* (a space where a person can comfortably interact with their nearest and dearest ones, i.e., friends, family and acquaintances), or *public space* (a more anonymous space) [8, 9]. Accordingly, intimate loneliness is experienced when a person someone very close to them, either due to death or a breakup in their relationship, and which can be understood to be *"the perceived absence of a person on whom one can rely on for emotional support at the time of crisis, a person who can provide mutual assistance, and who affirms one's value as a person"* [3, 10]. Social or relational loneliness arises due to the absence of perceived connections with the 'sympathy group', which usually comprises family members and close friends, who are understood to represent 'core social partners' and are prepared to support the person during times of need. Collective loneliness includes a lack of connections with people who are part of a network, i.e., people with whom one can connect due to nationality, political affiliation, etc. The collective network is usually the outermost social layer, with whom ties are not very strong but who can provide information and low-cost support [3]. Another conceptualization of loneliness includes emotional versus social loneliness. Emotional loneliness is understood to be an outcome of a lack of a close, intimate attachment to another person. In contrast, social loneliness is understood to be an outcome of a lack of a network of social relationships in which a person is a member of a group of friends sharing common interests and activities [11].

To summarize, it can be said that loneliness has been variously defined by different authors and understood to be a multidimensional negative subjective experience characterized by qualitative, rather than quantitative, lack of satisfaction with one's relationships or perceived social acceptance. There is a need to reach to a consensus definition, and future definitions should also include things like material positions when defining loneliness.

Various authors have also attempted to describe the different stages of the development of loneliness. Rokach [12], in the context of psychotherapy, described six stages of development of loneliness: pain and awareness, denial, alarm and realization, search for causes and self-doubt, acceptance, and coping with the loneliness. It was further elaborated that sufferers' recognition and appreciation of the fact that they are lonely depends upon the particular stage they are in.

THE DISTINCTION OF LONELINESS FROM SOLITUDE, SOCIAL ISOLATION, AND DEPRESSION

It is crucial to distinguish loneliness from other related phenomena in clinical practice (Table 1). In contrast to loneliness, solitude is a positive experience in which a person chooses to be with self and avoids people [13]. In contrast to loneliness, social isolation is understood to be a harmful physical state in which a person lacks social contact, and arises as a result of loss of mobility (due to illness or disability, unemployment, or health issues). The socially isolated person has a small network

Table 1. Distinguishing features of loneliness, solitude, social isolation, and depression

Characteristics	Loneliness	Solitude	Social Isolation	Depression
Mental/ Physical State	A negative state of mind	A positive state of mind	A negative physical state	Negative mood state, along with somatic symptoms
Crowd	One can feel lonely even among a crowd, and emotionally connecting with people can alleviate loneliness	One needs to be physically isolated from others to feel solitude	Lack of contact with other people or having few or no people with whom to interact	May or may not have contacts, just connecting with people may not help to bring all patients out of depression
Subjective/ Objective	Subjective		Objective	Both subjective and objective signs and symptoms
Company	Being without company	Prefer to be without company		
Reasons	Lack of satisfaction with relationships	Self-determined	Loss of mobility — due to illness or disabilities, unemployment, or health issues	Stressors, life events. Loneliness can lead to depression
Emotional state or distress	Sad due to being alone	Peaceful and pleasant	Sadness, restlessness, loneliness	
Consequences	Producing feelings of bleakness or desolation	Inner peace and quietness		

of kin and non-kin relationships [14, 15]. Loneliness also differs from depression, which is understood to be a negative mood state, along with somatic symptoms.

EPIDEMIOLOGY OF LONELINESS

Many studies have evaluated the prevalence of loneliness among the elderly. A recent systematic *review and meta-analysis, which evaluated the data of* loneliness amongst the elderly residing in residential and nursing care homes concluded that there is wide variation in its prevalence across different studies. The prevalence of moderate loneliness ranged from 31 to 100% with a mean of 61%, and that of severe loneliness ranged from 9 to 81%, with a mean prevalence of 35% among the elderly residing in residential and nursing care homes [16]. The review also suggested a lack of any significant difference in the prevalence of loneliness between males and females, although there is some data to suggest that females are more likely to admit to being lonely than males [16]. Another systematic review and metanalysis, which included data from 39 studies from high-income countries involving 1,20,000 older adults from 29 countries, reported a pooled prevalence of 28.5% (95%CI: 23.9%–33.2%). In terms of severity of loneliness, the pooled prevalence for moderate loneliness was 25.9% (95%CI: 21.6%–30.3%), and that for severe loneliness was 7.9% (95%CI: 4.8%–11.6%). The authors did not find any increase in the prevalence of loneliness with increasing age [17]; other data, however, suggest that there is such an increase [18, 19]. Recent evidence also suggests that there has been an increase in prevalence of loneliness during the ongoing COVID-19 pandemic [20].

FACTORS ASSOCIATED WITH LONELINESS AMONG THE ELDERLY

The perception that other people have rejected them and having disappointing relationships have been reported to be associated with the development of loneliness. Different systematic reviews suggest the association of loneliness with age (U-shape relationship), the female sex, poor quality of social contacts, low competence, socio-economic status, and chronic medical illnesses [21]. In terms of risk factors, some authors fail to distinguish the factors associated with loneliness and social isolation and have associated these with the death of a spouse, significant others, or friend. Other factors that have been linked to the development of loneliness and social isolation include loss of family involvement, loss of neighborhood network due to various reasons, retirement, loss of ability to drive due to physical or cognitive changes, extreme weather situations reducing mobility, sensory deprivation, and increased frailty [15]. Available data also suggest a higher prevalence of loneliness among the elderly experiencing ‘empty nest’ syndrome [22].

The authors of a study that evaluated the influence of environmental resources, health, and psychological factors on loneliness and depression concluded that psychosocial factors/barriers have the maximum impact on the etiology of loneliness [23].

CONSEQUENCES OF LONELINESS

Loneliness can lead to significant detrimental mental and physical health conditions and health outcomes. Loneliness is associated with a higher risk of cardiovascular diseases, stroke, diabetes mellitus, arthritis, depression, anxiety, and dementia. It has also been linked to increased cholesterol levels, platelet aggregation, poor immunological functioning, autonomic instability, low physical activity, malnutrition, insomnia, increased smoking, and alcohol use. It has also been linked to increased suicide rates, higher risk of mortality, health care costs, poor quality of life, and elder abuse [15, 24–26]. One study equated the adverse impact of loneliness to being the equivalent of smoking 15 cigarettes a day [15]. Emerging data also shows an association between loneliness with regular internet use and problematic internet use [27, 28].

ASSESSMENT OF LONELINESS

Different instruments have been designed to assess loneliness (Table 2) [15]. The available questionnaires vary from a single-item questionnaire to a 20-item questionnaire. These scales also differ in terms of being unidimensional or two-dimensional, with the De Jong Gierveld Loneliness Scale assessing both social and emotional loneliness. Clinicians choose the scale according to the feasibility of administering these scales to the elderly in their working conditions [15].

MANAGEMENT

Many interventions (Table 3) have been evaluated to address loneliness among the elderly [15]. The suggested interventions range from one-on-one, group therapy, and community interventions [10].

Table 2. Scales for assessment of loneliness [15]

Scales	Number of items	Remarks
Campaign to End Loneliness Measurement Tool	3	• Positively worded scale • Do not use the word loneliness • Three items – I am content with my friendships and relationships – I have enough people I feel comfortable asking for help at any time – My relationships are as satisfying as I would want them to be
De Jong Gierveld Loneliness Scale [5,29]	11	• Evaluates two types of loneliness, i.e., social (five items) and emotional (six items) loneliness • It can be used both in face-to-face interviews or as a self-administered questionnaire • It consists of positively (five items) and negatively (six items) specified items • High internal consistency — alpha coefficients ranging from 0.8 to over 0.9
De Jong Gierveld Loneliness Scale (De Jong & Tilburg, 2006) [5,29]	6	• Evaluates two types of loneliness, i.e., social (three items) and emotional (three items) loneliness
Revised University of California Los Angeles Loneliness Scale (UCLA-LS) (Russell et al., 1980, 1996) [30,31]	20	• Half of the items are positively worded and half are negatively worded • Avoids the use of the word loneliness in any of the items • High internal consistency, with an alpha coefficient of greater than 0.9
Three-item University of California Los Angeles Loneliness Scale (UCLA-LS) (Hughes et al., 2004) [32]	3	**Items** • How often do you feel that you lack companionship? • How often do you feel left out? • How often do you feel isolated from others?
Four-item University of California Los Angeles Loneliness Scale (UCLA-LS)		**Items** • How often do you feel that you are “in tune” with the people around you? • How often do you feel that no one really knows you well? • How often do you feel you can find companionship when you want it? • How often do you feel that people are around you but not with you?
Single-Item Questions (The direct measure of loneliness) (Office for National Statistics, United Kingdom) [33]	1	• How often do you feel lonely?

Table 3. Suggested interventions for loneliness

- **Improving social skills:** speaking on the phone, giving and receiving compliments, enhancing non-verbal communication skills
- **Enhancing social support:** mentoring programs, buddy-care program, conference calls
- **Increasing opportunities for social contacts:** social recreation intervention
- **Addressing maladaptive social cognition:** cognitive behavioral therapy
- **Psychological interventions:** mindfulness interventions, reminiscence therapy, laughter therapy, Tai Chi Qigong meditation
- **Animal interventions**
- **Befriending interventions**
- **Leisure/skill development intervention:** exercises, computer training, video gaming, gardening, general activities
- **Social facilitation:** videoconference program, group meetings/discussions

Different authors have categorized these interventions differently; some that are suggested to benefit persons experiencing loneliness include improving social skills, enhancing social support, increasing opportunities for social contacts, and addressing maladaptive social cognition [34]. In a systematic review of such studies, the authors reported that addressing maladaptive social cognition was the most effective intervention for loneliness [34].

Further, it is suggested that one-on-one interventions be better than group interventions [34]. A recent literature review also supports the beneficial role of psychological interventions targeting maladaptive social cognition [35]. Cognitive behavior therapy involves educating individuals to recognize their automatic negative thoughts about others and their social interactions and consider these thoughts to be possibly faulty hypotheses that require verification, rather than considering them to be facts and acting on the same. Accordingly, the maladaptive social perceptions and cognitions are challenged to reduce loneliness [34, 36].

In terms of pharmacological interventions, there are none such that have been shown to be useful. Data from animal studies suggest that antidepressants like selective serotonin reuptake inhibitors (SSRIs), neurosteroids, and oxytocin may help to reduce loneliness to some extent [10].

CONCLUSION

Loneliness is highly prevalent among the elderly in today's world. It is suggested that the prevalence of loneliness has been increasing over the years. It is also recognized that loneliness is associated with significant adverse mental and physical health outcomes. Hence, there is an urgent need to increase awareness about the psychological construct of loneliness and carry out interventions to reduce its adverse health outcomes. Many assessment instruments are available to assess loneliness among the elderly. Although many interventions have been evaluated in terms of their ability to mitigate loneliness, addressing maladaptive social cognition appears to be an essential strategy to manage it.

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Technology-based Neurocognitive Assessment of the Elderly: a Mini Review

Оценка нейрокогнитивных функций на основе компьютерных технологий у пожилых людей: краткий обзор

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Review

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ABSTRACT

Neurocognitive disorders in the elderly are on the rise all over the world. Neuropsychological assessment is vital to monitoring the progress of cognitive deficits. Over the years, there has been significant development in neuropsychological assessment to predict the development and progression of MCI and dementia. One such area of recent advancement in the field of neuropsychology is technology-based assessment. There are several types of technology-based assessments available based on the type of usage, site of the assessment, type of administration, type of device used for assessment, etc. Virtual reality-based assessments and digital assessments of neurocognitions for early identification of subtle cognitive deficits in patients with mild cognitive impairment (MCI) and major neurocognitive disorders (MND) represent two newly developed technologies. A few studies have demonstrated their efficacy; however, there remain several limitations and drawbacks to their usage within the elderly population. In this review, we have briefly discussed technology-based neuropsychological assessment, along with their usage and limitations.

АННОТАЦИЯ

Распространенность нейрокогнитивных расстройств у пожилых людей растет во всем мире. Для мониторинга прогрессирования когнитивного дефицита решающее значение имеет нейропсихологическое тестирование. В течение последних лет наблюдается значительное усовершенствование системы нейропсихологической оценки, на основании которой возможно прогнозировать развитие и прогрессирование легкого когнитивного расстройства и деменции. Одним из важных достижений в области нейропсихологии является оценка на основе компьютерных технологий. Существует несколько видов тестирования на основе компьютерных технологий, которые различаются по месту и способу проведения оценки, по типу применения, виду используемого оборудования и т.д. Недавно были разработаны методы оценки нейрокогнитивных функций, основанные на виртуальной реальности и электронных шкалах: они предназначены для раннего выявления легкого когнитивного расстройства (mild cognitive impairment, MCI) и грубых нарушений когнитивных функций, соответствующих деменции. Результаты нескольких исследований продемонстрировали их эффективность, однако по-прежнему существует ряд ограничений и недостатков, связанных с их использованием у пожилых людей. В этом обзоре приводится краткое обсуждение нейропсихологического тестирования на основе компьютерных технологий, особенностей их использования и существующих ограничений.

Keywords: *neurocognitions; technology; dementia; digital; assessment*
Ключевые слова: *нейрокогнитивные функции; компьютерные технологии; деменция; цифровые методы; оценка*

INTRODUCTION

Aging is an inherent process that accompanies changes in the cognitive competencies and functionality of an individual. It is also now a well-known fact that, worldwide, the pace of population aging is much faster than in the past, and neuropsychiatric conditions have become a leading contributor of disability in the ageing population [1]. Neurocognitive disorders form the bulk of the neuropsychiatric conditions affecting the elderly, of which Alzheimer's dementia is the most common.

Dementia is an umbrella term used to describe the various symptoms associated with cognitive impairment. There is a gradual progression of neurocognitive impairment in the elderly, starting from the preclinical stage to mild cognitive impairment (MCIs) and, finally, major neurocognitive disorders (MND). Therefore, it is necessary that there should be appropriate assessment of cognitive functions for early identification of neurocognitive disorders in the elderly to develop strategies to slow down the progression of cognitive impairment and develop proper management strategies for early intervention [2]. The diagnosis of MCI and MND largely depends on clinical and neuropsychological assessment. Neuropsychological assessment is also vital to monitoring the progress of cognitive deficits. Over the years, there has been significant development in neuropsychological assessment to predict the development and progression of MCI and dementia. One such area of recent advancement in the field of neuropsychology is technology-based assessment. This review focuses on the technology-based neuropsychological assessment methods used for the elderly.

Methodology: A comprehensive literature search was conducted on digital technology neurocognitive assessment in the elderly using various search engines (PubMed, Scopus, PsyInfo, and Google Scholar) and through the cross-references included in relevant articles up to January 2021. Keywords included "technology", "digital", "neurocognition", "assessment", "elderly", "dementia", and "mild cognitive impairment" in various combinations. Only original articles (abstract and full text) and review articles published in English prior to January 2021 were reviewed and checked thoroughly. More than 300 articles related to the topic were found, out of which those relevant to technology-based neurocognitive assessment methods for the elderly have been included. Commentaries, viewpoints, and letters to editors related to the topic were excluded.

PROBLEMS WITH TRADITIONAL NEUROPSYCHOLOGICAL TESTING METHODS

There are several significant limitations to traditional neuropsychological tests and testing methods [3]. Some of these include: (1) findings cannot be correlated with real-time brain functioning in functional imaging studies; (2) traditional tests require the patient to travel to the hospital; (3) the scoring process can be complex; (4) many times, it depends on the administrator to decide alternative forms to avoid practice effect; (5) there can be an impact due to the 'white coat effect' while testing; and (6) there is occasionally a need to perform multiple tests in longitudinal studies, which can be quite cumbersome for the patient.

Another issue with the traditional neuropsychological tests is that they usually compare the findings of cognitively challenged individuals with normative data, i.e., those who are cognitively normal in the same age group, who themselves may not actually be entirely free of the markers of dementia. Therefore, there is a need to validate such tests with the biomarkers of dementia. There is also a need to explore the correlation of cognitive functioning with amyloid plaques over time [4]. For this, we need to have sensitive tests to pick up early cognitive changes associated with biomarker evidence of preclinical Alzheimer's dementia. To overcome these issues and for better assessment, technology-based assessments have come to the fore in recent times.

TECHNOLOGY-BASED ASSESSMENTS

Any instrument or method that utilizes a computer/ digital tablet/ handheld device, or other digital interface instead of a human examiner to administer, score, or interpret tests of brain function and related factors relevant to neurologic health and illness questions is understood to represent a form of technology-based assessment [5]. For neuropsychological assessment purposes, these can be broadly categorized as computer-based, tablet-based (mostly touchscreen devices), and mobile/smart phone-based assessments, and wearable devices. The number of tests based on digital cognitive assessments had increased exponentially in last few years.

Types of technology-based assessment

1. ***Based on type of usage, digital assessments can be of two types.***
    - Stand-alone apps and programs are digitized versions of traditional paper and pencil neuropsychological tests.

- Web-based apps that can be either completed on personal computers or on tablets are designed to be completed without active participation or the presence of an examiner [6].

2. ***Based on the site of assessment,*** technology-based assessments can be divided into office-based assessment and remote location assessment. However, there are certain problems with remote location assessments such as difficulty in maintaining participant engagement, issues related to data privacy, digital unsupervised evaluations, and frequent changes in the versions/updates to web-based apps, which often pose challenges to the administrator as well as the participant, etc. [6].
3. ***Based on type of administration,*** technology-based assessments can be categorized as either self-administered or clinically administered assessments
    - While self-administered tests have the advantage of being less time-consuming and less costly, there are also several disadvantages, such as difficulty in controlling environmental factors and distractions, problems with evaluating feigned performance, and problems with ensuring whether the examinee understands the task instructions perfectly or otherwise [5].
    - Clinician-administered assessments overcome the limitations of self-administered assessments, although they are more time-consuming and the patient needs to visit in person the clinician or needs to be actively engaged through video conferencing with the patient.
4. ***Based on the type of device***, the assessments can be categorized as Managed devices and Bring your own device (BYOD).
    - Managed devices — These are dedicated devices for cognitive assessment rather than the examinee's own device. They have the advantage of reducing the error variance associated with different hardware and software. However, high cost, reduced flexibility, and low familiarity with the device amongst the elderly are just some of the associated limitations.
    - BYOD-based cognitive assessment — These are primarily smartphone- and browser-based tests. These have the added an advantage of having a wider audience without the added expense of a managed device, and smartphones offer novel data collection methods too. However, there can be issues related to device size/type, touchscreen responsiveness, software-related problems (iOS or Android, updates, etc.), and unstable internet connectivity might also affect browser-based tests [5]. Therefore, when choosing a BYOD approach, it is essential to ensure or check the compatibility of the device's software and hardware with the minimum requirements as specified in the software manual.

Virtual reality-based assessments

Another development in the area of technology-based assessments is virtual reality (VR)-based assessments. VR-based assessments include variety of technologies and devices to assess the manipulation of objects in virtual space and time. They have virtual environments that can act as basic rooms for navigation tasks or bigger spaces like office room/classrooms. Initially, VR-based cognitive assessment was developed to integrate computerized versions of traditional paper and pencil-based tests into virtual environments [7]. This has the advantage of being able to assess multitasking in a simulated virtual environment (like running errands and completing kitchen tasks, etc.). Task completion in a simulated environment has the advantage of better representing everyday life as there will be distractions that represent real-world interruptions. In other words, these improve the ecological validity of the tasks. When compared to the manual administration of the Wisconsin Card Sorting Test, participants appeared to do more poorly on the VR-based version but reported enjoying the VR test far more than the manual one [7].

Different types of immersions have been used in VR-based assessments. These are non-immersive three-dimensional computer screens with mouse/joystick or sensor-based gloves, or semi-immersive large screen displays using shutter glasses or full immersive environments with a "green screen" and head-mounted display [7].

There can be two types of exploration within VR environments: active exploration, or passive exploration. In active exploration, participants are immersed within and navigate a virtual environment guided by a research assistant, or otherwise navigate and move around by themselves using a joystick. There is 360-degree 'first person view' of the environment in active exploration. In passive exploration, participants immersed in the virtual world do not move around or explore it. They stay in a fixed location and are exposed to stimuli but can look around and can have a 360-degree 'first person' view of the environment [8].

Cognitive assessment via wearable devices

In recent years, mobile and wearable technologies (such as smartphones, tablets, smartwatches and rings, smart suits) present a unique opportunity to massively detect neurodegenerative diseases in a timely and economical fashion. The onboard sensors at the hearts of these systems are able to provide metrics by means of active (prompted) or passive (unnoticed) measurements, with a considerably flexible approach [9]. There are several advantages to wearable devices. These are: (1) widespread usage of these newer technologies, (2) immediate access of information due to the internet connectivity, (3) increasing sensitivity and plurality of onboard sensors, (4) near accurate monitoring of physical and cognitive symptoms/abilities, and (5) extremely low burden on the healthcare system, as large segments of the population are increasingly using these devices [9]. There are also two types of data collection by the wearable devices, i.e., either active data collection (for example, prompted voice test by the device to note tremors in the vocal cords suggesting the possibility of Parkinson's disease) or passive data collection (for example — smartwatch-based step counter). Table 1 depicts some of the common sensors used in wearable devices and their respective domains they measure/interpret.

Table 1. Commonly used sensors and the respective domains they interpret [9]

Sensor	Metrics and sense domain measured
Microphone	• Voice power spectrum and tremor — voice features of speech and language • Vocabulary, pauses — cognition • Ambient noise level — environment
Touchscreen	• Swipe pattern efficiency — fine motor movement • Keyboard typing/Tapping speed — fine motor • Vocabulary — written text
Geoposition	• Location patterns — behavior and movement — mobility • Driving patterns and navigational efficiency — executive function and spatial memory
Device usage	• Reminder use, PIN and password attempts — memory • Number of apps used — executive function • Behavior disruptions, frequency of interactions — social interactions

Digital assessments

Some of the instruments developed for digital applications and that have also been validated [6] include (1) Cogstate Brief Battery, (2) the Computerized National Institutes of Health Toolbox Cognition Battery (NIH-TB), and (3) the Cambridge Neuropsychological Test Automated Battery (CANTAB).

- **Cogstate Bried Battery (CBB):** This was developed to mitigate the effects of language and culture on cognitive assessment. This test battery was initially developed in the early 2000s for PCs (where participants could respond via keystrokes) but is now available for tablets too. It measures response time, working memory, and continuous visual memory using the universal stimulus set of common playing cards. However, there are a few additional non–card-playing tasks (e.g., a paired associative learning task and a maze learning task). The Cogstate system was designed to be administered by an examiner, but there have been recent efforts to effect remote administration; additionally, once logged into the platform, the tasks are easy to progress through independently. More recently, the CBB has been made available for unsupervised testing using a web browser.

  It is being used in the Healthy Brain Project in Australia with a high acceptability and usability and low rates of missing data. The psychometric characteristics of the CBB were similar to those collected from supervised testing [6].

  A recent iteration of the Cogstate tasks is the C3 (Computerized Cognitive Composite) which includes the CBB in addition to two measures that are potentially sensitive to changes in early Alzheimer's, i.e., the Behavioral Pattern Separation–Object Version (BPS-O) and the Face-Name Associative Memory Test (FNAME). Behavioral versions of the FNAME and a modified version of the BPS-O were selected as they have been shown to be sensitive to activity in the medial temporal lobes in individuals at risk of AD based on biomarkers [6]. Additionally, Cogstate C3 battery's memory tasks were found to be best at identifying individuals' subtle cognitive impairments, as defined by paper and pencil measures (PACC) performance. It has been found to correlate well with paper and pencil measures of performance.
- **Computerized National Institutes of Health Toolbox Cognition Battery (NIH-TB):** This was designed as an easily accessible and low-cost

means to provide researchers with standard and brief cognitive measures for various settings. It was released in 2012 for PC, and a tablet version is also now available. Some tests have recently been implemented for remote administration via screen sharing in a web browser. It has been validated against standard neuropsychological measures, as well as against established cognitive composites for use in preclinical Alzheimer's dementia [6].
It consists of seven established neuropsychological tests, selected and adapted to a digital platform by an expert panel. The cognitive domains covered include attention and executive functions, language, processing speed, working memory, and episodic memory.

- **The Cambridge Neuropsychological Test Automated Battery (CANTAB) [10]:** This was intended as a language-independent and culturally neutral cognitive assessment tool initially developed by the University of Cambridge in the 1980s. It mostly uses non-verbal stimuli, and includes measures of working memory, planning, attention, and visual episodic memory. Administration of CANTAB was initially on PC but is now available through CANTAB mobile (tablet-based). It offers an online platform for recruitment by pre-screening patients using their cognitive assessment instruments.
- **Mobile/Tablet Versions of existing tests: These are some of the mobile/tablet versions of the commonly used tests.**
  - ◊ eSAGE — paper-based Self-Administered Gerocognitive Examination (SAGE) [11]
  - ◊ e-CT — K-T paper-based cancellation test, consisting of two blocks of stimuli composed of 30 symbols displayed on a tablet touch screen
  - ◊ Cambridge University Pen to Digital Equivalence assessment (CUPDE) — Saint Louis University Mental State Examination (SLUMS) CogState PC
  - ◊ eMOCA — standard paper-based Montreal Cognitive Assessment
  - ◊ Digital version of the Trail Making Test (dTMT)
- **Mobile/Tablet Versions of new tests:**
  - ◊ **Cognitive assessment for dementia, iPad version (CADi):** This is being used for mass screening for dementia. It has ten items including immediate recognition, semantic memory, categorization, subtraction, repeating backwards, cube rotation, pyramid rotation, trail making A and B, and delayed recognition tests [12].
  - ◊ **Smartphone-Based Color-Shape Test (CST):** This measures cognitive processing speed and attention. Participants match color and shape according to a legend showing paired colors and shapes at the top of screen by touching the color pad at the bottom of the screen. It records the number of attempts and the number of correct answers. CST scores correlate with scores on the MMSE and other speed and attention tests, showing the possibility of using smartphones for cognitive assessment in older adults [12].
  - ◊ **Computerized cognitive screening (CCS):** This consists of a symbol-matching task, a memory task, and an object matching task used to assess concentration, memory, and visuospatial functioning. A few studies have found a significant correlation between CCS scores and Montreal Cognitive Assessment (MoCA) scores [13, 14].
  - ◊ **Mobile Cognitive Screening (MCS):** This is a mobile-based neuropsychological test. It consists of 33 questions from 14 types of test that assess eight cognitive domains including arithmetic, orientation, abstraction, attention, memory, language, visual, and executive function. All test questions have been modified for a mobile platform [15].
  - ◊ **Brain Health Assessment (BHA):** This is a 10-minute tablet-based cognitive assessment to detect MCI and dementia. When compared with the MoCA, BHA demonstrated higher accuracy in detecting mild cognitive decline and similar accuracy in detecting dementia [15].
  - ◊ **Computerized Cognitive Composite for Preclinical Alzheimer's Disease (C3-PAD)**: This assesses episodic memory and working memory. It has demonstrated significant association between the in-clinic tests and the at-home tests, suggesting home-based cognitive assessment with mobile devices is feasible if sufficient training is provided [12].
  - ◊ **National Center for Geriatrics and Gerontology function assessment tool (NCGG-FAT):** This includes eight tasks used to assess memory, attention, processing speed, visuospatial, and executive function. It has high test–retest reliability and high validity in comparison with conventional neurocognitive tests, suggesting that the NCGG-FACT may be useful in assessing cognition in population-based samples [16].

- ◊ **Toronto Cognitive Assessment (TorCA) [17]:** This is a more comprehensive test than screening tests but shorter than a neuropsychological battery. It has 27 subtests to evaluate multiple cognitive domains. It can be administered on paper or on an iPad, with each mode using the same questions. TorCA demonstrated statistically significant ability to differentiate between MCI and normal cognition.
- ◊ **Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (CANS-MCI) [18]:** This is a 30-minute eight-task battery that can be self-administered. It measures episodic memory, executive functions, and language with good test-retest reliability and moderate correlations with standard neuropsychologic measures. It has the advantages of automated scoring, result interpretation, and provides care recommendations.

STRENGTHS OF DIGITAL ASSESSMENTS

Digital assessments are more accessible and cost-effective due to self-administration. These tests automatically generate alternative forms which may help minimize practice and version effects. They have automatic scoring recording and give immediate access to results. These tests utilize artificial intelligence (AI) methods and hence are faster, novel, and provide more sensitive cognitive data analysis [7]. These tests are highly scalable, and therefore can be used for remote assessment in a much larger population. These can be used for more frequent assessment with potentially more sensitive cognitive paradigms. Moreover, as these are performed in a familiar environment, they may accordingly increase the ecological validity. Another major advantage of digital assessments is that they provide cognitive assessment outside clinics with rapid data transfer to healthcare providers. Certain time-sensitive parameters, such as reaction time or inspection time, can be measured more accurately with digital tests [19].

In some tests, there are algorithmically defined approaches to a particular test (e.g., organization, planning), evaluation of pauses, perseverations, domain-specific errors, and/or response times in very specific measurements that add value to neuropsychological assessment data [7, 20].

Added advantages of smartphone-based assessments include reduced risk of the “**white-coat effect**”. They provide additional opportunities for an individual to track their own cognitive health over time, potentially leading to increased commitment to their well-being. They further reduce the need for in-clinic visits among participants of various trials and encourage those in more remote areas to participate. They also help with short- or long-term monitoring through repeated assessment outside the clinic to detect early, subtle signs of cognitive decline.

Collating these new data streams results in a composite description of a person’s behavior which is known as the **“Digital phenotype”**, i.e., alternative measurement of health-related behaviors. Digital phenotyping incorporates data from mobile sensors, keyboard interactions, voice, speech, and other streams obtained during everyday use of social media, wearable technologies, and mobile devices [7]. GPS technology in these devices can record daily movement data that can aid in the recognition of behavioral symptoms of incipient dementia.

LIMITATIONS OF DIGITAL ASSESSMENTS

Several variables can influence the outcome of a technology-based cognitive assessment, including test characteristics, test duration, test frequency, and training and prior technology experience of the person being assessed. Privacy issues are paramount when obtaining health data from any internet-connected device, especially someone’s personal device. Some of the authors caution against using these technologies as a sole means of diagnosis, but advocate their use in conjunction with comprehensive evaluations by trained clinicians [7].

Little attention has been paid to person-centered care and person-centered assessment concepts. Modern neuropsychological tests might only be available in some of the world’s regions. In many countries, there are large proportions of the population with little education, and for whom these modern neuropsychological tests might not be appropriate. Tests developed with culturally specific stimuli will not be applicable in some cultures [21].

Moreover, there can be technological issues, such as variations in computer hardware. Currently, only limited information on psychometric and normative properties for different clinical population is available for digital tests. These tests can be influenced by knowledge of computers or other technology. Limitations unique to virtual reality are dominated by physiological concerns (e.g., motion sickness) [7].

CRITIQUE OF TECHNOLOGY-BASED ASSESSMENTS

There is lack of consistent, consensual definitions of key neuropsychological concepts, which poses an ongoing challenge to the profession and researchers, resulting in problems in communication within and outside the field. Neuropsychologists tend to be molecular in their approach, dividing behaviors into abilities such as language, memory, and the like. In fact, behavior in the environment rarely involves using these abilities in isolation [22].

There is also a lack of consensus as to what constitutes a neuropsychological domain. For example, to assess executive functioning, there is no consensus about what constitutes this domain, and some theorists have even questioned its validity. Working memory is typically considered a part of executive functioning. When one is assessing working memory, whether one is actually setting attention, working memory, executive functioning, or a combination of these, is still not clear. Only a few studies have addressed the long-term reliability of neuropsychological assessments in stable patients. Moreover, the reliability of memory tests is consistently lower.

In addition to the above-mentioned, there are also issues related to patients' preferences and it is frequently seen that patients use devices less often due to cumbersome procedures related to wearing them or difficulty in logging in and out from their systems. Additionally, many of the elderly do not want to be dependent on caregivers or assessors to help them to use these devices daily.

Among all such devices, cognitive tests based on tablets are most acceptable. Studies have suggested that adults of more than 55 years of age have a greater preference for the use of touchscreen devices, as these devices have more direct and intuitive interaction, lower motor demands, and are relatively easy to use. Moreover, tablets offer greater mobility than personal computers and are more user-friendly than smartphones for older adults owing to the larger screen sizes and better response field views. In recent years, there had been a growing interest in developing and validating tablet-based cognitive assessment tools. Many neuro-cognitive tests have been validated for use with tablets [5].

Further, there are emerging legal and ethical issues related to technology-based monitoring. Some authors have raised privacy concerns with trackable wearable devices and the feeling of constantly being monitored during every activity. As wearable devices can also collect user data regardless of time and place, uploading data to the cloud can easily make the wearable device's system vulnerable to attack and data leakage. Defects in technology can sometimes cause problems such as lack of control over data flow links in wearable devices, and data and privacy leaks are more likely to occur. All these issues have raised serious privacy concerns and the elderly, being a vulnerable population, could be extremely vulnerable to attack by cybercriminals. Hence, proper data security should be taken care of by the wearable device manufacturers or technology software developers to tackle these emerging concerns [23].

Further, a vast majority of the aging population reside in low- and middle-income countries (LMICs), where these technology-based assessments and subsequent interventions are in a nascent stage. These technology-based devices are expensive and the patient population in LMICs is less educated as to their usage. More awareness and education programs are needed to propagate the message to the lay public regarding early identification of cognitive decline in the elderly and the subsequent need for monitoring and assessment.

CONCLUSIONS AND THE WAY FORWARD

It is essential to establish a neuropsychology data archive as an Open-Access Global Resource and develop a global collaborative network. It is also necessary to specify the latent traits assessed by each test and identify each trait's most efficient measurement models [24]. There should be constant efforts to improve the reliability and validity of mobile assessments and attempts to incorporate person-centered assessment and digital phenotyping in conjunction with mobile technologies. Patterns of mobile phone data can be used to identify changes in cognitive function, sleep patterns, mood, mobility, exploration of novel environments, social engagement, and other features that may provide critical indications of clinically meaningful change.

There is need for further validation when existing normed tests are translated to mobile platforms because the change in the delivery method may bias the test results, especially for self-administration. Future usability studies must include older adults with cognitive impairment to implement monitoring technologies to identify trends and acute changes outside the clinic in people with cognitive impairment.

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Symptomatic Profile of Cariprazine in the Context of ICD-11 Domains for Schizophrenia: Review of Clinically Oriented Studies

Симптоматический профиль карипразина в контексте доменов шизофрении в МКБ-11: обзор клинически ориентированных исследований

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Review

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ABSTRACT

INTRODUCTION: One of the innovations in the ICD-11grouping "Schizophrenia and Other Primary Psychotic Disorders" is the implementation of six symptom domains intended to improve diagnostics and treatment of these mental conditions in clinical practice. In this respect, evaluation of the effects of various psychotropic drugs, primarily antipsychotic agents, on the specified psychotic symptom domains is a critical task. The antipsychotic agent cariprazine, registered in many countries worldwide (including Russia) for schizophrenia treatment, was selected as the psychotropic drug model for the purposes of the present review.

METHODS: For the purposes of this review the MEDLINE, Cochrane Central Register of Controlled Trials, and PubMed databases were searched for randomized controlled trials comparing cariprazine with a placebo, or a placebo and one or several antipsychotic agents, and that was performed within the period from January 2014 to March 2021.

RESULTS: Cariprazine has proved its efficiency in relation to all symptom groups of the ICD-11 domain "Positive Symptoms'', and may be considered a front-line therapy for treatment of the first and multiple episodes of schizophrenia, disorganized thinking, and behavioral disorders in the form of aggressiveness and hostility. Cariprazine has the best evidential base for treatment of various symptoms within the ICD-11 domain "Negative Symptoms'' among all antipsychotic agents. The data with regard to the effects of cariprazine on the domain "Depressive Mood Symptoms'' are controversial. No data concerning the effects of cariprazine on the domain "Manic Mood Symptoms'' are available, but the effectiveness of cariprazine monotherapy for manic episodes without any psychomotor agitation signs in the instance of bipolar disorder has been demonstrated. The effectiveness of cariprazine therapy for the ICD-11 domain "Psychomotor Symptoms" has not been investigated, either within the framework of monotherapy or in the course of adjuvant therapy. The effectiveness of cariprazine has been demonstrated in treatment of the domain "Cognitive Symptoms", and the pro-cognitive effect of the drug has developed regardless of its impact on any other schizophrenia symptoms. The drug's capability to improve the functioning of patients with schizophrenia was demonstrated regardless of the impact on psychotic symptoms.

CONCLUSION: Cariprazine is the first-line drug for treatment of the domain "Negative Symptoms" as well as representing front-line therapy for the treatment of ICD-11 domains "Positive Symptoms" and "Cognitive Symptoms". Additional studies will be required in order to evaluate the effects of cariprazine on the ICD-11 domains "Manic Mood Symptoms" and "Depressive Mood Symptoms".

АННОТАЦИЯ

ВВЕДЕНИЕ: Одним из нововведений раздела МКБ-11 «шизофрения и другие первичные психотические расстройства» является имплементация 6 дополнительных доменов, которые должны улучшить диагностику и лечение данных состояний в клинической практике. В связи с этим, актуальной задачей является оценка влияния различных психотропных средств, в первую очередь, антипсихотиков, на выделенные домены психотических расстройств. В данном обзоре в качестве психотропного средства был выбран антипсихотик карипразин, который зарегистрирован во многих странах мира, включая Россию, для лечения шизофрении, который зарегистрирован для лечения шизофрении во многих странах мира, включая Россию.

МЕТОДЫ: Для данного обзора был осуществлен поиск рандомизированных контролируемых исследований, сравнивающих карипразин с плацебо, с одним или несколькими антипсихотиками. Поиск произведен по базам данных MEDLINE, Cochrane Central Register of Controlled Trials и PubMed. Глубина поиска с января 2014 по март 2021 года.

РЕЗУЛЬТАТЫ: Результаты свидетельствуют о том, что карипразин эффективен в отношении всех групп симптомов домена МКБ-11 «позитивные симптомы» и может рассматриваться как препарат выбора при лечении первых и множественных эпизодов болезни, дезорганизации мышления и нарушенного поведения в виде агрессии и враждебности. Карипразин имеет наилучшую среди всех антипсихотиков доказательную базу для лечения разных симптомов домена МКБ-11 «негативные симптомы». Данные о влиянии карипразина на домен «депрессивные симптомы» являются противоречивыми. Отсутствуют данные о влиянии карипразина на домен «маниакальные симптомы», но доказана эффективность монотерапии карипразином маниакальных эпизодов без признаков психомоторного возбуждения при биполярном расстройстве. Исследования эффективности терапии карипразином домена МКБ-11 «психомоторные симптомы» не проводилось ни в рамках монотерапии, ни в рамках адьювантной терапии. Карипразин доказал эффективность в лечении домена «когнитивные симптомы» и прокогнитивный эффект препарата развивался независимо от его влияния на другие симптомы шизофрении. Была показана возможность препарата улучшать функционирования больных шизофренией, независимо от влияния на симптомы заболевания.

ВЫВОДЫ: Карипразин является препаратом первого выбора при лечении домена «негативные симптомы», а также препаратом выбора при лечении доменов МКБ-11 «позитивные симптомы» и «когнитивные симптомы». Необходимы дополнительные исследования для оценки влияния карипразина на домены МКБ-11 «маниакальные симптомы» и «депрессивные симптомы».

Keywords: *cariprazine; schizophrenia; ICD-11; symptom domains; PANSS*
Ключевые слова: *карипразин; шизофрения; МКБ-11; домены первичных психотических расстройств; PANSS*

INTRODUCTION

The main reason for the introduction of statistically identifiable psychopathological symptom groups or domains into clinical practice was the desire to reduce the clinical heterogeneity of schizophrenia, to describe the clinical pattern of the disease more comprehensively, and to identify homogeneous groups of patients for neurobiological research [1]. The following five dimensions are usually specified in studies of the dimensional structure of mental diseases: “positive symptoms”, “negative symptoms”, “cognition”, “disorganization”, and “affective symptoms” [2]. Drug abuse, early manifestation of the disease, absence of insight, cognitive functioning, hostility, behavioral disorders, and “motor symptoms” are considered to represent additional domain [2].

Dimensional models based on the Positive and Negative Symptom Scale (PANSS) have become widespread in psychiatry [3]. Although only three PANSS domains were initially identified by the authors (the sub-scales of positive and negative syndromes and general psychopathology) [3], other PANSS models were proposed in subsequent studies. In particular, these are the pyramidal model with the specification of negative, positive, and depressive symptoms [4], the five-factor Marder model (positive symptoms, negative symptoms, disorganization of thinking, hostility/agitation, and anxiety/depression) [5] and others, yet none of these are fully satisfactory [6]. This is apparently related to the fact that many variables (age, duration and phase of the disease, drug administration, etc.) can affect the symptoms of schizophrenia, and the same patients may fall into different groups in different models.

In ICD-11, dimensional evaluation is possible for disorders within the grouping “Schizophrenia and Other Primary Psychotic Disorders” (schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, any other primary psychotic disorders) as supplementary or additional according to the classification “for a better understanding of the condition and treatment selection” [7]. It is important to note that although the term “dimensional evaluation” is present in ICD-11, the term “dimension” itself is not used therein, and the terms “domain”, “symptomatic manifestations”, and “symptom qualifiers” can be found in a similar context. Six groups of symptomatic manifestations (domains) are proposed in ICD-11 for primary psychotic disorders: psychotic, negative, depressive mood, manic mood, psychomotor, and cognitive symptoms [7]. Only negative, depressive mood, manic mood, and psychomotor symptoms fully coincide in ICD-11 and DSM-5 [8, 9]. Two dimensions correspond to the ICD-11 domain “Psychotic Symptoms” in DSM-5: “hallucinations” and “delusional ideas”, and the dimension “cognition reduction” corresponds to the domain “Cognitive Symptoms”. The dimension “speech disorganization” is also absent in ICD-11. Each ICD-11 domain may be evaluated according to the following scale: 0 — no symptoms; 1 — symptoms are present, but only in mild form; 2 — symptoms are present in moderate form; 3 — symptoms are present in severe form; 9 — evaluation is impossible on the basis of the available data [7]. As in DSM-5, examples of the evaluation of the severity of the symptoms are given in ICD-11: for example, a severe degree of psychotic symptom manifestation assumes that delusional ideas determine the patient’s behavior and disturb his/her functioning considerably. The dimensional approach implemented in the revisions of the two main international classifications in many ways represent the scientific paradigm shift with regard to conceptualization of psychotic disorders. This transition should be gradual, and requires a clear understanding of its basic principles by specialists [9]. The online survey of the Russian psychiatrists’ attitudes in relation to ICD-11 showed their interest in ICD-11, especially among young colleagues [10].

Cariprazine is a partial D2/D3 receptor agonist with primary affinity to the D3 receptor, and produces a multi- functional effect on various types of 5-HT receptor [11]. Partial agonism in relation to D2 receptors is associated with treatment of positive and maniacal symptoms and a low frequency of “dopamine” side effects, such as extrapyramidal syndrome and hyperprolactinemia [11–13]. Blockade of D3 receptors is associated with the pro-cognitive, anti negative and antidepressive properties of the drug [14]. Further, a hypothesis was suggested that a high affinity of the drug to D2 and D3 receptors might enhance its antipsychotic activity and improve the treatment of negative and cognitive symptoms [15]. It was demonstrated with the use of animal models that partial agonism in relation to D3 receptors had a positive effect on cognitive deficiency and anhedonia [16]. Cariprazine also acts as a partial 5-HT1A receptor agonist and as a 5-HT2B, 5-HT2C, and 5-HT7 receptor antagonist [12]. Partial agonism in relation to 5HT1A can have a positive effect on negative and affective symptoms. Antagonism in relation to 5-HT2C and 5-HT7 may be associated with pro-cognitive and antidepressive properties of cariprazine [17, 18]. The elimination half-life of cariprazine is approximately 2–4 days, and for its active metabolite (didesmethylcariprazine), this period amounts to 1–3 weeks; therefore, the drug’s concentration in the plasma continues to increase for about a week despite the drug being administered in the same dose, and complete elimination of the drug from the blood after ending its administration can take up to several weeks [12].

Inclusion of the dimensional evaluation of the primary psychotic disorders within ICD-11 will result in the need to assess the effects of various psychotropic drugs, primarily antipsychotic agents, on the specified psychotic disorder domains. The antipsychotic agent cariprazine, registered in many countries worldwide (including Russia) for schizophrenia treatment, was selected as the psychotropic drug model for the purposes of the present review. In spite of the fact that the pharmacological profile of cariprazine is associated with effects on the positive, manic, negative, cognitive, and depressive symptoms, and its influence on various schizophrenia symptoms has been demonstrated by randomized clinical trials, the drug's efficiency with regard to the identified ICD-11 domains has never previously been evaluated.

The purpose of this article is to assess the efficiency of the effects of cariprazine on the ICD-11 domains identified for schizophrenia on the basis of clinically oriented studies, primarily randomized clinical trials.

METHODS

A search of English language publications for the current review was carried out with the use of the MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed databases. The search was performed according to the following keywords: "Schizophrenia" or "Psychosis" and "Cariprazine". The following inclusion criteria were adopted: trials based on the referred sample of adults; reliable diagnostics of schizophrenia; and structured interviews and standardized criteria based on reliable assessments of the results. Firstly, the final analysis included published randomized controlled trials that compared the effects of cariprazine with a placebo, or with a placebo and other antipsychotic agents, in the course of short-term and long-term therapy of various schizophrenia symptoms performed within the period from 2014 (when the first randomized controlled trials evaluating cariprazine efficiency in schizophrenia treatment were published) to June 2021. Secondly, the data from randomized controlled trials were used for analysis by means of post-hoc evaluation; the results of meta-analyses assessing the efficiency and safety of different antipsychotic agents, particularly cariprazine, in the treatment of various schizophrenic symptoms. Thirdly, randomized controlled trials of cariprazine's efficiency in the acute treatment of mania and depression in the frame of bipolar disorder were used in the review in order to assess the drug's effects on the ICD-11 domains "Depressive Mood Symptoms" and "Manic Mood Symptoms". Descriptions of the symptom domains were taken from the English language version of Chapter 6 of the International Classification of Diseases, Rev. 11 (ICD-11).

CARIPRAZINE'S EFFECTS ON THE DOMAIN "POSITIVE SYMPTOMS"

The ICD-11 domain "Positive Symptoms of Primary Psychotic Disorders" includes not only persistent delusional ideas, hallucinations, and severe behavioral disorders, but also disorganized thinking, which is considered an individual dimension of primary psychotic disorders in DSM-5 [8].

The efficiency of cariprazine within the framework of remitative therapy for schizophrenia was demonstrated by three double-blind placebo-controlled six-week multi-center trials (Table 1).

In the first trial [19], to assess cariprazine's safety and efficiency, 732 patients were randomized into

Table 1. Short-term studies of cariprazine efficiency for remitative therapy of schizophrenia

Trial 1 (Durgam et al., 2014)		**Trial 2 (Durgam et al., 2015)**		**Trial 3 (Kane et al., 2015)**	
Multi-center randomized double blind placebo-controlled					
Duration: total 9 weeks (wash-out period — 4–7 days; therapy period — 6 weeks; observation period — 2 weeks)					
5 groups		4 groups		3 groups	
N=732	PANSS score reduction	N=617	PANSS score reduction	N=440	PANSS score reduction
Fixed:		**Fixed:**		**Fixed/variable:**	
Placebo	11.8	Placebo	14.3	Placebo	16.0
Cariprazine 1.5 mg	19.4	Cariprazine, 3 mg	20.2	Cariprazine, 3–6 mg	22.8
Cariprazine 3.0 mg	20.7	Cariprazine, 6 mg	23.0	Cariprazine, 6–9 mg	25.9
Cariprazine 4.5 mg	22.3	Aripiprazole, 10 mg	21.2		
Risperidone 4 mg	26.9				

Primary endpoint: total score as per the PANSS scale in 6 weeks.
Additional endpoints: scores as per NSA-16, CGI-I, PANSS (positive/negative symptoms), SQLS-R4, CDR/CTT scales.

placebo, cariprazine (fixed doses of 1.5, 3.0, and 4.5 mg) or risperidone (4 mg) groups. By the end of the trial, all the cariprazine and risperidone doses were found to have caused statistically significant (as compared with the placebo) reductions of the total score (-19.4, 20.7, 22.3, and 26.9, respectively) and considerable improvement according to the Clinical Global Impression Scale (p <0.05) [19].

During the second trial, the patients took either a placebo (n=153), or fixed doses of cariprazine (3 mg/day and 6 mg/day), or an active comparator, aripiprazole (10 mg/day) [20]. As in the previously mentioned trial [19], a larger dose of cariprazine can be associated with a greater reduction in the total score, as per the PANSS scale (20.2 and 23.0, respectively) as well as the scale of positive symptoms (6.8 and 7.5 points, respectively) and the PANSS scale of general psychopathology (9.6 and 11.3 points, respectively). Further, the patients taking the active substance demonstrated significant improvement with regard to reduction of negative symptoms and depressive mood in comparison with the placebo, as measured via the use of the PANSS scale of negative symptoms and The 16-item Negative Symptom Assessment (NSA-16) scale for evaluation of negative symptoms. Improvements according to the The Clinical Global Impression — Severity scale (CGI-S) were also considerably greater for both doses of cariprazine beginning from the second week of therapy [20].

Efficiency, safety, and tolerability of two cariprazine administration regimes (3–6 mg and 6–9 mg respectively) for patients showing the manifestation of schizophrenia were assessed during the third nine-week trial (Kane et al., 2015) performed within the framework of the third drug registration stage [21]. Statistically significant differences in favor of the active substance were observed by the sixth week of therapy for the PANSS scales of positive and negative symptoms (3–6 mg/day, p <0.05; 6–9 mg/day, p <0.001) and the Clinical Global Impression Scale CGI-S (3–6 mg/day, p <0.05; 6–9 mg/day, p <0.001). The statistical difference compared to the placebo according to PANSS began to be observed from the first week of therapy onward for the group taking 6–9 mg of cariprazine, and from the second week of drug administration for the group taking 3–6 mg. In accordance with the CGI-S Scale differences, as compared with the placebo, began to be observed from the first week of therapy for the patients taking 6–9 mg of cariprazine, and from the third week for 3–6 mg [21].

Post-hoc analysis of cariprazine's effects (the doses of 1.5–9 mg) on the five PANSS domains identified [5] and individual points of this scale [22] (see Table 2) were performed on the basis of these three trials including 1466 patients with schizophrenia.

By the end of the sixth week of therapy, cariprazine was clearly superior to the placebo for all five PANSS domains identified in a statistically reliable manner. Statistically significant differences between cariprazine and the placebo with regard to reduction of individual symptoms as per the PANSS scale were determined for 26 out of 30 points of this scale (that is, with the exceptions of G1, G3, G7, P5) (See Table 3). The average effect size for treatment of positive symptoms was 0.38: it was the most prominent for the dose of 4.5 mg (effect size of 0.52) and the least prominent for 1.5 mg (effect size of 0.25). Cariprazine was superior to the placebo in the treatment of the symptoms within the domain "Disorganization of Thinking'' [5] by 46.7% on average; in this instance, the effect size was the most prominent for the dose of 4.5 mg (0.6) and the least prominent for 3 mg (0.38) [22]. Taking into account the description of the domain "Positive Symptoms" in ICD-11, only points P2 (conceptual disorganization) and N5 (abstract thinking difficulties) from among the points of this domain may be classified as positive symptoms. Cariprazine was superior to the placebo in the treatment of the domain "Hostility/ Agitation'' [5] by 34.8% on average, though to a greater degree for the dose of 1.5 mg and a lesser degree for the dose of 4.5 mg. P4 (agitation) and P7 from this domain may be classified as positive symptoms according to the ICD-11 definitions. The effects of cariprazine on manifestations of aggressiveness and hostility in the instance of schizophrenia through changes in "Hostility" (Point P7) with regard to PANSS by the end of the sixth week of therapy was investigated in a separate study [23]. Statistically significant differences in comparison with the placebo were observed for the patients taking cariprazine, with an initial score of 2 or 3 for Point P7 as early as the first week and up to the end of the trial, while in case of the initial score of 4 and higher statistically significant improvement in favor of cariprazine was observed from only the third week of therapy. By the end of the sixth week of therapy, a higher initial score for Point P7 was associated with an increased reduction in hostility.

The duration of the period up to relapse development (obvious aggravation of symptoms, admission to a mental

Table 2. Changes in the effect size for domains of the PANSS scale by the end of the sixth week of therapy with different cariprazine doses

Identified domains	1,5 mg	3,0 mg	4,5 mg	6,0 mg
Positive symptoms	0,25	0,32	0,52	0,42
Negative symptoms	0,44	0,34	0,62	0,51
Disorganization of thinking	0,4	0,38	0,6	0,49
Hostility/agitation	0,39	0,33	0,31	0,36
Anxiety/depression	0,15	0,1	0,15	0,29

hospital, aggressive behavior or suicidal risks) was selected as the primary end point for the randomized double blind placebo-controlled trial of the efficiency of different cariprazine doses (3, 6, and 9 mg) for stable patients with schizophrenia which lasted up to 72 weeks, where the total score as per the PANSS scale, whilst other scales was used as additional measures [24]. In the course of the observations, recrudescence occurred twice more rarely in the cariprazine group than in the placebo group (24.8% and 47.5%, respectively, the risk ratio — 0.45). The difference between the groups became significant from the eighth week of therapy. By the end of the observation period, the total score as per PANSS, CGI-S, NSA-16, and the Personal and Social Performance (PSP) scales had deteriorated to a greater extent for the placebo group as compared with the cariprazine group. It is also important to note that within the first four weeks of therapy, relapse occurred in only 3% of the patients in the placebo group, which might imply the residual antirelapsing effect of cariprazine partially associated with its long half-life to elimination from the body; its metabolite (didesmethylcariprazine) took 8.4 days to be eliminated. Further, administration of cariprazine is associated with considerably longer persistent remission and increased probability of persistent remission exceeding six months, as compared with the placebo [25].

Table 3. Changes in the effect size for individual points of the PANSS scale by the end of the sixth week of therapy

PANSS items	Cariprazine (1,5-9,0 mg)
Positive symptoms	
P1	0,32
P3	0,2
P5	0,07
P6	0,35
N7	0,23
G9	0,32
G12	0,30
Negative symptoms	
N1	0,25
N2	0,36
N3	0,31
N4	0,37
N6	0,28
G7	0,08
G16	0,38
Disorganization of thinking	
N5	0,26
G5	0,15
G10	0,27
G11	0,36
G13	0,25
G15	0,3
P2	0,44
Hostility/agitation	
G14	0,23
P4	0,25
P7	0,28
G8	0,34
Anxiety/depression	
G2	0,18
G3	0,02
G4	0,26
G6	0,17

Studies of cariprazine in routine clinical practice within the framework of the non-blind trial for the patients with schizophrenia without any response to previous therapy demonstrated that cariprazine administration was associated with significant positive changes beginning from the second week of therapy, and lasting until the end of the trial (sixteenth week of treatment) [26]. By the end of the trial, considerable improvement was observed in 38% of the patients, minimum improvement in 35% of the patients, and no improvement in 11% of the patients. It was also shown that not only was there a considerable reduction in the negative symptoms, but also a reduction in delusions and hallucinations over the course of the trial, which was evaluated via the use of the special-purpose questionnaire, including also questions about case histories and clinical appraisal. In this case, 70% of doctors participating in the trial were satisfied with cariprazine's efficiency [26].

Comparison of cariprazine with 31 other antipsychotic agents demonstrated that the drug was superior to placebos in the treatment of positive symptoms (the standardized mean difference (SMD) was equal to 0.3; cariprazine took a medium position with regard to this parameter, having almost half the efficiency of the leading antipsychotic agents (amisulpride, risperidone, clozapine) [27]. At the same time, cariprazine is superior to many antipsychotic agents with regard to such significant side effects as weight gain, and increases in prolactin and sedation. The authors of this study believe that in spite of the difference in efficiency between antipsychotic agents with regard to reduction of positive symptoms, the focus in therapy selection should be on investigation of the side effect profile where the differences between the drugs is quite evident. Subsequent to investigation of the entire symptom range, including the doses of antipsychotic agents, transition strategies, therapy duration, the role of concomitant therapy, and tolerability, the consensus amongst experts is to recommend the use of cariprazine as the front-line therapy for the treatment of patients with schizophrenia suffering from acute psychotic states (including the first psychotic episode) with attendant agitation and insomnia (in combination with benzodiazepines), metabolic syndrome, and concurrent drug abuse [28].

The majority of experts recommend maintaining a dose of 1.5–3 mg/day to treat a first psychotic episode, while rapid increase of the dose to the maximum (6 mg/day) is possible in cases of more severe psychotic symptoms [28]. In the case of resistant schizophrenia or cariprazine monotherapy for schizophrenic patients with attendant agitation, the majority of experts recommend rapidly increasing the dose of cariprazine to 6 mg/day. For patients with concomitant metabolic syndrome, experts often recommend a dose of 3 or 4.5 mg/day [28].

CARIPRAZINE'S EFFECT ON THE DOMAIN "NEGATIVE SYMPTOMS"

The modern concept of negative disorders includes the identification of five particular symptoms (abulia, anhedonia, lack of social activity, blunted affect, alogia) associated with functional reduction [29]. In ICD-11, the domain "Negative Symptoms of Primary Psychotic Disorders" includes the above-mentioned symptoms, where it is also specified that the symptoms should not be secondary ones in relation to depression, administration of antipsychotic drugs, and positive symptoms [7]. It was demonstrated in the early studies of cariprazine use for schizophrenia treatment [19–21] and subsequent meta-analysis of these studies [30] that reduction of negative symptoms against the background of cariprazine therapy did not depend on the reduction of positive symptoms, as the difference between cariprazine and the placebo remained statistically significant (the dose of 1.5–3 mg/day, p=0.0322, 4.5–6 mg/day, p=0.038), even after adjustment for changes in positive symptoms.

Post-hoc analysis of the studies with regard to cariprazine efficiency in acute therapy of schizophrenia [19–21] showed that cariprazine was superior to the placebo at the end of the sixth week of treatment by 47.8% on average; in this case, the effect was most prominent for a dose of 4.5 mg (the effect size — 0.62) and the least prominent for a dose of 1.5 mg (the effect size — 0.44) [22]. The Factor Score for Negative Symptoms (PANSS-FSNS), also known as the Marder factor, has become increasingly used in recent years to evaluate the manifestation of negative symptoms and their changes in the course of therapy instead of the PANSS scale of negative symptoms; it includes Points N1, N2, N3, N4, N6, G7 and G16 of PANSS [5]. Direct analysis of these points during administration of different cariprazine doses (1.5–9 mg) showed the following changes in the effect size (as compared with the placebo, 0.25; 0.36; 0.31; 0.37; 0.28; 0.08; and 0.38, respectively), indicating that cariprazine administration in all doses reduced all symptoms of the Marder factor — with the exception of motor retardation — to a statistically significant extent [22]. The above-mentioned meta-analysis showed that cariprazine demonstrated higher efficiency in cases of predominant negative disorders and short case history, although the studies analyzed did not distinguish between primary and secondary negative symptoms [30].

Cariprazine (average dose of 4.5 mg) and risperidone (average dose of 4 mg) were compared in a multinational randomized controlled trial of schizophrenic patients with predominant negative symptoms [31]. The difference between groups, as measured via the use of PANSS-FSNS, was in favor of cariprazine by the end of the trial (p=0.0022, the effect size in favor of cariprazine — 0.31). Post-hoc analysis of this trial showed that administration of cariprazine in comparison with risperidone was associated with more significant improvement for such PANSS points as affect flattening (N1), emotional withdrawal (N2), passive-apathetic social withdrawal (N4), and abstract thinking difficulties (N5), but not lack of lack of spontaneity and flow of conversation (N6) or stereotyped thinking (N7). In addition, these changes were not dependent on positive, depressive symptoms or the extrapyramidal syndrome, as their changes over the course of therapy were minimal [32]. Another post-hoc analysis including placebo, cariprazine, risperidone, and aripiprazole showed that in accordance with the Marder factor (PANSS-FSNS), reduction of negative symptoms by the end of the sixth week was only statistically significant only cariprazine and risperidone, but not for aripiprazole. After adjustment for changes in the positive symptoms in order to exclude any secondary negative symptoms, only cariprazine, but not risperidone and aripiprazole, was considerably superior to the placebo [33]. The conclusion drawn on this basis was that cariprazine had a direct, specific and independent effect on negative symptoms while risperidone apparently had a predominant effect on secondary negative symptoms, reducing together with the positive symptoms [33].

The capability of cariprazine to exert an effect on negative symptoms within the framework of long-term administration of the drug was also demonstrated in two trials. In particular, according to a non-blind 48-week trial, the PANSS-FSNS parameters reduced within the first eight weeks of therapy (the least-squares mean (LSM) was 9.0 in the eighth week), and were maintained for the subsequent 40 weeks (the LSM was 11.1 in the forty-eighth week) [34]. These data were close to the results of another trial lasting for 20 weeks when the negative symptoms were reduced primarily within the first 12 weeks of treatment and then changed only slightly thereafter (the change in LSM was 11.5 by the twelfth week and 12.1 by the twentieth week) [35]. On the basis of these trials, one might conclude that cariprazine had proved its efficiency with regard to treatment of the entire range of negative symptoms, both within the framework of acute and maintenance therapy of schizophrenia, and thus represents the first-line drug for treatment of schizophrenia with predominant negative symptoms [36]. This judgment was confirmed by meta-analysis of the efficiency of antipsychotic agents for treatment of schizophrenic patients with prevailing negative symptoms; according to this analysis, only amisulpride and cariprazine were superior to the placebo with regard to the treatment of this patient group to a statistically significant extent. However, while amisulpride simultaneously caused parallel reduction of depressive symptoms, the efficiency of cariprazine did not depend on any other symptoms [37]. Cariprazine may be also used as a second antipsychotic agent in cases when monotherapy with any antipsychotic drug is not sufficiently effective to treat negative symptoms [28].

At present, cariprazine is considered the first-line drug for treatment for negative symptoms in many international schizophrenia therapy algorithms [28, 36], including the clinical recommendations of the Russian Society of Psychiatrists for the treatment of schizophrenia [38].

The cariprazine dose for treatment of negative symptoms varies within the range of 1.5–6 mg, but it has been demonstrated that higher doses (4.5–6 mg) are associated with higher efficiency [22]. The majority of experts specify 4.5 mg (50%) or 3 mg (30%) as the optimal dose of cariprazine for treatment of negative symptoms [28].

EFFECT OF CARIPRAZINE ON THE DOMAIN “DEPRESSIVE MOOD SYMPTOMS”

The signs of the ICD-11 domain “Depressive Mood Symptoms of Primary Psychotic Disorders” do not fully correspond to known depressive episode criteria as they focus on the mandatory presence of low mood and suicidal behavior (for moderate and high severity cases) in the clinical pattern, while other important depressive episode criteria are omitted [7]. In all likelihood, this approach was chosen to allow for clearer differentiation between depressive and negative symptoms, as some of them, for example anhedonia, anergia, abulia and blunted affect, overlap [39].

Investigation of the PANSS scale domain “Anxiety/Depression'' [5] including anxiety (G2), guilt feelings (G3), tension (G4), and depression (G6) in the course of post-hoc analysis showed that the effect size in the cariprazine group was 0.21 by the sixth week of therapy (for a dose of 6 mg it was 0.29, and for a dose of 3 mg it was 0.1) which was a little less than the average score reduction in other domains, but nevertheless still statistically reliable [22]. The maximum score reduction for this domain was observed during cariprazine administration in a dose of 6 mg per day (effect size of 0.29). At the same time, no statistically significant difference between cariprazine and the placebo was observed for the most important PANSS signs with regard to the ICD-11 domain “Depressive Symptoms”: the effect sizes for the points “depression” (G6) and “guilt feelings” (G3) were 0.17 and 0.02, respectively [22]. It is supposed that such an insignificant reduction of the average score may be associated with the initial low score for these PANSS points in the analyzed studies [40]. Cariprazine did not show any difference in comparison to risperidone in terms of reduction of depressive symptoms [31] as measured via the Calgary Depression Schizophrenia Scale (CDSS) [41].

Taking into account the risk of affective disorder manifestation within a year after a diagnosis of schizophrenia increases more than six-fold in comparison with patients without this diagnosis [42], the proven efficiency of the drug in the treatment of affective disorders represents one of its additional advantages. To date, four randomized clinical trials of cariprazine therapy for depression in the frame of types I and II bipolar disorder have been performed. These trials showed that the drug, in a dose of 1.5–3 mg, reduced the manifestation of nine out of ten points (i.e., with the exception of internal stress) as per the Montgomery-Asberg Depression Rating Scale (MADRS) [43–46] in a statistically reliable manner, and was found to be safe and well-tolerated in the above-mentioned doses [47]. The trials were used as the basis for approval of cariprazine as a monotherapy to treat depression in the frame of bipolar disorder in the US [48] and treatment of depressive episodes in cases of type I bipolar disorder amongst adults in Russia, which was reflected in the updated pack insert for the drug [49].

Analysis of cariprazine administration in cases of bipolar depression showed that low doses were efficient [50]. In accordance with the updated pack insert for the drug in Russia, the initial dose is 1.5 mg and may be increased to 3 mg (the maximum dose for this indication) by the fifteenth day [49]. Further, the preliminary data also give evidence of cariprazine's efficiency as an adjuvant therapy for monopolar depression [51].

A comparison of cariprazine with other antipsychotic agents in the treatment of schizophrenia with concommitant depressive symptoms demonstrates a sufficiently high effect size for such patients (0.36), whilst cariprazine itself ranks one of the best among the 32 antipsychotic agents investigated [43]. The possibility of prescribing antipsychotic agents with antidepressive effects for correction of depressive symptoms that are not dependent on any other causes is considered in the modern schizophrenia treatment algorithms [52], and cariprazine may be apparently included with these drugs. Thus, pharmacodynamic and clinical data give evidence of the strong potential for cariprazine use in cases of schizophrenia with a high proportion of depressive symptoms, but additional studies involving the patients with higher initial scores for depressive PANSS points as assessed by the Calgary Depression Schizophrenia Scale are required for this purpose [41].

Although there are no recommendations on preferred cariprazine doses for the treatment of schizophrenia with a high proportion of depressive symptoms in the literature, it seems that lower doses of the drug (1.5–3 mg/day) can be used based on observations of treatment of bipolar depression [46] with cariprazine and, indeed, according to the pack insert for the drug [49].

EFFECTS OF CARIPRAZINE ON THE DOMAIN "MANIC MOOD SYMPTOMS"

The domain "Manic Mood Symptoms of Primary Psychotic Disorders" specified in ICD-11 includes the signs described in the maniacal episode criteria such as euphoria, irritancy, excited or expansive mood, increased purposeless activity, and other symptoms [7]. The effect size in relation of the PANSS domain "Hostility/ Agitation" [5], including the points "insufficient impulsivity control" (G14), "agitation" (P4), "hostility" (P7), and "non-cooperativity" (G8) was 0.35 on average, which was indicative of a sufficient antimaniacal effect of cariprazine on patients with schizophrenia [22]. The degree of reduction in the scores for this domain was approximately the same for regardless of cariprazine dose. Three trials demonstrated cariprazine efficiency for the patients with maniacal or mixed episodes in the frame of type I bipolar disorder [53–55], and in this case no exacerbation of depressive symptoms was observed in the patients. Post-hoc analysis of these trials demonstrated statistically significant differences compared to the placebo for all 11 points of the Young Mania Rating Scale (YMRS), including the four main points (excited mood, irritancy, speech tempo and quantity, and aggressive behavior) [56]. The effect size varied within the range of 0.31 to 0.55 and was a maximum for "irritancy" point, which was common in clinical practice for patients with mania and mixed states [56]. These trials give evidence of cariprazine efficiency for treatment of the entire range of manic symptoms including mixed ones, which afforded the grounds for the United States Food and Drug Administration (FDA) to approve cariprazine for treatment of manic and mixed states in the frame of type I bipolar disorder in the US. Recently cariprazine has been also registered in Russia for the same indication [49]. In this sense, cariprazine administered jointly with haloperidol, olanzapine, risperidone, or quetiapine is recommended in mania treatment algorithms for bipolar disorder [57]. On the other hand, at present, cariprazine is the second antipsychotic drug of choice after quetiapine approved for maintenance therapy of depressive, manic, and mixed episodes in the frame of type I bipolar disorder.

The recommended dose range for this indication in Russia is 3–6 mg [49]. The initial dose of 1.5 mg may be increased to 3 mg as early as the second day of treatment and further to 6 mg per day depending on the clinical response. Generally, rapid increase of the dose and the necessity to use maximum doses of the drug for treatment of manic states is also typical for other antipsychotic agents, for example, quetiapine and aripiprazole. It is believed that use of the optimal dose of cariprazine for the treatment of depression (1.5 mg) may be insufficient for the prevention of mania [56]. Thus, the use of higher doses of cariprazine (4.5–6 mg) with an initial rapid increase in dose is reasonable for treatment of schizophrenia with a high proportion of manic states.

EFFECT OF CARIPRAZINE ON THE DOMAIN “PSYCHOMOTOR SYMPTOMS”

The ICD-11 domain “Psychomotor Symptoms of Primary Psychotic Disorders” mainly includes, but is not limited to, catatonic symptoms, particularly psychomotor agitation, psychomotor retardation, negativism, and posturing [7]. The modern schizophrenia treatment algorithms recommend electroconvulsive treatment or combination of lorazepam and a second-generation antipsychotic drug with low risk of the development of neuroleptic malignant syndrome as the first-line treatment in cases of catatonic symptoms or catatonic schizophrenia [52, 58], especially when there is a high proportion of such symptoms as mutism, grimacing, staring, and disengagement [59].

As no increase in the risk of neuroleptic malignant syndrome development during cariprazine administration is observed in the course of any acute [21] and maintenance [60] therapy stages for patients with schizophrenia, the combination of lorazepam and cariprazine in this case may be considered a possibility for the treatment of these states. Besides, analysis of changes in individual PANSS points that are similar to catatonic symptoms in their structure (within the psychopathological meaning) evidences the statistically significant difference between cariprazine and the placebo in relation to the majority of symptoms, particularly (N7) stereotyped thinking (effect size of 0.23), (G5) mannerism and posturing (effect size of 0.15), and (G14) lack of impulsivity control (effect size of 0.15) [22]. Nevertheless, given our present knowledge about this state, the role of antipsychotic drugs in general, and cariprazine in particular, for the treatment of catatonic symptoms is not so significant as it seemed previously.

EFFECT OF CARIPRAZINE ON THE DOMAIN “COGNITIVE SYMPTOMS”

The neurocognitive deficit in cases of schizophrenia can be associated with the worst prognosis for the disease, reduction of functioning, and is often otherwise related to negative symptoms [61, 62]. Neurocognitive deficit is the most prominent of the long-term stages of the disease [63]. The significance of the cognitive symptoms for schizophrenia diagnostics in ICD-11 was enhanced, and the domain “Cognitive Symptoms of Primary Psychotic Disorders”, including the information processing rate, attention/concentration, orientation, abstract thinking, verbal or visual learning, and working memory, was introduced [7]. In the course of pre-clinical trials, cariprazine demonstrated its efficiency in relation to cognitive dysfunction [64]. Evidence of the positive effect of cariprazine on the cognitive functions is available. In particular, cariprazine in a dose of 1.5–9 mg demonstrated medium-to-high effect size (0.47) for the domain Disorganization of thinking (Points N5, G5, G10, G11, G13, G15, P2), also including the symptoms of neurocognitive disorder such as “Difficulty in abstract thinking” (N5), effect size 0.26; “disorientation” (G10), effect size 0.26; “Poor attention” (G11), effect size 0.36; and “conceptual disorganization” (P2), effect size 0.44 [22, 63]. Insufficient effect size (0.15) was only observed for the point “mannerism and posturing” (G5) [22]. Improvement of cognitive symptoms was also noted in a comparison of cariprazine with risperidone [31]: by the end of the twenty-sixth week of therapy, cariprazine was clearly superior to risperidone with regard to the PANSS factors identified related to cognitive functions in a statistically significant manner. Hence, this parameter in relation to the Marder factor for disorganized thoughts [5] was -4.16 vs. -3.53 (p=0.05), and for the Meltzer cognitive sub-scale [65] including the PANSS points N5, N7, P2, G10, and G11 it was -3.13 vs. -2.60 (p=0.028) in favor of cariprazine, respectively [32]. Besides, it was demonstrated that administration of cariprazine in a dose of 3 mg to patients with basic attention impairment resulted in statistically significant (as compared with the placebo) improvement of attention strength and stability, as measured via the CDR (Cognitive Drug Research) test [20]. Thus, in accordance with the initial hypothesis on the potential pro-cognitive effect of cariprazine, this drug has sufficient efficiency in relation to neurocognitive symptoms and which does not depend on any other symptoms (positive, negative, or depressive) and exceeds the relevant efficiency of other antipsychotic agents, for example risperidone. On the other hand, psychological interventions, primarily cognitive remediation, as well as their combinations with psycho-social and rehabilitation approaches, take the lead in modern schizophrenia treatment algorithms for correction of cognitive deficits, while the roles and positions of antipsychotic agents in the treatment of cognitive deficits are less significant [53]. Analysis of the PANSS points associated with neurocognitive disorder offers evidence of the pro-cognitive effect of this drug, especially in higher doses (4.5–6 mg) [22]. On the other hand, additional trials with the use of standardized banks of neurocognitive tests are required in order to identify the particular neurocognitive disorder domains associated with this effect.

Functional impairment

According to DSM-5, the presence of functional impairment in one or more areas, such as work, inter personal relations, or self-care (Criterion B), is necessary for diagnosis of schizophrenia apart from the certain threshold of symptoms (Criterion A) and their duration (Criterion C) [8]. Unfortunately, this criterion is not represented in ICD-11 or, indeed, in ICD-10, and diagnosis of schizophrenia are based solely on the clinical criteria [7]. On the other hand, neurocognition, positive symptoms, disorganization, and abulia have the most impact on the real functioning of patients with schizophrenia [66]. It is important that therapy should not only result in a reduction of the particular symptoms but also an improvement in the functional outcomes of the disease. Analysis of the treatment of psychotic episodes with cariprazine within the framework of maintenance treatment of schizophrenia showed that cariprazine was superior to the placebo in the statistically reliable manner, not only for reduction of psychotic symptoms but also in terms of improving the patient's quality of life, as measured by the reduction in total score of the Schizophrenia-Specific Quality of Life Scale (SQLS), as well as the vitality factors and the psycho-social factor of this scale [20, 21]. The conclusion drawn on this basis is that cariprazine administration can be associated with improved quality of life for schizophrenic patients from the first week up to the sixth week of therapy [67]. Post-hoc analysis of one of the cited studies [20] via the pro-social PANSS factor [68], including Points G16, N2, N4, N7, P3, and P6, showed that the difference between cariprazine and the placebo was statistically significant for a dose of 3 mg as early as the first week of therapy, and for 6 mg from the third week of treatment [67]. A Statistical difference was observed for both cariprazine doses and the placebo in relation to emotional withdrawal (N2), passive/apathetic social withdrawal (N4), active social avoidance (G16), and suspicion/persecution (P6) [67]. Post-hoc analysis of all short-term cariprazine trials suggests that the effect size for different doses of cariprazine, in relation to the pro-social PANSS factor, is 0.32, and is statistically significant for all points of this factor including hallucinatory behavior (0.2), and stereotyped thinking (0.23) [22].

Post-hoc analysis of cariprazine treatment in the frame of maintenance treatment of schizophrenia showed that transition to placebo for stable patients within the framework of the 72-week double blind trial was associated with considerable deterioration of psycho-social functioning, as measured via the Personal and Social Performance Scale (PSP) [69], while it remained unchanged in the cariprazine group with statistically significant differences in favor of cariprazine both in relation to the total score as per the PSP Scale and all its domains (socially useful activities; relations with relatives and friends; self-care; aggressive behavior) [67]. These results correlate with the comparative study results for cariprazine and risperidone [31], where not only statistically significant reduction of the total score according to the PSP Scale has been observed in the cariprazine group by the end of the twenty-sixth week of therapy and beginning as early as the tenth week, but more prominent improvement of three out of four domains of the PSP Scale (socially useful activities; relations with relatives and friends; self-care) have also been noted, which correlate with daily activities and better therapy commitment [70]. Thus, one might draw the conclusion that cariprazine administration is associated not only with efficiency in relation to various schizophrenia domains but also with improvement in psycho-social functioning in the course of both the acute and preventive schizophrenia treatment stages.

Cariprazine tolerability and safety

The tolerability and side effects of the new antipsychotic agent were also studied in the course of pre-approval double-blind placebo-controlled multi-center trials of acute treatment, in addition to determining its efficiency [19–21]. The side effects in the cariprazine group included insomnia, extrapyramidal symptoms, akathisia, sedation, nausea, dizziness, and constipation at least twice as often as in the placebo group. Higher doses of cariprazine resulted in additional efficiency of the drug without any increase of the frequency of any side effects. The severity of akathisia, extrapyramidal syndrome, and tremor manifestation was usually quite mild, and more frequent among patients taking higher doses of the drug. Metabolic syndrome was low in both groups; in particular, weight gain by more than 7% was observed in 8% of the patients taking 3–6 mg of cariprazine, 11% of the patients taking 6–9 mg, and 4% of the patients taking the placebo.

The study of safety and tolerability of different doses of cariprazine (3, 6, and 9 mg) for stable patients with schizophrenia lasting for 72 weeks within the framework of the non-blind trial phase showed that akathisia (19.2%), insomnia (14.4%), and headache were the most frequent side effects. Within the framework of the placebo-controlled stage of this trial, such side effects as akathisia (5% and 3%, respectively), extrapyramidal syndrome (5.9% and 3%, respectively), tremor (7.9% and 0%, respectively) and backache (5% and 2%, respectively) were reliably more frequent in the cariprazine group [24].

The tolerability and safety of various doses of cariprazine were also confirmed in the course of two non-blind trials lasting for 1 year [61] and 48 weeks [35]. Akathisia (16%), headache (13%), insomnia (13%), and weight gain of 1.5 kg on average (10%) were the most frequent side effects in the first trial (the dose of cariprazine was 3–9 mg, *n*=586), and the prolactin level decreased slowly in this case [61]. In the course of the second trial (the dose of cariprazine was 1.5–4.5 mg, *n*=93), such side effects as akathisia (14%), insomnia (14%), and weight gain of 1.9 kg on average were observed [35]. None of the treatments were terminated due to changes in metabolic parameters or body weight were registered. No changes in cardiovascular parameters were observed in the patients treated with cariprazine. Post-hoc analysis of these two trials showed that akathisia and the psychotic state recrudescence were the only causes of treatment termination [36]. Akathisia (19.6%), which more frequent within a dose range of 1.5–3 mg per day, insomnia (13.3%) for a dose of 9 mg, and headache (12.8%) for a dose of 1.5–3 mg, were the most common for patients treated with cariprazine. Prolactin levels were reduced in patients of all groups. Extrapyramidal syndrome was observed in 6.6% of the patients with approximately the same frequency in the different groups. Weight gain of ≥7% was observed in 34% of patients of normal weight, and more frequently for higher doses. This trial also demonstrated that adherence to the recommended doses (1.5–6.0 mg) in clinical practice was reasonable, and any dose increase did not generally result in an increased number of side effects and higher withdrawal of the patients from the trial [36].

DISCUSSION

In the course of our review, we have studied the efficiency of cariprazine for treatment of six of the schizophrenia symptom domains identified in ICD-11. At present, cariprazine has been approved for schizophrenia treatment within the framework of acute and maintenance treatment including in the US, the EU countries, and Russia. Further, it has been approved in some countries (the USA, Russia) for acute treatment of manic, mixed states and depression in the frame of type I bipolar disorder.

Analysis of the randomized controlled trial of cariprazine use for schizophrenia treatment based on analysis of the PANSS scale points enables one to conclude that the drug is efficient for the treatment of various positive symptoms, including delusion, hallucination, and abnormal behavior both within the framework of acute and maintenance therapy of schizophrenia for patients suffering their first psychotic episode, and with multiple ones. Although cariprazine took a medium position among all antipsychotic agents with regard to the reduction of delusions and hallucinations it has a positive effect on other schizophrenia symptoms associated with positive syndromes, mainly the secondary negative symptoms such as disorganization of thinking and depression, and also demonstrates a favorable profile of side effects.

On the other hand, cariprazine has a positive effect on other schizophrenia symptoms associated with positive syndromes, mainly the secondary negative symptoms such as disorganization of thinking and depression, and also demonstrates a favorable profile of side effects. Moreover, the modern schizophrenia treatment algorithms should focus on the safety of the drug rather than on its efficiency. Taking into account the above, cariprazine should be considered one of the preferred drugs for schizophrenic patients with dominating delusion and hallucination. In addition, the high effect size of cariprazine in the reduction of disorganized thinking symptoms and its proven, direct impact on the signs of aggressiveness and hostility make cariprazine one of the principal front-line drugs for all positive symptom groups noted in ICD-11. In case of apparent agitation and excitement in schizophrenic patients, it is recommended that benzodiazepine or any other sedative antipsychotic agent, for example, clozapine, quetiapine, or olanzapine, or an antihistamine drug be added to the treatment [31] .

For diagnostics of the updated symptoms within the ICD-11 domain “Negative Symptoms”, it is necessary not only to detect them in the mental state of a schizophrenic patient but also to demonstrate that they do not stem from any other causes (secondary negative symptoms) [8]. To date, it has been demonstrated that only two antipsychotic agents have a primary anti negative effect (amisulpride and cariprazine). However, taking into account other factors, particularly the side effect profile and availability of the trial on direct comparison with another antipsychotic agents (risperidone) for schizophrenic patients with prevailing negative symptoms in the course of long-term therapy, cariprazine is nevertheless considered the first-line drug for schizophrenic patients with dominant negative symptoms.

According to ICD-11 diagnostics of depressive symptoms for patients with schizophrenia, there should be a focus on the evaluation of mood and suicidal thoughts as other typical depressive symptoms, including anhedonia and retardation, overlap with the negative symptoms. Minimum or statistically insignificant differences between cariprazine and the placebo in reduction of the total score for the PANSS points “depression” (G6) and “guilt feelings (G3)” within the framework of Acute treatment of schizophrenia were obtained. Based on randomized clinical trials, at present it is difficult to discuss the advantages of cariprazine in comparison with other second-generation antipsychotic agents for the treatment of depression in cases of schizophrenia. On the other hand, frequent development of depressive episodes within the post-psychotic period and the proven efficiency of cariprazine in treatment of bipolar depression may potentially make cariprazine the front-line drug for such a cohort of patients, although this hypothesis requires additional studies.

There are no substantial differences in description of the ICD-11 domain “Manic Symptoms of Primary Psychotic Disorders” and the main (core) criteria of a manic episode, except for the indication that enhancement of psychomotor activity should be considered in another ICD-11 domain [7]. In this sense, the studies on the proven antimanic efficiency of cariprazine in cases of bipolar disorder may be extrapolated to the treatment of schizophrenic patients with apparent manic symptoms but without any signs of psychomotor agitation. On the other hand, at present, the inventory of any doctor contains various drugs for the treatment of manic states, and tolerability should apparently be the focus with regard to the selection of any particular drug. Certain advantages related to cariprazine in comparison with other antimanic agents are observed for schizophrenic patients with metabolic syndrome as well as those with a potential bipolar pattern of the disease, for example, the presence of manic and depressive episodes in the case history.

The modern treatment algorithms for catatonic symptoms in the cases of schizophrenia considered in ICD-11 within the framework of the domain “Psychomotor Symptoms of Primary Psychotic Disorders” propose benzodiazepines (mainly lorazepam) and electroconvulsive therapy as the first-line treatment, and the role of antipsychotic drugs here is secondary and possible only in combination with lorazepam. In this sense, the combination of lorazepam and cariprazine may be a possible option, together with the use of antipsychotic agents with a low risk of causing the development of neuroleptic malignant syndrome.

Inclusion of the domain “Cognitive Symptoms of Primary Psychotic Disorders” in ICD-11 has confirmed the importance of these symptoms for diagnostics, prediction, and therapy of schizophrenic patients as they become leading at the long-term stages of the disease. The pro-cognitive effects of cariprazine, independent of any other symptoms and supposed on the basis of the drug receptor profile analysis and animal studies, was confirmed for schizophrenic patients within the framework of short-term and long-term therapy stages, and exceeded the same effects of other drugs, particularly risperidone. This effect was primarily observed by analysis of changes in the "cognitive" points of the PANSS scale, and further studies with the use of the tools for precise evaluation of different neurocognitive disorder components, including memory, attention, psychomotor ability rate, and executive functions, should demonstrate the efficiency of cariprazine in this area.

Improvement of functioning for patients with schizophrenia does not always correlate with a statistically significant reduction of positive, negative, or cognitive symptoms of the disease, and the necessity to verify functional impairment in one or several areas is an important stage of the diagnostic process in some international classifications of diseases [7]. Subsequent to randomized clinical trials, cariprazine demonstrated the capability to improve the functioning of schizophrenic patients, regardless of the effect on the disease symptoms, based both on the reduction of the "pro-social" PANSS points and positive impact on the various components of the Personal and Social Performance Scale (PSP) that are valid for these purposes.

Such side effects as akathisia, extrapyramidal syndrome, insomnia, and slight weight gain were the most frequent issues observed during cariprazine therapy. As a rule, these symptoms were mild and did not require termination of treatment, although additional drugs had to be prescribed in some cases. In particular, addition of benzodiazepine, for example, lorazepam and clonazepam or propranolol [53] is the front-line therapy in cases of akathisia, whilst addition of benzodiazepine, an antihistamine drug, trazodone or a sedative antipsychotic agent [29] should be considered in cases of insomnia.

Implementation of the ICD-11 schizophrenia domains in clinical practice can face certain difficulties. In particular, as the diagnostics of the schizophrenic spectrum disorders have focused on detection of psychotic and negative symptoms for many years, there is some concern that other domains will only be evaluated by clinicians in cases of their severe manifestation. Besides, it is highly probable that clinicians will often use Point 9 ("evaluation is impossible on the basis of the available data") in the compressed time frame for evaluation of various domains, except for the most obvious ones (psychotic, manic) that can depreciate dimensional assessment. The necessity to develop particular tools (questionnaires, scales) for rapid evaluation is one of the possible options to facilitate the transition to the full implementation of the schizophrenia symptom domains identified in ICD-11 at the global level. This is especially relevant for the evaluation of the degree of cognitive deficits as it is difficult for practitioners in the course of the clinical interview. It should be also explained to doctors how often they have to evaluate the domains at different stages of care, when to begin the treatment, or whether dynamic observation is sufficient. Proactive efforts to enhance the psychiatric community's awareness of the advantages of this classification in the clinical practice and development of training programs on its application for different target audiences are required [10].

The online survey of European clinicians and researchers engaged in the treatment of schizophrenic patients enabled the identification of the states in the frame of schizophrenia where use of cariprazine might be considered the first-line therapy: the first psychotic episode, positive symptoms, negative symptoms, psychomotor agitation (in combination with other drugs, for example, benzodiazepine), presence of metabolic syndrome, and comorbid drug abuse [29].

Absence of any studies into the use of the schizophrenia symptom domains identified in DSM-5/ICD-11 to evaluate the efficiency of antipsychotic agents, including cariprazine, should be considered the main limitation to the present review. The majority of studies comparing cariprazine with a placebo and/or other antipsychotic agents used different PANSS sub-scales or clusters of symptoms only partially corresponding to all schizophrenia domains, as per DSM-5/ICD-11. Analysis of the PANSS scale points enables the evaluation of the ICD-11 domains "Positive Symptoms", "Manic Mood Symptoms", and "Psychomotor Symptoms" with a sufficient degree of accuracy. At the same time, the direct correlation between the PANSS points and other ICD-11 domains ("Negative Symptoms", "Depressive Mood Symptoms", "Cognitive Symptoms") is not always apparent. Other tools, for example, the Brief Negative Symptom Scale (BNSS) [71], the Calgary Depression Schizophrenia Scale (CDSS) [42], or the Brief Scale Assessment of Cognition in Schizophrenia (BACS) [72], should be involved due to their more precise evaluations in any future studies. Scarcity of independent trials for the comparison of cariprazine's efficiency and tolerability with placebos and/or other antipsychotic agents without any participation of the company producing this drug should also be pointed out.

CONCLUSION

It was demonstrated in the present review — through the example of cariprazine, an antipsychotic agent — that the implementation of the identified ICD-11 domains into clinical practice might facilitate the development of more individualized approaches to therapy and the improvement of quality of care for schizophrenic patients. Cariprazine is the first-line drug for treatment of the ICD-11 domain “Negative Symptoms” as well as front-line therapy for the treatment of the domains “Positive Symptoms” and “Cognitive Symptoms”. Additional studies are required in order to evaluate the effect of cariprazine on the ICD-11 domains “Manic Mood Symptoms” and “Depressive Mood Symptoms”. Application of cariprazine monotherapy for the domain “Psychomotor Symptoms” is not considered reasonable. Cariprazine results in improved functioning of patients with schizophrenia. Additional tools should be implemented in clinical practice that enable doctors to evaluate schizophrenia domains in their clinical practice both rapidly and reliably.

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“Love in the Later Years…”: Perceptions of Sex and Sexuality in Older Indian Adults — a Qualitative Exploration

«Любовь в позднем возрасте…»: восприятие секса и сексуальности у пожилых людей в Индии (качественный анализ)

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Original Research

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ABSTRACT

BACKGROUND: The world faces global population ageing. With this demographic shift and increased life-expectancy, healthcare services are focused on healthy ageing. Sexual health is a vital yet neglected dimension of general health and wellbeing in older adults. This study aimed to explore sexual experiences and perceptions of sexuality among older people in India.

METHODS: A qualitative approach with social constructivist paradigm was used. 20 participants aged above 60 years were recruited through purposive sampling until thematic saturation was reached. In-person, in-depth interviews were conducted using a semi-structured guide after an initial pilot study. They were audio-recorded, transcribed, and translated verbatim. Thematic analysis was conducted, and rigor ensured through triangulation and respondent validation.

RESULTS: The overarching categories were “sexuality as a mode of resilience”, “emotional stability and intimacy as attributes of sexual pleasure”, and “lack of sexual rights awareness”. The main categories (themes) were sexual experiences (intimate touch, non-penile sex, personal meanings of sexuality), partner expectations (companionship, support, continuity of care, proximity), and barriers against sexual expression (social stereotypes, stigma, lack of audience in healthcare services). The older people were accepting of their sexual difficulties and coped through relationship dynamics. Participant voices are discussed with regard to the socio-cultural context.

CONCLUSION: Sexual wellbeing is connected with “ageing well”. Our findings suggest that older people retain sexual desires and fantasies through changed patterns and expectations. Healthcare services, policymakers and academia need to be informed about older people’s sexual needs and rights.

АННОТАЦИЯ

ВВЕДЕНИЕ: Население мира стареет, в условиях демографических изменений и увеличения ожидаемой продолжительности жизни ресурсы здравоохранения направлены на поддержание здорового старения. Сексуальное здоровье — важнейший аспект поддержания общего физического и психологического здоровья пожилых людей, при этом ему уделяется недостаточно внимания. Цель проведенного исследования — изучение сексуального опыта и восприятия сексуальности у пожилых людей в Индии.

МЕТОДЫ: Проведен качественный анализ с применением парадигмы социального конструктивизма. 20 участников в возрасте старше 60 лет включались в исследование путем целенаправленного отбора до достижения тематического насыщения. Были проведены индивидуальные очные углубленные опросы с использованием полуструктурированного руководства, составленного по результатам предварительного пилотного исследования. Аудиозапись опросов была расшифрована и переведена. Выполнен тематический анализ, точность которого обеспечивалась с помощью перекрестной проверки и проверки респондентами.

РЕЗУЛЬТАТЫ: Были выделены следующие общие категории тем: «сексуальность как проявление психологической устойчивости», «эмоциональная стабильность и близкие отношения как атрибуты сексуального удовольствия» и «недостаточное понимание сексуальных прав». Определены следующие основные темы: сексуальный опыт (интимные прикосновения, секс без проникновения, восприятие своей сексуальности), ожидания от партнера (дружеское общение, поддержка, постоянная забота, психологическая близость) и факторы, препятствующие сексуальным проявлениям (социальные стереотипы, стигматизация, отсутствие поддержки со стороны структур здравоохранения). Пожилые люди признавали наличие трудностей в сексуальной сфере и пытались справиться с ними в процессе построения отношений. Анализ ответов респондентов выполнен с учетом социокультурного контекста.

ВЫВОД: Сексуальное благополучие связано с концепцией здорового старения. Согласно результатам нашего исследования, у пожилых людей сохраняются сексуальные фантазии и сексуальное влечение, но при этом наблюдается изменение моделей сексуального взаимодействия и ожиданий от партнера. Медицинские учреждения, законодатели и научное сообщество должны обратить внимание на сексуальные потребности и права пожилых людей.

Keywords: *sex; sexuality; experiences; older people; old age; qualitative*
Ключевые слова: *секс; сексуальность; опыт; пожилые люди; пожилой возраст; качественный анализ*

INTRODUCTION

Sexuality is defined as a *"capacity for sexual feelings and includes a person's sexual orientation, gender identity, intimacy, eroticism and social aspects of sex"* [1]. Besides the reproductive significance, anthropologists consider sexuality to be a core aspect of socio-cultural organizations that is influenced by lifestyle, religious beliefs, and family structure [1, 2]. Sex and sexuality remain the primitive tenets of living and have been associated with health and wellbeing. Sexual wellbeing among older persons thus assumes importance as the global population above 60 years is projected to reach 2.1 billion by 2050 [3]. Despite the popular myth, older people cannot be considered as asexual [4]. They are known to have sexual desires, fantasies, varying sexual expectations, as well as change in sexual approaches with ageing [4, 5]. However, the majority of evidence to date focuses on the psychobiology of ageing and sexuality, whereas their lived sexual experiences are hidden and laden with taboo.

In *"Sexuality, health care and the older person"*, Bauer et al. [6] stress the importance of sexuality to older people and underline that it remains a *"neglected area necessitating research"*. In particular, there is a need to explore experiences of sexuality and sexual diversity in later life. A recent systematic review of qualitative research on *"sexual aging"* revealed that couplehood, socio-cultural aspects of sexuality, and illness impacted sexual behavior among older persons. The authors stressed upon the importance of *"personal meanings and relevance"* attached to sexuality in later life and the research gap in this particular field [7]. Several longitudinal ageing studies have supported the fact that sexual health forms are an integral component of wellbeing in later life as older people retain their sexual desires in spite of the physiological changes that come with age. These aspects are frequently neglected both in clinical settings and in the literature [8, 9]. With increased life expectancy and myths surrounding sexual life in older age, it is vital to hear their sexual *"experiences"* and *"unmet needs"*. This may help to break the stigma, promote help-seeking behavior, and incorporate the findings in healthy ageing policy interventions. Furthermore, considering that healthcare services have undergone a paradigm shift towards rights-based approaches and healthy ageing, the dimension of sexual health in older people needs to be highlighted in research.

In light of this, our study aimed to understand the perceptions of sexuality in older people in India and the barriers they face in expressing them.

METHODOLOGY

Approach

The study followed a qualitative approach with a social constructivist paradigm. This paradigm conceptualizes knowledge as socially based and the researcher can seek multiple social truths as opposed to the hypothesis-driven direction of a positivist approach [10]. We were interested in understanding the experiences and perceptions of sexuality in older people. Lived experiences cannot really be rated and are best expressed in rich verbal and written accounts. Hence, we chose the qualitative approach, which enables in-depth gathering and analysis of non-numerical data.

Setting

The study was conducted in the Psychiatry Department, JSS Medical College and Hospital, Mysore. Individuals were interviewed in separate rooms outside out-patient hours based on their convenience and willingness. These interviews took the form of one-to-one meetings between the participant and researcher, which was audio-recorded with consent.

Sampling and recruitment

Men and women above the age of 60 years, irrespective of marital status, living arrangements, and sexual orientations were invited to participate in the study. We tried to ensure maximum socio-demographic diversity in the sample. However, each participant was screened for mental health conditions using the MINI Neuropsychiatric Interview 7.0.2 [11]. (Institute purchase) and also the Hindi Mental Status Examination (HMSE) [12]. Only cognitively healthy (HMSE >24) individuals without any psychiatric issues were included in the study as experiences of mental illness or neurocognitive disorders can potentially color their perceptions about sexuality. Individuals with severe mobility restrictions and neurological conditions were also excluded.

Overall, 20 older adults were recruited through purposive sampling from senior-care centers, the psychiatry out-patient department, and other old-age support organizations via advertisements. The recruitment notice was also shared via personal networks and social media.

Procedure

The purpose and mode of study was explained to the participants in their own language and written informed consent was obtained. Separate consent was obtained to allow audio-recording of the interviews. In-depth interviews were conducted by the first author using the interview guide. Open-ended questions were supplemented by probes and memo writing to elicit rich responses. The interviews were conducted in the clinic (November 2019 – February 2020) based on mutual convenience of the participant and researcher. The average duration of interview was 98 minutes but could last between 1–3 hours. Sampling was continued until thematic saturation was reached.

Our main research question was, *"How do older people view and experience sexuality, what do they expect from their partners, and what role does sexuality play in their lives?"*. Based on the existing literature and clinical experience of the researchers, a semi-structured interview guide was formed, which was further refined after a pilot interview phase conducted with four participants. The key questions of the final interview guide are reported in Table 1.

Table 1. Semi-structured interview guide used for the study (only key questions)

- *What role does sex and sexuality have in your life?*
- *How do you perceive sexual relationships?*
- *How do you feel about your sexual fantasies and desires?*
- *How do you think your age influences your sexual experiences?*
- *How would you describe your romantic and sexual encounters with your partners?*
- *How has your sexual life changed?*
- *How often do you describe your sexual concerns? What are your experiences related to the same?*
- *What do you think about 'sexuality in later life'?*
- *Please describe your current sexual life*

Transcription and translation

Interviews were conducted in English, Hindi, and Kannada as appropriate. Each interview was transcribed and translated verbatim to English. The translation and transcription were conducted by the second author, who spoke all three languages. To ensure reliability, translations were back-translated to the respective languages (by other members of the team) to retain what the content was supposed to convey. Each participant's data was numbered, and these serial numbers were used for all purposes related to documentation and analysis. With the exception of the researchers, no one else could gain access to this data.

Research governance or ethical approval

The study was approved by the Institutional Ethics Committee, JSS Medical College and Hospital, JSS University, Mysore (Approval Letter No. JSSAHER/BeSc/Psy/281-76B dated 21st September 2019).

Data analysis

Braun and Clarke's thematic analysis was used to analyze the data [13]. The analysis was completed independently by the first and second authors, who were both trained in qualitative research. Initially, line-by-line coding was conducted throughout the transcribed content. Initial coding was followed by a focused coding to group the codes into meaningful categories, themes, and sub-themes. Finally, axial coding was used to help establish an appropriate hierarchy among the generated themes. The theoretical perspective of research question was taken into account along with the interview memos to ensure that the generated themes coherently convey the participants' stories. A constant comparison between the generated themes and the interview content was performed throughout the analysis to ensure that the participants' voices were reflected in the results. After independent analysis, the final results were collated, discussed, and merged.

The trustworthiness and rigor of the study were ensured through methodological triangulation. Methodological triangulation was achieved by independent coding by two reviewers and respondent validation. The preliminary results of the study were presented and discussed with 50% of participants. Following respondent validation, researchers refined the results, ensuring that they accurately reflected the participants' views [14]. We were mindful of the possible psychological reactions among the participants that could be incited while describing their sexual experiences. In such cases, they were offered professional help by a qualified sexologist who was not otherwise involved in this study.

RESULTS AND DISCUSSION

The results described here reflect participants' perceptions and experiences of sexuality. The relevance of their experiences needs to be understood based on the individual context. Hence, there can be *"multiple truths"* in their experiences.

Table 2. Socio-demographics of the sample

	Characteristic	No. (*n*=20)
1	AGE (years)	
	60–69	8
	70–79	10
	>80	2
2.	CURRENT PARTNER	
	Married/cohabiting	11
	Single	2
	Divorced/separated	2
	Widowed	5
3.	ORIENTATION	
	Heterosexual	18
	Transgender — male	2
4.	RESIDENCE	
	Urban	12
	Semi-urban	5
	Rural	3
5.	EDUCATION	
	Never formally educated	3
	Up to Class 10	6
	Up to Class 12	5
	Graduate and above	6
6.	LIVING ARRANGEMENT	
	Alone	3
	With partner	12
	With family	5
7.	WORKING STATUS	
	Still in employment	5
	Pensioner	10
	Financially dependent	5
8.	SELF-REPORTED HEALTH STATUS	
	Excellent	5
	Good — average	11
	Poor	4
9.	REPORTED NUMBER OF LIFETIME SEXUAL PARTNERS	
	None	1
	One	16
	More than one	3
10.	MEDICAL CONDITIONS (as per reports)	
	Diabetes mellitus	5
	Hypertension	6
	Hypothyroidism	5
	Osteoarthritis	4
	Gout	2
	Vision difficulties	8
	Hearing impairment	5

Theoretical saturation was achieved after interviewing 17 participants. Three more participants were interviewed in order to add richness to the obtained data. The average age of the participants was 69.2 years. 10 were men, eight women, whilst two identified themselves as transgender. The majority of participants were from urban and semi-urban backgrounds, lived with their partners, and were formally educated. Only a few availed themselves of social support services while nearly half received a pension. Medical conditions were documented as per the records available. 15 participants welcomed the research and were keen to discuss their sexual experiences, while the others needed some time to feel comfortable. Eventually, all the participants stated that they were glad they had participated in this study. Socio-demographics of the sample are depicted in Table 2.

In qualitative research, verbatim excerpts of the interviews with the participants form the real data which needs to be understood and interpreted based on their individual social context are used. The discussion here involves contextualizing a particular theme supported by verbal excerpts from participants' interviews. Separating the participant excerpts and discussion thus becomes redundant and the lived experiences (results) lose their relevance. Hence, we choose to present results and discussion together. The categories and themes generated are reported in Table 3. The overarching categories were *"sexuality as a mode of resilience"*, *"emotional stability and aging well as attributes of sexual pleasure"*, and *"lack of awareness about sexual rights."*

Perceptions related to sexual encounters in later life

This theme was central to our study objectives defining main experiences of our participants related to sexuality. These were "touch as an index of intimacy", "perceived sexual satisfaction beyond physical stimulation/pleasure", and "personal meanings/contexts attached to sex". Here we discuss these themes and the participant excerpts that support them.

Ageing brings about physiological changes which may affect sexual life. 12 participants expressed their interest in non-vaginal sexual practices and considered various forms of 'touch' to constitute measures of erotic pleasure. In fact, in our sample, sensual touch and affectionate touch (stroking, fondling, kissing, holding hands, hugging, etc.) were the most common forms of expressing intimacy.

As **Mr. M (67 years) noted:**

"Every time she held my hand tightly, I could feel a sensation in my chest. The same feeling as the olden days. I wanted to keep her close to me and convey my love to her."

Mrs. P (76 years) remembered similar forms of intimacy with her late husband:

"The best moments of togetherness that we shared were when we hugged. I wanted him to stroke my hair as always. At this age, this makes me so happy. I cannot recall a better moment of pleasure. It changes so much with age, doesn't it!"

Table 3. Categories and themes generated in the study

Categories	Themes
Perceptions related to sexual encounters in later life	• Touch as an index of intimacy • Perceived satisfaction beyond physical pleasure • Personal meanings attached to sex
Expectations from partner	• Companionship and support • Continuity of care • Physical proximity and intimacy
Barriers in discussing sexual health issues	• Stigma • Social stereotypes about sex in later life • Dismissal in healthcare services
Unmet needs related to sexuality	• Lack of audience/understanding • Orientation and age-based discrimination
Overarching categories	
• *Sexuality as a mode of resilience* • *Emotional stability and aging well as attributes of sexual pleasure* • *Lack of awareness about sexual rights*	

Affiliative touch can serve as a reward stimulus that is known for evoking feelings of pleasure and reducing negative mood state [15]. A 1988 study among 80–102 year-old people found caressing to be the most common form of sexual expression [16]. Since the landmark experiment of Harlow, social touch is known for expressing companionship, social cohesion, sexual intimacy, and emotional bonds. Modulation of hedonic touch sensations depends on attention, contexts, mood, and expectations, varying widely based on central sensory processing [17]. Medical comorbidities such as chronic pain can exist in old age, and the motivation-decision model of pain shows how pain modulation can occur by varying motivational state, which is in turn dependent on perceived closeness with one's partner [18]. Research has shown that the experience of sexuality and sensitivity of erogenous zones change with age [4, 5, 8], as older people prefer physical closeness, emotional warmth, and intimacy over sexual intercourse, which was also noticed among our participants.

Mr. S (70 years) added: *"We retained our sexual desire just like before. But how we enjoyed it kind of changed. We turned on in the company of another, especially when I could sense her leaning against me. I cannot see well enough, but her closeness was enough to make me feel loved."*

Similarly, emotional intimacy was considered to be far more important than physical pleasure while discussing sexuality.

Mr. M (65 years) remarked: *"Frankly, my private parts were not enough sensitive like younger ages. But that never prevent me from getting aroused now. It's difficult to explain you know, it's like a sensation, a fulfilment in your mind. Being loved, knowing that you have your partner to love you. That is what makes it so pleasurable (...)"*

Mrs. T (68 years) said: *"You must be knowing that sexual desire will decrease over time. I am no exception! Still, you know what — age can never really deprive you of sexual pleasure. Just the meaning changes. It is so intense (...) All throughout our 20s–40s, I have thought these are the best moments you can spend with your partner. Now things have slowed down, but even when we are together and when we have better times — this sensation deep inside me keeps my desire alive."*

According to traditional Indian practices, old age has been associated with acceptance and renunciation [19]. Sexual changes in normal ageing are wrongly attributed to asexuality and unattractiveness. However, sexuality is not just about sexual intercourse. The emotional component is equally vital to perceived satisfaction. Our participants mentioned that even though there were variations in arousal, erection (in males) and vaginal lubrication (in females), these responses mattered less than the 'emotional satisfaction' that they derived from their partners' company. 15 of them equated a sense of orgasm with the perceived pleasure of being *"emotionally secure"* with their spouses or partners. Based on the existing literature, existential anxiety and loneliness in later life are often mitigated by strong interpersonal bonds and social cohesion [20, 21]. Sexual intimacy in later life manifests in more abstract ways than measurable genital responses among our participants, indicating that the index of pleasure differs with age. Also, the response and perceptions about sexual cycle in older people is non-linear. A recent qualitative study by Towler et al. [22] explored older adults' experiences of societal stigma towards sexuality in later life. The authors concluded that body-image focus changes from aesthetics to functionality and emotional wellbeing, and this discordance often leads to difficulties among participants. On the other hand, older people in our study were comfortable with this change in "body-image focus" and rather perceived it as a component of healthy ageing. This seems possible, as this sense of 'withdrawal' from the body and focus on the soul and inner attraction of one's soulmate is advocated in the Vedic traditions and in the Indian treatise of sexual literature, the Kama Sutra [23].

This brings us to the next theme within the perceptions, namely the personal contexts to sexuality. Our study responses show that each individual has unique meanings attached to their sexual experiences in later life. The majority had a positive outlook towards sexuality. This also had socio-cultural and religious connotations and varied between men and women.

Mr. T (71 years) noted:

"Every time I had a successful sexual encounter with my wife, I felt that I am still alive and that live is worth living. It made me feel like myself."

While sexuality was associated with vitality and masculinity, sexual vigor was linked to physical health among men and past marital relationships, time lived with husband/partner, loss of spouse, and companionship among women.

Mrs. L (72 years), while discussing her husband's demise, added:

"I miss him very much. He left us two years ago. I remember the times that we shared, our togetherness and how dearly I missed him when he was away. That still arouses me at times, in a better way... you know what I mean. I feel so complete..."

"Oh, it's very difficult for us you know, you cannot even imagine... It is so difficult to find a right partner among us who truly understands you, knows what you desire from them. Once he is gone, you are so, so alone. The world rarely cares for you, it never bothered about our identity, more so now that I am old."

Western literature mentions that change of partners or "second couplehood" due to divorce or widowhood to have a positive effect on sexual encounters in older people [24, 25]. Sense of freedom, sexual experimentation, openness, and attempts to meet unfulfilled desires are increased [26]. However, in our study, the widowed women preferred to remain single, either cherishing the perceived satisfaction and memories of their spouses or wanting to retain their autonomy and the social barriers to finding another suitable partner. They also found self-worth in alternative familial roles.

According to **Mrs. D (62 years):**

"It has never been difficult for me even though it's been six years that my husband passed away. Financial challenges, yes! But rather than again going through the hassles of finding a suitable partner, I am rather happy enjoying my role as a mother and grandmother."

16 of our participants felt that medical conditions, medications, and physical mobility concerns adversely affected their sexual experiences.

Mrs. S (67 years) added, *"I could hardly move. The gout was all over. Movement caused pain. How could I enjoy intimacy even at its best when it was always paining!"*

Mr. W (65 years) felt that his medication list was too long, *"Firstly there were 15 pills throughout the day, and I need to remember them. Then, most of the afternoon and evening I am drowsy and feel difficult to focus. Even if I wish to, how do I enjoy sex?"*

Expectations from partner

Relationship expectations from partners change with age. The main themes that emerged under this category were 'compassion and emotional support', 'trust in continuity of care', and 'physical closeness/intimacy'.

Existing qualitative literature has shown that the perception of sexual pleasure changes with age [5, 22, 27]. Our study further adds that our participants felt trust, compassion, closeness and emotional support to be associated with sensuality, even when actual sexual intimacy was challenging for the couple. Intimacy was more associated with safety rather than sexual pleasure through physical stimulation.

Mr. M (78 years) told: *"Things were changing. Now I am barely able to walk. She has been there beside me my whole life. We have had our own ups and downs. When you ask what sensuality means to me now, I can say 'her company'. The times when she is with me, even in silence, I feel that there is someone to take good care of me till I die. That is an immense amount of pleasure, whichever way you put it..."*

According to **Mrs. S (67 years)**: *"Our marital life hasn't been very smooth. But now after 35 years, I expect I can trust him for the rest of my life. Sex is not the same as it was years back, now it is more of closeness... in body and mind!"*

Even though the search for new relationships has been mentioned in the literature [28, 29], in our study such a theme was absent. This could be due to the social norms associated with age that expects one to mourn the loss of and remain loyal to one's spouse. Also, sexuality was limited to fantasies, visual and print media, in contrast to online dating. Digital literacy among older people is minimal in India which, together with generation stereotypes, could have contributed to this [30].

There are a number of gender differences that are worth mentioning. For men, ability to maintain an erection and ability to ejaculate was a central point of concern. However, a few also mentioned difficulties with sexual fantasies and arousal. As mentioned previously, sexual vigor was correlated with masculinity.

Mr. W (65 years) was worried, *"Sex was there. Sexual interest was there. But due to joint pains and weakness, I was too slow. It didn't feel like a 'man'. I was afraid what my wife will think about me. We have had so many good moments..."*

Mr. P (69 years) expressed shame, *"I could not even face myself. Did the decline of hormones rob me of my manhood? I even avoided speaking to her. It was shameful!"*

Although previous studies have shown that sexual dysfunction with ageing is associated with low self-esteem, negative affect, and marital discord [31, 32], our study showed that despite issues with arousal and erection, men coped with acceptance and practiced alternate forms of intimacy (foreplay: cuddling, caressing, stroking, etc.) and quality couple time. The supportive nature of relationships often compensated for such sexual difficulties. This 'buffering' effect of couples' relationships in old age has been also seen in the findings of the English Longitudinal Study on Ageing (ELSA) [33]. For five of our participants, who had pre-existing marital issues, sexual satisfaction was reduced irrespective of sexual performance.

As **Mr. F (70 years)** mentioned: *"I knew that I am not the same as before. I had even problems in turning in bed. It took me quite some time to come to terms with it. But I could — sexuality for me was different. It was no longer aggressive and hours of passion. It was much more peaceful. Hours spent together in the presence of my wife, made me happy and loved for..."*

Mrs. P (69 years) added: *"Yes we still have sex. Quite often even. Do we enjoy it? Maybe yes. But you know, the age-old scars that you have developed in marital life — it cannot really make you satisfied or provide you with pleasure no matter how intimate you are. You need that inner connection in this age, that's what matters!"*

This is in line with a British study by Hinchliff and Gott showing that sexual problems amongst older people have a negative impact on their long-standing relationships with their partners/spouses [34]. However, the transgender men in our study expressed negative attitudes towards sex, reduced expectations from partners, reluctance in search of new relationships, and acceptance of their gender identity. This was also influenced by social stigma and ageism.

Mr. N (61 years) replied, *"I won't say I have lost interest in sex. It's more like I have been oblivious to it now. Years of difficulties, abuse, and challenges in survival — I have now come to terms with what I am, my sexuality, much more than before. Just that, I miss my partner and really do not want to engage in a relationship again at this age."*

In general, our female participants were more descriptive in their responses about sexuality. All of them concluded that although the frequency of sexual activity and sexual expectations of their partners changed with age, the desire for intimacy did not. Common challenges were partner's medical issues, caregiving, lack of partner (widowhood), and social expectations.

Mrs. S (68 years) mentioned: *"It is wrong to say that I do not want to get aroused any further. However, his osteoarthritis causes a lot of pain... you know... making things difficult."*

90% of our female participants felt that they were relieved to discuss their sexual experiences, yet this was a rare opportunity.

Mrs. L (72 years) noted: *"You really expect us to talk about sex! An old woman talks about sexuality instead of spirituality and prayers — how will people around me take it?"*

In traditional societies such as India, gender roles are quite fixed and there are sexual inhibitions especially among older women [35, 36]. They are usually expected to be *"passive and subordinate"* towards their male partners. The choice of initiation is left to their spouses and fulfilling their desires is considered to be their *"obligation"*. With age, the associated expectations change, but the connotations continue to be the same. Women are expected to be supportive of, and act as caregivers to their husbands, which effectively makes their voices invisible. In an action research carried out in another developing nation, Brazil, the sexual experiences of six older women from rural settings were analyzed [37]. Obligatory sexual participation based on partner's wishes, sexual control by society, and over-importance of family expectations were predominant themes. Older women in our study expressed reduced sexual freedom as well. All our female participants agreed that this study provided them with some form of catharsis with respect to sexual experiences. They welcomed sexual fantasies and desires, unlike an earlier qualitative study from Poland where the themes among women were *"I am glad that sex does not concern me anymore"* and *"I am just happy with my memories"* [38].

Mrs. M (64 years) complained: *"We are expected to always remain supportive and good. Why is that? Because society expects us. What are our sexual needs? Nobody has asked. I am glad that this age finally someone wanted to know about my experiences!"*

The older women in our study emphasized the importance of emotional bonding in comparison with intimacy. They were accepting of the sexual challenges associated with ageing but considered intimacy important to their wellbeing. However, sexual freedom outside relationships was discouraged. The majority did not approve of the usage of aphrodisiac medication in their partners and were afraid of *"sexually unrestrained men"*. They feared that this will take off the *"feel good inner experience"* that they would rather enjoy at this age. These findings differ from a systematic review on sexuality and sexual health in older adults, suggesting that more sexual freedom and experimentation in older women is what? Common? [7]. However, disapproval of medication and considering *"aggressive sex"* to be a *"risky business"* were themes that were similar to those in our study. The body-image narrative in our participants changed from aesthetic-focused to inner peace and *"beautification of soul"*, as they felt that their partners now know them *"close enough to just stay attracted physically"*.

Mrs. F (75 years) concluded: *"Times change, we change. It mattered less to me how much physically handsome my husband was anymore. It was about closeness — how much of him do I get for myself? Do I perceive that as enough? That was what I really wanted."*

Mrs. T (65 years) mentioned, *"I do not want sexuality to be masked by medicines. Every age has its own beauty. Let us accept each other as we are and find new ways of being closed rather than depend on a pill for momentary pleasure..."*

Social norms, religion, education, financial independence and general health were other factors that influenced their sexual desires. These factors have also been found in earlier studies [9, 25, 28].

Mr. P (70 years) spoke about his beliefs, *"I have always seen my parents and grandparents move away from worldly pleasures when they aged. I considered that possibly thinking about sex at this age is bad. Somehow, even though I enjoyed sex, in some corner of my mind it did not feel right."*

Mrs. T (61 years) was worried about privacy, *"My pension was stuck, and my husband never got one. We had to depend on our children and whatever space we got in the house. Intimacy cannot occur without a relaxed space."*

The other interesting theme was caregiving and sexuality. Most women were caregivers for their male partners which led to the role transition and, hence, impaired sexual experiences. The caregiver often perceived child-like feelings for the person they cared for, the intensity of which was related to the degree of caregiving. Earlier studies have both reported sexual challenges and improved intimacy associated with caregiving [39, 40]. In our sample, most of these couples stayed alone and, due to the lack of social support, the burden associated with caregiving must have been significant.

Mrs. P (68 years) told: *"Most of my time was spent in looking after him, just like a baby. I even had to lull him to sleep and keep him calm. He would not listen to the paid caregiver. Now you tell me — how do I have sexual excitement in these circumstances! I even felt guilty!"*

Barriers and unmet needs

Sexuality is widely considered as a tabooed topic in India especially in old age [41]. Social stigma, myths related to sexuality in late life and stereotyped thoughts (both in general public and healthcare providers) formed the main barriers in our participants while discussing sexual issues. Such beliefs are internalized and perpetuated by media discourse leading to the consideration that active sexual life and ageing are mutually exclusive. The common myths included the following statements:

- *Older people are asexual*
- *People should not discuss or talk about sex in later life*

- *Spirituality and sexuality are antagonistic in older people*
- *Sexual discussions are akin to sin which deserve shame and punishment*
- *Body gets unhealthy and weak with age, thus incapable of sex*
- *One needs to be ashamed and guilty if sexual thoughts occur in old age*
- *Masturbatory practices are absent in older people*
- *Older people from the LGBTQIA+ population rarely exist*

Few participants mentioned that these myths are still present.

Mrs. S (76 years) mentioned: *"Why do you even ask? Who expects us to talk about sex in this age! Isn't it a heinous crime — I cannot even desire to be with my husband in private"?*

Mr. M (67 years) commented: *"Age is a crime, you know. Suddenly everything is expected to change. As if the person inside me has died! I have even heard words like degenerate and pervert if heard speaking sexual terms. Why — have I lost the right?"*

These quotes also demonstrate ageism. The recently released GLOBAL REPORT ON AGEISM by the WHO highlights that one in three adults worldwide share ageist attitudes [42]; indeed, overlap with other forms of discrimination is common. According to the Report, *"Ageism often intersects and interacts with other forms of stereotypes, prejudice and discrimination, including ableism, sexism and racism. Multiple intersecting forms of bias compound disadvantage and make the effects of ageism on individuals' health and wellbeing even worse"* [42]. Evidently, our participants shared that ageist-discriminatory attitudes as discussing sexual experiences with family and healthcare providers was challenging for them. An Indian epidemiological study in 2015 showed a concerning myth that sexuality is only for reproductive purposes and sexuality is "wrong in the old". Negative reactions related to sexuality in old age were also noted by the family members in this study [43].

In light if this, participants expressed that there is a lack of understanding, audience, and sensitivity to their sexual issues among healthcare providers. It was also associated with self-stigma as many considered sexuality no longer relevant to their lives and not an integral component of health. Hence, these issues were not discussed during physician consultations. Such beliefs have been discussed in earlier studies [39, 44, 45]. The common reasons for visiting doctors were sexual dysfunction, marital discord, and lack of perceived satisfaction, but these rarely formed the primary reason and were less frequently expressed in reality. 50% of the sample also mentioned lack of guidance if they wanted to know how to improve their sexual health.

Mr. T (72 years) replied: *"I don't even understand how to discuss sex with my doctors at this age! Every time I plan to ask him about certain related issues, I feel so deeply ashamed. I somehow divert the topic. Till date I am waiting (...)."*

Mrs. P (65 years) added: *"My doctor was just dismissive. She said that this age I should go for pilgrimage and read scriptures. Sexuality should be the last thing on my list. I felt offended but you know that's what specially a woman in our society is expected to..."*

Mrs. S (63 years) noted: *"You do not say, and they never ask. My diabetes and gout were greater problems, and so I did not have a right to discuss sex at this age!"*

Feelings of shame and embarrassment were common, as it is expected that one should not discuss sexuality and erotic content at this age [46, 47]. As mentioned previously, this resulted in greater stigmatization amongst women and the LGBTQIA+ community. The latter is nearly invisible in the popular media and health discourse in India [41]. They share the dual brunt of ageism and gender-based discrimination. This can be addressed by putting together sexual health and general issues related to wellbeing, training in sexual health among physicians, and continuous and holistic care. Schaller et al. [48] performed a qualitative study on *"how older adults experience talking about sexual issues with healthcare personnel"* and defined that Communication dynamics, physician attitudes, knowledge and competence, understanding of sexuality and finally structural conditions influenced help-seeking patterns related to sexual problems among the participants. The authors recommended culture-sensitive attitudes and further research into late-life sexuality, which it was felt could sensitize healthcare providers at all levels [48].

Transgender individuals faced particular difficulties with help-seeking and the literature is nearly absent of any discussion in relation to their sexuality in India. A recent qualitative study during COVID-19 showed impaired psychosexual health, increased othering and multifaceted survival threats in the older LGBTQIA+ community [49]. Their sexual rights are also neglected. Due to other healthcare and social priorities, sexual needs are often neglected in this community.

According to **Mr. F (68 years**), a transgender male, *"People do not even ask us about how we are living — sex is the least that we expect! Even if we are able to make it to the doctor's chamber someday, there are so many other pressing challenges to talk about..."*

Overarching themes

Certain themes emerged throughout the analysis and were considered to represent overarching categories.

These were central to the sexual experiences and expectations of the older persons in our study. These categories are *"sexuality as a mode of resilience", "emotional stability and 'aging well' as attributes of sexual pleasure"*, and *"lack of awareness about sexual rights."* Positive sexual perceptions were associated with better coping in adverse life situations while emotional bonding, better communication, and healthy ageing (with lesser focus on age-related bodily changes) influenced sexual pleasure. Also, the participants largely lacked awareness about sexual and reproductive rights. "Emotional stability as an attribute of sexual pleasure" has already been discussed, so here we will discuss the other two categories.

Awareness about sexual rights was largely absent in our sample.

Mr. N (61 years) was ignorant of such terms, *"Are you sure such rights exist... they sound funny. At this age, do I really deserve them?"*

Mrs. F (60 years) was surprised as well, *"You mean to say that I can approach the court if such rights are not granted. It sounds so surreal that too being a senior citizen. Please tell me more about it."*

Sexual rights not only encompass prevention and treatment of sexual disorders or dysfunctions but also autonomy, dignity, respect and pleasure related to sexuality and sexual relationships [50]. Various international organizations consider them as fundamental human rights which are necessary for overall wellbeing. Human rights of older people are threatened globally leading to marginalization, sidelining from health services and elder abuse. It is thus important that based on the World Association for Sexual Health (WAS), irrespective of age, individuals stay free from sexual coercion and sexual violence, enjoy freedom of sexual expressions and privacy, sexual justice (legal protection in case of any sexual right deprivation or dispute) and have safe sexual experiences [51]. Hopefully, an international UN Convention for the Rights of Older People, that many organizations are globally in support of, may serve as a tool to protect the sexual and reproductive rights of older people [52].

Finally, sexuality was considered to be resilience-promoting factor among the participants. It helped them in overcoming negative mood states and interpersonal discords. Nearly all the participants mentioned that although sore sexual act was important, *"emotional connection" and "intimacy"* played a crucial role in building resilience.

Mr. S (69 years) said: *"It's not really about your penis or orgasm you know...it's different. The closeness matters. The arousal, feeling good, time spent with my wife makes it so easier even when I am under a lot of stress."*

Mrs. T (71 years) added: *"Sex is just one way of describing it. We were no longer having intercourse. But his presence mattered. This is a way of sexuality, at least for me. This is my best stress-buster at this age."*

There are few Indian studies in this regard. Most research on positivism and resilience in older adults have not factored in sexual health. Popular recommendations suggest seclusion and alternate leisure activities for self-esteem in old age [53]. Alternatively, in the Western literature healthy ageing is associated with better sex life and self-growth. This is further correlated with better self-confidence and freedom from other [46, 54]. Positive sexual expression and better sexual agency have been linked with positive emotions in the Australian "baby boomer generation" study [25, 55]. Psychosocial resilience helps one navigate through stress and is vital for healthy ageing [56]. Since this is a qualitative study, we cannot form any definitive link between sexual health and resilience but our participant experiences offer insights for exploring the link. Though this link has been studied in sexual minorities and individuals living with HIV, this warrants further research in older people, especially during the present times of COVID crisis.

Strengths and Limitations

To the best of our knowledge, this is the first study to explore experiences of sex and sexuality in older people of India. In spite of the challenges related to social stigma and taboo about the topic, we managed to get a decent sample and all participants provided rich detail of their perceptions. The semi-structured interview guide was framed after a successful pilot which helped elaborate the participant experiences. Another strength of this study is related to its rigorous methodology and measures taken to ensure trustworthiness.

On the other hand, our study has several limitations. Firstly, similar to any other qualitative study, generalized conclusions are rather impossible. However, generalization was not the aim and our findings themselves suggest that sexuality can have unique “personal relevance” to each participant. Secondly, even though we tried to secure a heterogenous sample, most participants were educated, married and from urban/semi-urban areas. Also, representation from the LGBTQIA+ community was limited. Thirdly, adopting a purposive sampling comes with a risk of subjective bias, which we tried to address through bracketing and triangulation. Further, our participants had lesser medical burden which is often exception rather than usual in old age. None of our participants resided in nursing homes or senior care facilities, which form a large proportion of old age population. Sexuality dynamics can be very different in these places due to a number of factors including lack of partners, reduced privacy, overcrowding, personal comfort, etc. Due to inclusive nature of the society in India and stigma related to the subject of our study, we could not get participants from senior living facilities. Lastly, some linguistic nuances may have been missed in the translation-back translation used in our study.

CONCLUSION

To our knowledge, this is the first study from India, exploring sexual experiences in older people. Sexual and reproductive health rights are an integral part of human rights, and older adults cannot be an exception. Our findings show that older people do enjoy sexuality, retain their sexual desire and interest, even though the forms and intricacies of expression vary. Emotional closeness and companionship were the central core of intimacy, whereas there were several gender differences. Societal myths related to late-life sexuality, misinformation, media portrayals, ageism and inadequate audience in the health sector serve as barriers for them to voice out challenges in this area. According to the UN Decade of Healthy Ageing (2021–2030) [57], physicians and policy makers need to be sensitive towards this neglected dimension of sexual health because it is intricately linked to successful ageing. Sexual minorities suffer from additional stigma which needs to be addressed. Elucidation and education in the healthcare professionals and media are warranted to elicit a general better understanding of sexual desires and their diversity in later life. Older adult’s sexual needs should be recognized, respected and implemented in healthcare training, services, research and policy interventions. Physicians irrespective of their specialty need to be trained in protecting sexual rights among older people free of discrimination. Such training needs to be implemented from early days of medical curriculum. Our participants also linked sexuality with resilience and positivity, and it was considered to be a *“powerful tool to better couple relationships.”* This remains a subject for further research, especially if sexuality can mitigate loneliness, the socio-cultural influences and differences in sexual experiences in older people across gender and orientations. Considering sexual wellbeing as a natural part of health, our research provides a preliminary yet firm background to initiate academic and clinical discourse on sexual needs, challenges and experiences of older people.

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A Comparison of Regional Brain Volumes in Older Adults With and Without History of COVID-19

Региональные объемы мозга у пожилых людей с наличием и отсутствием COVID-19 в анамнезе

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Original Research

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ABSTRACT

BACKGROUND: Recent studies have shown that SARS-CoV-2 can have neuropsychiatric consequences and has the ability to penetrate the blood-brain barrier. If SARS-CoV-2 has a specific route of entry into the brain, it may leave imprints in the form of specific changes in brain morphology. Older individuals are most vulnerable to the neuropsychiatric COVID-19 complications. This study aims to compare regional brain volumes in older adults individuals with and without COVID-19 history (COVID+ and COVID-, respectively).

METHODS: Individuals over 65 years old who applied for treatment to the Memory Clinic (Mental-Health Clinic No. 1 named after N.A. Alexeev, Moscow, Russia) were assessed between October 2020 and April 2021. Their COVID-19 history was determined by the self-report and COVID-19 certificate. Individuals with severe neuropsychiatric or acute or severe chronic somatic or infectious disease and those taking medications potentially affecting cognitive functioning were excluded. All participants underwent MRI examinations followed by image segmentation and morphometric quantitative analysis. Regional brain volumes were compared in COVID+ and COVID- people.

RESULTS: 207 participants were included in the study. The COVID+ group consisted of 24 participants. The comparison between groups revealed statistically significant differences in left amygdala area (median 1199.3 mm^3 in COVID+ vs. 1263.7 mm^3 in COVID-) and right postcentral gyrus volumes (median 8055.5 mm^3 in COVID+ vs. 8434.0 mm^3 in COVID-). Then case-control analysis was performed in individuals matched for gender, age and common somatic causes of structural brain changes (hypertension and/or diabetes mellitus type 2) for 22 subjects in each group. Statistically significant differences in regional brain volumes between groups were absent.

CONCLUSION: We did not find strong evidence for any regional brain volumes changes in people older than 65 years with a history of COVID-19 in comparison to those without history of COVID-19. Though, given study limitations, these results cannot be generalized to other people who recovered from COVID-19.

АННОТАЦИЯ

ВВЕДЕНИЕ: В недавних исследованиях было показано, что SARS-CoV-2 может иметь нейропсихиатрические последствия и обладает способностью проникать через гемато-энцефалический барьер. Если коронавирус имеет специфический путь проникновения в головной мозг, то это может оставлять отпечатки в виде характерных изменений морфологии мозга. Лица старшей возрастной группы являются наиболее уязвимой популяцией в отношении последствий COVID-19. Данное исследование нацелено на сравнение морфологии головного мозга у лиц пожилого возраста, перенесших (COVID+) и не перенесших (COVID-) новую коронавирусную инфекцию.

МЕТОДЫ: В период с октября 2020 по апрель 2021 года отбирались лица старше 65 лет, обратившиеся в Клинику памяти (Москва), у которых путем анкетирования определялся статус перенесенного COVID-19. Не включались лица, имеющие тяжелые нейропсихиатрические и соматические заболевания и принимающие лекарственную терапию, потенциально сказывающиеся на когнитивном функционировании. Всем участникам проведено МРТ-обследование с последующей сегментацией изображений и количественным анализом морфометрических данных. Сравнивались региональные объемы головного мозга.

РЕЗУЛЬТАТЫ: 207 участников включено в исследование. COVID+ группу составили 24 участника, из которых 4 были госпитализированы вследствие COVID-19. Сравнение выявило наличие статистически значимых различий объемов левого миндалевидного тела (медиана 1199.3 мм^3 у COVID+ vs. 1263.7 мм^3 у COVID-, U=1839.0, p=0,044, тест Манна-Уитни) и правой постцентральной извилины (медиана 8055.5 мм^3 у COVID+ vs. 8434.0 мм^3 у COVID-, U=1821.5, p=0,045, тест Манна-Уитни). При проведении анализа методом случай-контроль у лиц, сопоставленных по полу, возрасту и распространенным соматическим причинам структурных изменений головного мозга, не было выявлено статистически значимых различий между COVID+ и COVID- группами.

ЗАКЛЮЧЕНИЕ: Мы не обнаружили значимых свидетельств изменений региональных объемов головного мозга у лиц, перенесших и не перенесших COVID-19. Однако, учитывая имеющиеся ограничения исследования, эти результаты не могут быть перенесены на всех пациентов после COVID-19.

Keywords: *COVID-19; SARS-CoV-2; elderly people; MRI; brain morphology; regional brain volumes*
Ключевые слова: *COVID-19; SARS-CoV-2; пожилые люди; МРТ; морфология мозга; региональные объемы мозга*

INTRODUCTION

Studies have shown that advanced age is one of the greatest risk factors for higher severity and worse outcome of COVID-19 [1–4] with neurological and psychiatric symptoms affecting 33–62% of patients within six months of recovery [5]. Some researchers suggest that SARS-CoV-2 may have an ability to invade the brain via the olfactory tract, circumventricular organs, leaky blood-brain barrier due to inflammation or direct damage of brain vascular endothelium or with migrating immune cells [6].

If specific routes of SARS-CoV-2 to enter the brain do exist than it may be associated with the distinct patterns of brain morphology changes. A recent article systematically reviewed brain imaging case series, case-control and cohort studies in patients with COVID-19 and found that alterations associated with COVID-19 predominated in the olfactory brain network, limbic and prefrontal structures [7]. About half of these studies used only visual evaluation of MRI scans, and among studies that used image statistical processing approach there were none that used matched control of age, gender and comorbidity (hypertension and/or diabetes mellitus type 2) in brain morphology analysis in older population affected and non-affected by COVID-19.

Moreover, none of these studies evaluated brain changes specifically in older (65+ years old) population. Therefore, case-control study of MRI scans using image statistical processing approach and matched case-control analysis of elderly individuals with and without COVID-19 history is relevant.

Since October 2020 a longitudinal cohort study of patients with mild cognitive impairment (MCI) compared to healthy control was initiated in Psychiatric clinical hospital No 1 (Moscow, Russia) to identify unmet needs of MCI patients during COVID-19 pandemic. One of the aims of this study is a MRI-morphometry of brain scans in patients with mild cognitive impairment (MCI) and healthy control with and without reported COVID-19 history.

Our research question was: are there specific brain alterations in older people with reported history of COVID-19 infection compared to those without COVID-19 history?

METHODS

Study population

This study is a part of multidisciplinary project 'Impact of the COVID-19 pandemic on the mental health of the elderly' and is supported with grant of RFFI 20-04-60546. Individuals over 65 years old were eligible in the study. The study participants were selected among those who attended the Memory Clinic to treat cognitive impairment or at the outpatient unit of Moscow outpatient clinic No 152 (both are the branches of the Mental-Health Clinic No. 1 named after N.A. Alexeev) to treat somatic disorders other than acute or severe chronic somatic or infectious disease. Individuals with contraindications to MRI, with a history of dementia, Parkinson's disease, Huntington's disease, psychotic or other severe psychiatric disorders known to affect cognitive functioning, mood and anxiety disorders with onset before 45 years old, exacerbations or severe forms of chronic somatic diseases were not included. Also, people taking drugs with known negative or positive effect on cognitive functions were not allowed to participate in the study (see Supplements for a full list of exclusion criteria). The COVID-19 history was determined by the self-report and COVID-19 certificate. Current COVID-19 status was not checked with polymerase chain reaction rest (PCR) and none of participants were vaccinated as the study period ended before national vaccination campaign had been initiated.

Study design

This one-year study has longitudinal observational cohort design. Enrollment of subjects was performed 4th October 2020 to 30th April 2021. All participants underwent clinical examination by a psychiatrist and collection of medical history using checklist designed specifically for this study, including a checklist of individually significant neuropsychiatric and cognitive symptoms. Cognitive performance was assessed using Mini-mental state examination scale (MMSE) [8] and Montreal cognitive assessment scale (MoCA) [9]. After examination MRI-scanning was performed.

MRI scanning and Image processing

A MRI scanner (Toshiba, 1.5 Tl) at the Mental-health Clinic No1 Named After N.A. Alexeev was used to obtain structural MRI scans. The structural study was performed using a Sg 3d T1-weighted sequence (TR=12 ms, TE=5 ms, 200 sagittal slices, FOV 256 mm, FA 180, TI=300 ms, voxel size 1x1x1 mm^3, average 2).

Image processing and segmentation were performed using Freesurfer v6.0 software package and morphological indices (thickness and volume of gray matter, volume of white matter, gyrification index, volume of gray matter by subcortical structures, etc.) were derived. Regional brain volumes (gray matter and white matter volumes) were selected for the purpose of this work.

FreeView imager (v7.1.0) was used to visually assess segmentation quality. Reproducibility of results was ensured by means of quality control of structural MRI (T1) images based on mriqc package and Image Quality Metrics (IQM) [10].

All calculations were performed on a cluster at Skoltech (Skolkovo Institute of Science and Technology), consisting of two computing units of the following configuration each: CPU: Intel Xeon 6 cores; RAM 64 GB; Storage: 1 TB GPU: 3 NVIDIA GeForce GTX 1080 Ti with 3584 Cuda cores, Memory capacity 11 GB, frequency 1500 MHz.

Statistical processing

Database was extracted on 9 September 2021. The primary endpoint was finding the differences in MRI volumes between those who experienced COVID-19 (COVID+) and those who had not (COVID-) in a whole study population. Mann-Whitney test was used to compare continuous variables while participant's distribution by the categorical variables between groups was performed using Fisher exact test. All regional brain volumes were n-1 normalized to standardize the variables using the unbiased standard deviation. Group profiles of brain volumes means and medians of received z-scores were than additionally visually analyzed using parallel coordinates plots. In all statistical tests two-tails $p < 0.05$ considered as statistically significant. We didn't use multiple p correction because it would preclude finding of any significant differences given large number of regions (109 regions) to compare highly variable volumes.

To compare regional brain volumes, we also used case-control approach in subpopulations of COVID+ and COVID- groups matched by age, gender and history of hypertension and type II diabetes. The following strategy was used to search for matched subjects: exact matches on gender, hypertension stage and type II diabetes and fuzzy search for age within 2 years range.

Statistical processing was performed using Addinsoft (2022), XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com/en.

Ethics

The study was conducted according to Helsinki declaration and Good Clinical Practice (GCP) principles. It was approved by the local Ethical Committee of State Budgetary Institution of Health Care "Research Clinical Institute of Otorhinolaryngology named after L.I. Sverzhevsky" of the Department of Health of the City of Moscow (Protocol №5 from 20.09.20). All study participants signed informed consent.

RESULTS

Study population

Overall, 207 participants had processed Visit 1 MRI scan information in the study database as of 9th September 2021. Among them 24 indicated that they had a history of COVID-19 (either outpatient or hospitalization) before Visit 1 of the study (before October, 2020), with 4 of 24 (16.7%) were hospitalized with COVID-19. Thus, 24 participants were categorized in COVID+ group and *n*=183 in COVID- group. Their socio-demographic and medical characteristics are summarized in the Table 1.

Table 1. Clinical and socio-demographic characteristics of study population

	Valid n	COVID- (*n*=183)	COVID+ (*n*=24)	Test Statistic
Age, median, 1st and 3rd quantile	207	71 (66, 77)	71 (68.4, 77.0)	U=1973, *p*=0.418*
Gender: Male, *n* (%)	207	33 (18.0%)	3 (12.5%)	*p*=0.774**
Education, *n* (%)	205			*p*=0.539**
College		52 (28.7%)	8 (33.3%)	
School		15 (8.3%)	3 (12.5%)	
University		114 (63.0%)	13 (54.2%)	
Work type in the life: Intellectual, *n* (%)	200	144 (81.8%)	21 (87.5%)	*p*=0.774**
Still working, *n* (%)	200	6 (3.4%)	2 (8.3%)	*p*=0.247**
Family: Yes, *n* (%)	203	125 (69.8%)	18 (75.0%)	*p*=0.812**
Self-efficient: Yes, *n* (%)	202	135 (75.8%)	18 (75.0%)	*p*=1.000**
Hobby: Yes, *n* (%)	207	132 (72.1%)	18 (75.0%)	*p*=1.000**
Somatic health				
Any chronic disease: Yes, *n* (%)	207	166 (90.7%)	22 (91.7%)	*p*=1.000**
Diabetes type II: Yes, *n* (%)	204	24 (13.3%)	5 (20.8%)	*p*=0.350**
Hypertension, *n* (%)	207			*p*=0.459**
1 stage		46 (25.1%)	5 (20.8%)	
2 stage		58 (31.7%)	9 (37.5%)	
3 stage		16 (8.7%)	4 (16.7%)	
No		63 (34.4%)	6 (25.0%)	

Table 1. Clinical and socio-demographic characteristics of study population (continued)

	Valid n	COVID- (*n*=183)	COVID+ (*n*=24)	Test Statistic
Ischemic heart disease: Yes, *n* (%)	204	51 (28.3%)	7 (29.2%)	*p*=1.000**
Myocardial infarction history: Yes, *n* (%)	207	6 (3.3%)	1 (4.2%)	*p*= 0.584**
Oncology history: Yes, *n* (%)	204	27 (15.0%)	7 (29.2%)	*p*=0.087**
Obesity: Yes, *n* (%)	204	38 (21.1%)	4 (16.7%)	*p*=0.790**
Takes any antihypertensive drug: Yes, *n* (%)	204	97 (53.9%)	14 (58.3%)	*p*=0.828**
Takes any antidiabetic drug: Yes, *n* (%)	204	7 (3.9%)	2 (8.3%)	*p*=0.286**
Takes any anticoagulant: Yes, *n* (%)	204	14 (7.8%)	1 (4.2%)	*p*=1.000**
Takes aspirin: Yes, *n* (%)	204	44 (24.4%)	10 (41.7%)	*p*=0.086**
Mental health				
MMSE total score, median, 1st and 3rd quantile	204	27.0 (26.0, 28.0)	28.0 (27.0, 29.0)	U=1719, *p*=0.099*
MoCA total score, median, 1st and 3rd quantile	204	24.0 (21.0, 26.0)	25.0 (22.4, 27.0)	U=1789, *p*=0.170*
Any affective disorder history: Yes, *n* (%)***	204	23 (12.8%)	4 (16.7%)	*p*=0.533**
Any anxiety disorder history: Yes, *n* (%)***	204	5 (2.8%)	3 (12.5%)	*p*=0.054**
OCD: Yes, *n* (%)***	204	1 (0.6%)	0 (0.0%)	*p*=1.000**
Significant symptoms				
Apathy: Yes, *n* (%)	203	16 (8.9%)	4 (16.7%)	*p*=0.267**
Headache: yes, *n* (%)	203	47 (26.3%)	1 (4.2%)	*p*=0.019**
Vertigo, dizziness: Yes, *n* (%)	203	39 (21.8%)	5 (20.8%)	*p*=1.000**
Sleep: Yes, *n* (%)	203	89 (49.7%)	13 (54.2%)	*p*=0.828**
Poor attention, concentration: Yes, *n* (%)	203	41 (22.9%)	7 (29.2%)	*p*=0.609**
Inaccurate movements: Yes, *n* (%)	203	15 (8.4%)	1 (4.2%)	*p*=0.699**
Fatigue, retardation: Yes, *n* (%)	203	55 (30.7%)	9 (37.5%)	*p*=0.492**
Hypothymia: Yes, *n* (%)	203	26 (14.5%)	2 (8.3%)	*p*=0.541**
Gastro-intestinal: Yes, *n* (%)	203	38 (21.2%)	3 (12.5%)	*p*=0.423**
Irritability: Yes, *n* (%)	203	37 (20.7%)	8 (33.3%)	*p*=0.190**
Affective liability: Yes, *n* (%)	203	45 (25.1%)	5 (20.8%)	*p*=0.803**
Heart palpitations: Yes, *n* (%)	203	26 (14.5%)	6 (25.0%)	*p*=0.229**
Weakness in legs: Yes, *n* (%)	203	39 (21.8%)	6 (25.0%)	*p*=0.794**
Anxiety: Yes, *n* (%)	203	38 (21.2%)	5 (20.8%)	*p*=1.000**
Spatial orientation: Yes, *n* (%)	203	20 (11.1%)	2 (8.3%)	*p*=1.000**
Memory fixation: Yes, *n* (%)	203	101 (56.4%)	15 (62.5%)	*p*=0.663**
Calculation: Yes, *n* (%)	203	44 (24.6%)	5 (20.8%)	*p*=0.804**
Tinnitus: Yes, *n* (%)	203	44 (24.6%)	8 (33.3%)	*p*=0.454**

Note: Valid n — number of non-missing value. * — Mann-Whitney test. ** — Fisher exact test. *** — With onset after 45-year-old.

Matching for the age (fuzzy matching ±2 years), gender (exact match), hypertension stage (exact match) and history of type II diabetes (exact match) revealed 22 matched pairs of participants leaving 2 COVID+ participants without match. These characteristics are depicted in the Table 2.

In both instances of comparison between COVID+ and COVID- subjects (Tables 1 and 2) there were no significant differences on most of variables. Most of the participants were women, retired, with the background of higher education. More than two thirds of them lived with their families and described themselves as self-efficient

Table 2. Clinical and socio-demographic characteristics of study subpopulations matched by age, gender, hypertension stage and type II diabetes history

	Valid n	COVID- (*n*=22)	COVID+ (*n*=22)	Test Statistic
Age, median, 1st and 3rd quantile	44	71,5 (68; 75,8)	71 (68,3; 77)	U=238,5, *p*=0,953*
Gender: Male, *n* (%)	44	2 (9,10%)	2 (9,10%)	*p*=1,000**
Education, *n* (%)	44			*p*=0,555**
College		5 (22,70%)	8 (36,40%)	
School		2 (9,10%)	3 (13,60%)	
University		15 (68,20%)	11 (50,00%)	
Work type in the life: Intellectual, *n* (%)	44	17 (81,00%)	19 (86,40%)	*p*=0,698**
Still working, *n* (%)	44	1 (4,50%)	1 (4,50%)	*p*=1,000**
Family: Yes, *n* (%)	44	11 (50,00%)	17 (77,30%)	*p*=0,116**
Self-efficient: Yes, *n* (%)	44	18 (81,80%)	16 (72,70%)	*p*=0,721**
Hobby: Yes, *n* (%)	44	132 (72.1%)	18 (75.0%)	*p*=1.000**
Somatic health				
Any chronic disease: Yes, *n* (%)	44	22 (100,00%)	20 (90,90%)	*p*=0,488**
Diabetes type II: Yes, *n* (%)	44	3 (13,60%)	3 (13,60%)	*p*=1,000**
Hypertension, *n* (%)	44			*p*=1,000**
1 stage		4 (18,20%)	4 (18,20%)	
2 stage		9 (40,90%)	9 (40,90%)	
3 stage		3 (13,60%)	3 (13,60%)	
No		6 (27,30%)	6 (27,30%)	
Ischemic heart disease: Yes, *n* (%)	44	4 (18,20%)	5 (22,70%)	*p*=1,000**
Myocardial infarction history: Yes, *n* (%)	44	0 (0,00%)	1 (4,50%)	*p*=1,000**
Oncology history: Yes, *n* (%)	44	6 (27,30%)	6 (27,30%)	*p*=1,000**
Obesity: Yes, *n* (%)	44	5 (22,70%)	4 (18,20%)	*p*=1,000**
Takes any antihypertensive drug: Yes, *n* (%)	44	14 (63,60%)	12 (54,50%)	*p*=0,760**
Takes any antidiabetic drug: Yes, *n* (%)	44	0 (0,00%)	1 (4,50%)	*p*=1,000**
Takes any anticoagulant: Yes, *n* (%)	44	2 (9,10%)	1 (4,50%)	*p*=1,000**
Takes aspirin: Yes, *n* (%)	44	6 (27,30%)	8 (36,40%)	*p*=0,747**
Mental health				
MMSE total score, median, 1st and 3rd quantile	44	27 (26; 28)	27,5 (27; 29)	U=183,5, *p*=0,170*
MoCA total score, median, 1st and 3rd quantile	44	25 (21; 27)	25 (23; 27)	U=221, *p*=0,843*
Any affective disorder history: Yes, *n* (%)	44	2 (9,10%)	3 (13,60%)	*p*=1,000**
Any anxiety disorder history: Yes, *n* (%)	44	0 (0%)	3 (13,60%)	*p*=0,233**
OCD: Yes, *n* (%)	44	0	0	
Significant symptoms				
Apathy: Yes, *n* (%)	44	2 (9,10%)	4 (18,20%)	*p*=0,664**
Headache: yes, *n* (%)	44	9 (40,90%)	1 (4,50%)	*p*=0,009**
Vertigo, dizziness: Yes, *n* (%)	44	8 (36,40%)	5 (22,70%)	*p*=0,510**
Sleep: Yes, *n* (%)	44	13 (59,10%)	12 (54,50%)	*p*=1,000**
Poor attention, concentration: Yes, *n* (%)	44	3 (13,60%)	7 (31,80%)	*p*=0,281**
Inaccurate movements: Yes, *n* (%)	44	1 (4,50%)	1 (4,50%)	*p*=1,000**

Table 2. Clinical and socio-demographic characteristics of study subpopulations matched by age, gender, hypertension stage and type II diabetes history (continued)

	Valid n	COVID- (*n*=22)	COVID+ (*n*=22)	Test Statistic
Fatigue, retardation: Yes, *n* (%)	44	5 (22,70%)	9 (40,90%)	*p*=0,332**
Hypothymia: Yes, *n* (%)	44	4 (18,20%)	2 (9,10%)	*p*=0,664**
Gastro-intestinal: Yes, *n* (%)	44	5 (22,70%)	3 (13,60%)	*p*=0,698**
Irritability: Yes, *n* (%)	44	6 (27,30%)	7 (31,80%)	*p*=1,000**
Affective liability: Yes, *n* (%)	44	6 (27,30%)	5 (22,70%)	*p*=1,000**
Heart palpitations: Yes, *n* (%)	44	3 (13,60%)	5 (22,70%)	*p*=0,698**
Weakness in legs: Yes, *n* (%)	44	5 (22,70%)	5 (22,70%)	*p*=1,000**
Anxiety: Yes, *n* (%)	44	6 (27,30%)	5 (22,70%)	*p*=1,000**
Spatial orientation: Yes, *n* (%)	44	2 (9,10%)	2 (9,10%)	*p*=1,000**
Memory fixation: Yes, *n* (%)	44	13 (59,10%)	15 (68,20%)	*p*=0,755**
Calculation: Yes, *n* (%)	44	4 (18,20%)	4 (18,20%)	*p*=1,000**
Tinnitus: Yes, *n* (%)	44	5 (22,70%)	6 (27,30%)	*p*=1,000**

Note: Valid n — number of non-missing value. * — Mann-Whitney test. ** — Fisher exact test.

in most life areas. Somatic disorders had generally equal distribution between groups and prevalent (more than 90% had any chronic medical condition). Mental disorders and individually significant symptoms report (yes / no in a specific checklist, Table 1 and 2) were equally distributed except headaches (significantly more frequent in the COVID- group). Cognitive status (total scores on MMSE and MoCA) was similar in both groups.

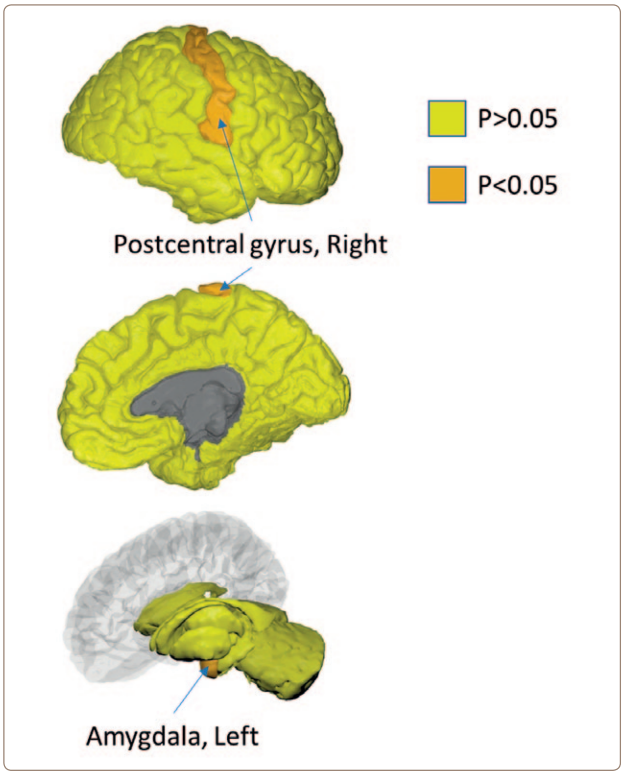

Figure 1. Significant differences between COVID+ and COVID- groups on regional brain volumes (Mann-Whitney test) in whole study population (*n*=207).

Both MMSE and MoCA total scores in all subjects (*n*=207) showed a significant weak correlation with total brain volume (Spearman R=0.23, *p*=0.001 and Spearman R=0.20, *p*=0.004, respectively) and cerebrospinal fluid (CSF) total volume (Spearman R=-0.23, *p* <0.001 and Spearman R=-0.27, *p* <0.001, respectively).

Regional brain volumes in COVID+ and COVID- groups

Comparison of brain regional volumes in whole study population (*n*=207) revealed differences only in two regions: right postcentral gyrus (median 8055.5 mm^3 in COVID+ vs. 8434.0 mm^3 in COVID-, U=1821.5, *p*=0.045, Mann-Whitney test) and left amygdala (median 1199.3 mm^3 in COVID+ vs. 1263.7 mm^3 in COVID-, U=1839.0, *p*=0.044, Mann-Whitney test) (Figure 1).

Detailed statistical results can be found in Supplementary 1.

Though, comparison of matched (age, gender and medical conditions) subpopulations (n=44) did not find any significant differences in regional brain volumes (Supplementary 2).

Parallel coordinate plots of normalized (n-1) MRI regional volumes are depicted on the Figure 2.

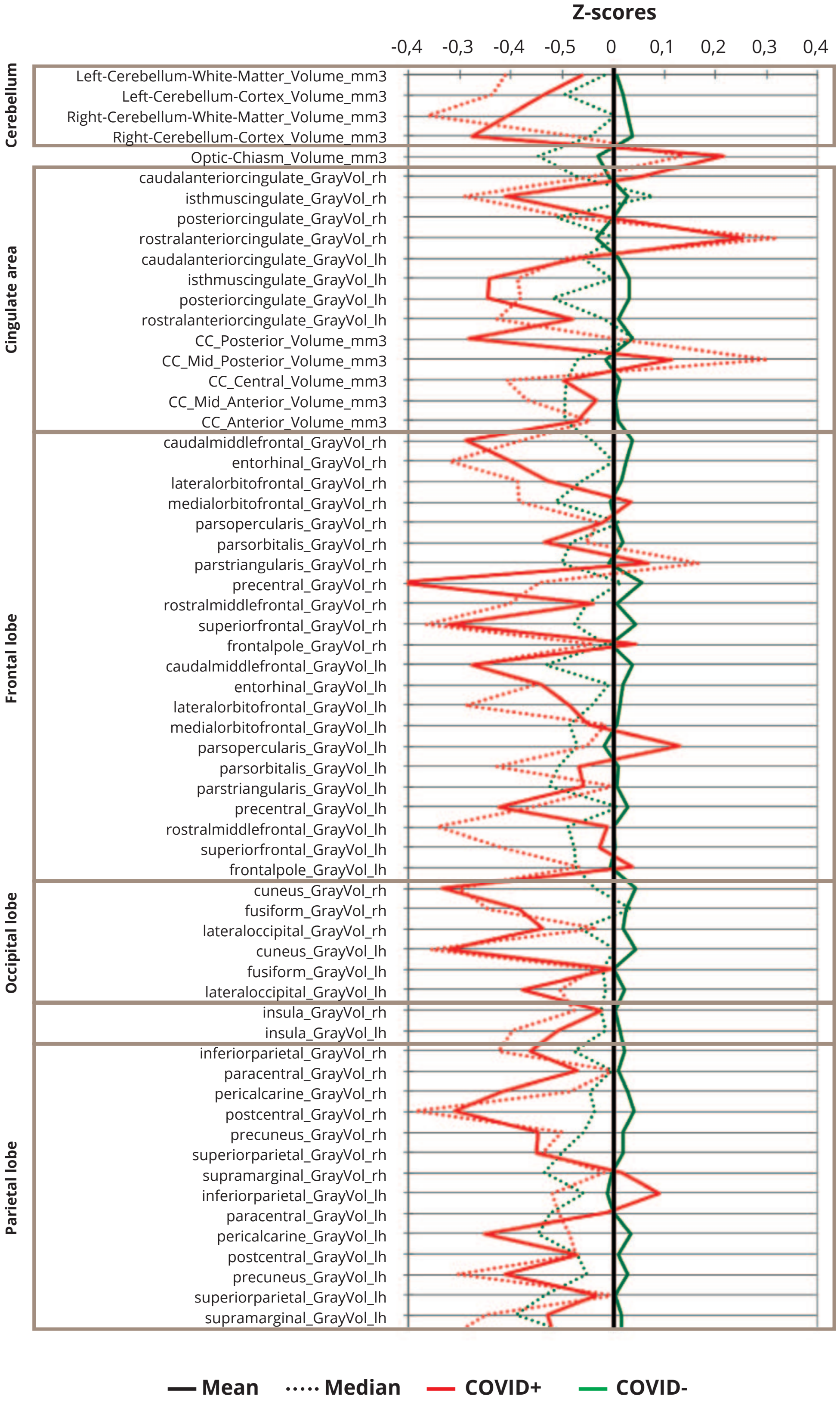

Figure 2. Standardized brain volumes profiles in COVID+ and COVID- participants (*n*=207).

Note: All means (solid line) or medians (dashed line) of residuals of regional brain volumes in both COVID+ (red) and COVID- (green) participants were within 1 standard deviation from mean values.

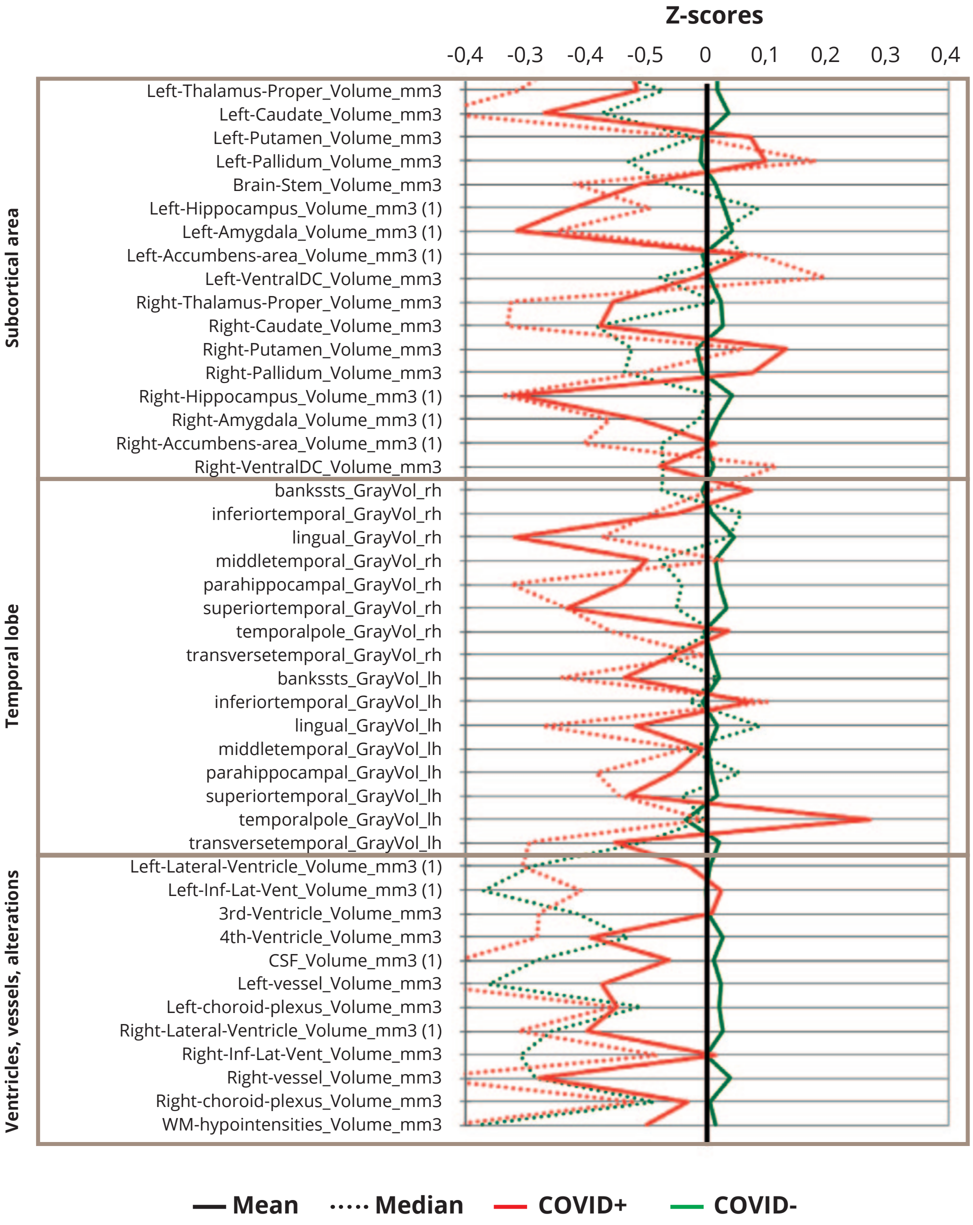

Figure 2. Standardized brain volumes profiles in COVID+ and COVID- participants (*n*=207) (continued).

Note: All means (solid line) or medians (dashed line) of residuals of regional brain volumes in both COVID+ (red) and COVID- (green) participants were within 1 standard deviation from mean values.

None of means or medians of z-scores exceed 1, reflecting that there were no differences in regional brain volumes larger than one standard deviation of study population means, though, generally most of z-scores are slightly decreased in COVID+ against COVID- subjects.

DISCUSSION

Our study revealed differences in regional brain volumes between COVID+ and COVID- groups: right postcentral gyrus gray matter and left amygdala volumes found to be significantly lower in older people who had a history of COVID-19. These differences were not supported with any differences in reporting of personally meaningful neurocognitive and neuropsychiatric symptoms, including anxiety and somatic complaints with except of headaches that were more prevalent in COVID- group.

Olfactory tract projections are considered as a possible gateway of SARS-CoV-2 invasion into the brain. Amygdala is a part of limbic system that receives projections from olfactory bulbs [11,12]. According to recent research [13] a comparison of MRI scans before and after COVID-19 found that patients after COVID-19 had greater grey matter loss in the central nucleus of the amygdala than those who had no history of COVID-19. Another study [14] found hypometabolism in the right temporal lobe, including amygdala in patients with long COVID-19. Though, in these studies changes in amygdala were accompanied with alterations in other brain regions, including central olfactory complex (piriform cortex, enthorhinal cortex) and secondary olfactory areas (hippocampus, thalamus, orbitofrontal cortex) [7, 13, 14].

Contrary, in our study we did not find significant morphological changes in other brain regions. One possible explanation is that our study included population who experienced mild forms of COVID-19 (only 4 of 24 reported that they were hospitalized) that did not associate with brain tissue lesions. This explanation is supported by the fact that we did not find bilateral morphological changes that can be expected from olfactory route of virus penetration through blood-brain barrier. Also, this may result from a selection bias while enrolling patients into the study, those who had more severe forms of COVID-19 may not had applied for treatment to Memory clinic due to either restriction on transit for people older than 65 years or precaution/incapacity to move across the city.

Many MRI studies of brain structural changes in patients experienced COVID-19 reported alteration in different brain areas other than olfactory system [7]. Nevertheless, most of these studies did not include control sample and studied patients with COVID-19 severe enough to be hospitalized. The recent brain imaging study before and after COVID-19 included patients with second MRI scan after 35–407 days after recovery from in most cases mild forms of the disease in comparison to healthy control [13]. This study revealed decrease of cortical thickness in the lateral orbitofrontal cortex, generally greater brain size reduction, increase in diffusion indices and CSF volume. Though, a comparison of hospitalized cases with either non-hospitalized or control subgroups failed to detect marked differences due to decrease in the sample size. While this study that was conducted on a population that was very close to our study revealed significant differences in brain morphology, it didn't account control for comorbid disorders like hypertension and type II diabetes that also associated with brain structure changes. Moreover, these comorbid disorders are known to be associated with increased risk of COVID-19 complications [15,16]. Thus, underestimation of these medical conditions may lead to bias in the results.

In our study we attempted to control these conditions. When compared subpopulations matched on gender, age and comorbid medical condition (hypertension and/or type II diabetes) regional brain volume differences disappeared. This may be due to that controlled conditions account for more of the variability in regional brain volumes than COVID-19 history. The median MMSE score before matching was mathematically lower in the COVID- compared to COVID+ group and in opposite to our results one could expect that if COVD-19 is associated with brain leisure than the matching on MMSE score will make differences even larger. Nevertheless, as expected, total MMSE (and MoCA) scores in whole study population showed significant positive correlation with total grey matter volume and negative correlations with total CSF volume showing adequate association between structural brain alterations and cognitive functions. This may indicate that an alternative explanation can take place: the decrease in sample size reduces the statistical power to detect brain differences between groups.

Study limitations

One of the study limitations was that COVID-19 status was not confirmed in the laboratory at the study entry but only with history and COVID-19 certificate provided by the participants. Thus, it is possible that we misclassified those participants who recovered from COVID-19 but is not aware about that. Only four subjects in our study had COVID-19 severity enough to be hospitalized, thus the rest 20 subjects possibly experienced only mild forms of a disease limiting generalizability of study results. There can be a selection bias originating from personal precautions and governmental restrictions on movement amid COVID-19 pandemic. Also, we did not analyze the time between COVID-19 and MRI scan though this time unlikely exceeded a 13-month period as by 31.03.2020 only 1836 cases of COVID-19 were totally registered in Russia. Finally, only 24 participants had a known reported history of COVID-19 thus this study may be underpowered to detect brain morphology changes.

CONCLUSION

We didn't find definite associations of any regional brain volumes differences with COVID-19 history in people older than 65 years. Our study results are based on a population exposed to relatively mild forms of COVID-19. Thus, given study limitations, these results can't be generalized to other people who recovered from COVID-19. Further better balanced and controlled and larger studies on an association of brain morphology with COVID-19 experience stratified by the severity in older people would help to disentangle relationships between COVID-19 severity and brain morphology changes.

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Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: 10.17816/CP145

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Healthy Longevity Among the LGBTQIA+ Population: From Neglect to Meeting Their Needs

Здоровое долголетие представителей сообщества ЛГБТКИА+: от игнорирования к удовлетворению потребностей

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Commentary

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ABSTRACT

The world is facing rapid population aging. This is associated with an increase in the number of older people from the lesbian, gay, bisexual, trans, queer, intersex, or asexual (LGBTQIA+) community. This population faces unique challenges, including ageism, sexual identity stigma, and self-stigma. The older LGBTQIA+ population are neglected by, and invisible to, healthcare interventions, research, and policy changes. In light of the paradigm shift in healthcare towards a rights-based approach, healthy aging has become an important construct. Healthy aging, according to the World Health Organization (WHO), is a "continuous process of optimizing opportunities to maintain and improve physical and mental health, autonomy, and quality of life throughout the life course". This commentary highlights the unique vulnerabilities of the aging LGBTQIA+ population, advocates the inclusion of their voices at all levels of the healthcare system, and discusses the way forward to enable their 'healthy aging'.

АННОТАЦИЯ

Население мира стремительно стареет. В связи с этим увеличивается число пожилых представителей сообщества ЛГБТКИА+ (лесбиянки, геи, бисексуалы, трансгендеры, квиры, интерсексуалы, асексуалы). Они сталкиваются с уникальными проблемами, в числе которых дискриминация по возрастному признаку, стигматизация сексуальной идентичности и самостигматизация. Общество игнорирует пожилых представителей ЛГБТКИА+, их интересы не учитываются при внедрении и модернизации программ здравоохранения, при проведении исследований. В свете повышения внимания к вопросам защиты прав человека важной концепцией стало здоровое старение. Согласно определению Всемирной организации здравоохранения, здоровое старение — это непрерывный процесс расширения возможностей для поддержания и улучшения физического и психического здоровья, независимости и качества жизни людей на протяжении всей жизни. В этом документе подчеркивается уязвимость пожилых представителей сообщества ЛГБТКИА+, делается акцент на важности учета их мнения на всех уровнях принятия решений в системе здравоохранения и обсуждается дальнейший путь обеспечения здорового старения этой популяции.

Keywords: *longevity; healthy ageing; LGBTQIA+; sexual minorities; human rights*
Ключевые слова: *долголетие; здоровое старение; ЛГБТКИА+; сексуальные меньшинства; права человека*

Due to the increasing world population and average life expectancy, one in five people will be over 65 years old by 2050 [1]. This will create a growing and unprecedented demographic milestone not only for older people in general [1], but for older people who identify themselves as part of the LGBTQIA+ community. Increased visibility of older LGBTQIA+ people also poses important challenges in terms of promoting and achieving their healthy longevity. Despite being a diverse group, many older LGBTQIA+ people are exposed to discrimination based on both their age (agism) and sexual orientation and/or gender identity (homophobia, biphobia, transphobia), with a resultant traumatic impact on their physical and mental health [2].

Although political and social advances in many Western countries have legitimized LGBTQIA+ people's rights in the recent decades, the historical circumstances in which they lived when they were younger cannot be neglected. LGBTQIA+ people were invisible, excluded, perceived as mentally ill, and discriminated against. This created a huge gap in scientific research and social and political legitimation measures, making it impossible to describe their specific needs in a timely and detailed manner. This formal and informal neglect forced older LGBTQIA+ people to deal with rejection, sexual stigma, discrimination, and stress associated with their sexual minority or gender minority status, leading to social isolation and poor well-being [3]. As recent research indicates, older LGBTQIA+ people consistently experience worse mental and physical health outcomes when compared to older heterosexual and cisgender people [4]. In particular, older LGBTQIA+ people suffer more from the signs of depression, anxiety, and loneliness, and demonstrate a higher risk of suicide [4]. These outcomes are generally worsened by a lack of social, emotional, or family support, and exposure to discrimination throughout their lives.

In light of this extensive historical neglect, it is very difficult to create formal and informal environments intended to promote the healthy longevity of older LGBTQIA+ people. Clearly, there is a need for a paradigm shift, challenging invisibility and stigma, and advocating that healthy longevity is possible for LGBTQIA+ people. That includes adoption of discrimination-free healthcare perspectives and adjusted interventions (health/social/policy) to meet their needs. Health inequalities, social stigma and accelerated ageism often impair successful aging in this community. Healthcare professionals need to be sympathetic to these factors to allow for the meaningful care of the LGBTQIA+ population. This shift is critical given that psychological and social resilience resources cannot always offset the impact of the disadvantages, especially in circumstances of increased adversity as in the case of the COVID-19 pandemic [5, 6].

In order to meet the specific needs of older LGBTQIA+ people, the impact of healthcare access, social isolation, loneliness, well-being, health behaviors, quality of life, HIV/AIDS-related conditions, independence and autonomy, loss of decision making, life course trajectories, lifelong trauma, the impact of sexual stigma discrimination, spirituality, religion and religiosity, cultural/affirmative competence, and the COVID-19 pandemic on older LGBTQIA+ people may need to be defined. Examining different generations in the context of various cultural perspectives and global initiatives, alongside adopting intersectional approaches and longitudinal, population, qualitative and innovative study designs, also seems necessary [7].

Advancing research data in the abovementioned areas will allow interventions to be guided in a manner adjusted to the unique needs of older LGBTQIA+ people through (a) critical models of healthy longevity that challenge heteronormativity, heterosexism, homophobia, biphobia, and transphobia, and allow barriers to access to formal and informal care from psychosocial support structures to be overcome; (b) the creation of affirmatively positioned theoretical models to accommodate intersectional and multilevel resilience-based views aimed at the explicit validation of older people's LGBTQIA+ identities; (c) promoting visibility that prevents older LGBTQIA+ people from returning to the closet at this stage of life, giving them voice and dignity; (d) developing appropriate infrastructure where their needs, values, and wishes are respected; and (e) providing formal education and training opportunities for professionals working with older people on LGBTQIA+ issues and healthy and dignified longevity [7].

Although the combined effects of agism and sexual stigma can affect the well-being of older LGBTQIA+ people, there are other factors mediating their healthy longevity. Some examples of these factors include resilience, a positive sense and acceptance of their LGBTQIA+ identity, regular access to sources of social and emotional support from their families of choice, disclosure of sexual orientation and/or gender identity, and positive levels of self-esteem, self-efficacy and hope [8]. Thus, it is clear that the ability to transform adverse experiences into opportunities for personal growth and resilience may allow life trajectories, as based on a valid and legitimate meaning of their marginalized status despite having outlived decades of sexuality-related stigma, to be redefined.

The physical and mental health needs of older LGBTQIA+ people also define what can be considered important for a legitimate understanding of their healthy longevity. For example, older LGBTQIA+ people with dementia (usually institutionalized) end up losing their sense of identity, directly experiencing barriers and negative attitudes from professionals and often-absent family members that prevent their holistic inclusion in society and that act as barriers to receiving competent care [9]. Similar problems are attributable to physical health issues such as HIV/AIDS because older HIV-positive LGBTQIA+ people systematically demonstrate worse physical and mental health outcomes that are aggravated by a lack of social support, poverty, and increased lifelong experiences of victimization [10].

Thus, above all, the healthy longevity of older LGBTQIA+ people should be understood as a right to visibility. An explicit challenge of such 'double stigmatization' (due to gender and sexual identity as well as ageism) should be taken into account for any healthcare or policy interventions meant for them. Inclusion of the voices of the older LGBTQIA+ population is necessary to the creation of a safe environment for their healthy ageing. The concept of healthy ageing does not focus exclusively on a period when an individual turns older but covers the changes in lifestyle and influence of environmental factors throughout a lifetime. The creation of conditions for healthy longevity of older LGBTQIA+ people requires the replacement of models that neglect sexual and gender minorities with multi-level resilience models that challenge the multiple stigmatizations associated with the occurrence of health inequalities. Following this attitude, we will be contributing to the better quality of life of LGBTQIA+ people worldwide.

Despite the risks and vulnerabilities that LGBTQIA+ people continue to experience, they still can enjoy healthy longevity if society stops neglecting their unique needs and challenges and begins to reinforce the adoption of health-based behaviors that fight social stigma and ageism. This will improve the 'positive' visibility of their identities and affirmative social connections. Social networking and social cohesion are powerful tools that knit a community together, and the LGBTQIA+ population is no exception in this regard. Healthy longevity for older LGBTQIA+ people should be considered a global challenge, prioritizing trust, intersectionality, recognition of their unique and heterogeneous life paths, and assessment of the impact of social disadvantages. The rights of the older LGBTQIA+ population need to be reflected in national and global conventions, which, in turn, will influence public perceptions and policies.

To conclude, we all need to attempt to mitigate, reduce or even eliminate negligent and discriminatory attitudes and practices that perpetuate sexual stigma and impede access to dignified and healthy longevity of older LGBTQIA+ people. This will have a significant impact on improving the quality of life of millions of older LGBTQIA+ people worldwide, and reduce the barriers and costs associated with structural disparities in caring for older LGBTQIA+ populations and, indeed, older populations in general.

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The WPA-IPS-SPF-AFPA Joint Panel Discussion Organized by the IPA: Voices from South Asia Regarding Older People's Mental Health Advocacy and Services

Дискуссия экспертов WPA-IPS-SPF-AFPA под эгидой Международной психогериатрической ассоциации: услуги по охране психического здоровья и защита интересов пожилых людей в Южной Азии

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Conference Report

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ABSTRACT

Kicking off on 1 October with the United Nations' International Day of Older Persons (UNIDOP) and concluding on 10 October in conjunction with World Mental Health Day, the OLDER ADULT MENTAL HEALTH AWARENESS WEEK was a brand-new ten-day initiative launched by the International Psychogeriatric Association (IPA). It was focused on raising awareness of the importance of Better Mental Health for Older People with virtual programs from all around the world on each of these ten days. As part of this Awareness Week, the IPA hosted a discussion entitled "Mental healthcare services and advocacy for the older people amidst COVID crisis: Voices from South Asia", organized on October 6th, 2021 in conjunction with the World Psychiatric Association (WPA), Indian Psychiatric Society (IPS), Indian Association of Geriatric Mental Health (IAGMH), SAARC Psychiatric Federation (SPF), and the Asian Federation of Psychiatric Associations (AFPA). This is the event report of the same panel discussion which highlights the unique challenges to old age mental healthcare among the SAARC nations, calls for urgent collaborative action, and focuses on human rights and dignity-based mental healthcare for older adults in these rapidly ageing countries.

АННОТАЦИЯ

НЕДЕЛЯ ОСВЕДОМЛЕННОСТИ О ПСИХИЧЕСКОМ ЗДОРОВЬЕ ПОЖИЛЫХ ЛЮДЕЙ, начавшаяся 1 октября с провозглашенного ООН Международного дня пожилых людей (UNIDOP) и завершившаяся 10 октября, во Всемирный день психического здоровья, — это новая десятидневная инициатива, запущенная Международной психогериатрической ассоциацией (IPA). Она проводится с помощью виртуальных программ во многих странах мира и нацелена на повышение осведомленности о важности улучшения психического здоровья пожилых людей. В рамках Недели осведомленности 6 октября 2021 г. IPA провела дискуссию на тему «Охрана психического здоровья и защита интересов пожилых людей в условиях пандемии COVID: позиция Южной Азии», организованную совместно со Всемирной психиатрической ассоциацией (WPA), Индийским психиатрическим обществом (IPS), Индийской геронтологической ассоциацией психического здоровья (IAGMH), Психиатрической федерацией СААРК (SPF) и Азиатской федерацией психиатрических ассоциаций (AFPA). Это отчет об экспертной дискуссии, в котором освещаются особые проблемы в области охраны психического здоровья пожилых людей в странах СААРК, содержится призыв к срочным совместным действиям, а также уделяется пристальное внимание правам человека и охране психического здоровья пожилого населения в этих быстро стареющих странах.

Keywords: *International Psychogeriatric Association; Indian Psychiatric Society; conferences; older people; South Asia; mental health services*

Ключевые слова: *Международная психогериатрическая ассоциация; Индийское психиатрическое общество; конференции; пожилые люди; Южная Азия; службы охраны психического здоровья*

THE IPA OLDER ADULT MENTAL HEALTH AWARENESS WEEK

For more than 40 years, the International Psychogeriatric Association (IPA) has provided global leadership and training in the mental wellbeing, mental healthcare, and rights of older persons. Comprised of multi-disciplinary members from across the world, the IPA is involved in education, care, and innovation across various societal segments enabling healthy ageing, longevity, participation, and inclusion among older people so that they can be a vital resource to their families, communities, and economies.

As a unique initiative this year, the IPA organized the Older Adult Mental Health Awareness Week, RUNNING from October 1st (United Nations International Day for Older Persons) to October 10th (World Mental Health Day). This ten-day span was made up of daily programs that witnessed global societies, associations, and leaders coming together to advocate the promotion of mental health, mental wellbeing, and successful ageing among older adults. There was a wide variety of online resources for older adults and their caregivers on mental health education, dementia caregiver training, healthy ageing initiatives, etc., followed by downloadable graphics and social media promotions. Also, there were video messages from international dignitaries (including the World Health Organization Director General), virtual sessions from delegates worldwide, and a curated list of books, movies, podcasts, etc., for public awareness as an attempt to battle stigma and ageism.

VOICES FROM SOUTH ASIA: THE PREMISE

As a part of this special initiative, the IPA organized a session on October 6th entitled *"Mental healthcare services and advocacy for the older people amidst COVID crisis: Voices from South Asia".* This program was jointly coordinated by **the World Psychiatric Association (WPA)**, the **Indian Psychiatric Society (IPS)**, the **Indian Association of Geriatric Mental Health (IAGMH)**, the **SAARC Psychiatric Federation (SPF)**, and the **Asian Federation of Psychiatric Associations (AFPA)**. This was the first time that two international psychiatric associations came together with the regional bodies of South Asia to discuss and advocate mental healthcare in older people.

Asia has some of the fastest developing economies and largest conglomerations of populations in the world. One such geographically unique region is South Asia, which accounts for nearly 25% of the global population and one-fifth of the psychiatric morbidity worldwide.

This region is also ageing rapidly compared to rest of the world due to modifications in healthcare facilities, hygiene, and lifestyle, as well as improved sanitation and infection control. Further, some of the South Asian countries have also been amongst the worst-hit by the COVID-19 pandemic, which has led to an exaggerated psychosocial crisis among their older populace. Many of these nations face issues with community psychiatric care, trained manpower, socio-economic resources, legislation catering to psychological care, and health inequalities. However, recent years have also witnessed a paradigm shift in mental health policies, infrastructure, and technology among these nations. Climate changes, migration, displacement, and ecological characteristics further make South Asia unique in terms of the region's mental health needs and challenges.

Participants:

This first-of-its kind discussion was attended by a panel of global leaders: **Dr. Afzal Javed (President, WPA)**, **Dr. Gautam Saha (President, IPS)**, **Dr. G. Prasad Rao (President, IAGMH and President Elect, AFPA)** as well as **Dr. Sudarshan Narsingh (President, SPF).**

It was moderated and organized by **Dr. Debanjan Banerjee (Consultant Geriatric Psychiatrist, India on behalf of the IPA organizing committee)**.

The panel discussion was centered around the following themes:

- A global perspective on the challenges facing older people during the ongoing COVID-19 pandemic: Why prioritize?
- Specific challenges in the mental healthcare of older people in South Asian countries
- Role of the various regional psychiatric societies (IPS, IAGMH, SPF, AFPA) in dealing with this problem statement
- Rights and dignity-based mental healthcare in older people during the COVID-19 pandemic: lessons learnt in these nations
- Role of the WPA in coordinating with the regional societies for the betterment of promotive, preventive, curative, and rehabilitative mental health services for older people
- Cross-nation collaboration and evidence-based interventions: future directions

SETTING THE DISCUSSION IN CONTEXT

Dr. Banerjee kickstarted the session by setting the premise. The South Asian region is facing rapid population ageing, which has strategic implications. Aging populations present a plethora of challenges with regard to the economy, societies, and governments. It can slow financial growth, leading to inequality and poverty among older people with unequal intergenerational wealth transfer. This can be further compounded by labor market inefficiencies, a shift of dependency ratio, and unsustainable pensions. Such socio-economic and demographic challenges have been reflected in the recent Longitudinal Aging Study of India (LASI), the first of its kind, modelled on the classic Health and Retirement Study. The first-wave data (2017–2018) not only reveals an increase in depression, anxiety, and neurocognitive disorders but also decreased social participation, reduces perceived life satisfaction, results in financial crisis in the older population, and inadequate awareness about the limited policies and social schemes geared towards their welfare. These factors become all the more relevant in the psychosocial care of older people, as this World Mental Health Day 2021 was themed *"Mental Health in an unequal world"* by the World Federation for Mental Health (WFMH).

Dr. Javed summarized the existing evidence that older people face biopsychosocial vulnerabilities and existential threats during the COVID-19 pandemic. Further, the risk of increased morbidity and mortality due to the infection, the direct neuropsychiatric effects of the virus, and increased propensity for 'long COVID', and other specific challenges are highlighted in Table 1.

The WPA has always been on the forefront of advocating for older person's rights and person-centered mental healthcare. The WPA Section of Old Age Psychiatry (WPA-SOAP), presently led by Dr. Carlos Augusto de Mendonca Lima, has been phenomenal in terms of its work towards elder abuse prevention, fighting ageist attitudes, encouraging inclusion among people living with dementia, and caregiver education, all of which have become even more relevant during the pandemic. Several researchers across the world, including members of WPA-SOAP, the International Longevity Centre (ILC), Canada, and IPA have contributed to the recently published Special Issue of the American Journal of Geriatric

Table 1. Unique challenges among older people during the COVID-19 pandemic

Medical	Psychosocial
Chronic physical illnesses	Risk of elder abuse
Pulmonary comorbidities	Loneliness and social isolation
Multiple hospital visits/stays	Existential threats
Frailty	Grief and bereavement
Polypharmacy	Ageism
Gait and mobility concerns	Lack of domestic help and social support
Sensory and cognitive deficits	Reduced independence
	Prone to misinformation
Vulnerable groups: women, migrant workers, frontliners, lower socio-economic status, sexual minorities, etc.	

Psychiatry, entitled *"Combating Ageism, Mentalism and Ableism: It's time for a United Nations Convention on the Human Rights of Older Persons"*. It specifically focused on human rights, dignity, ageism, and discrimination in older adult mental healthcare.

Dr. Javed also gave a reminder of the Consensus Statement on Ethics and Capacity in older people with mental disorders developed by the WPA-SOAP in 2008. This offers clinicians, allied professionals, and the general public a constructive yet practical framework for upholding the ethical needs and standards of older people living with mental illnesses. However, the implementation and awareness in many low- and middle-income countries (LMIC) remain a real world challenge.

Dr. Sudarshan Narsingh concurred that Nepal has been ravaged by both the waves of COVID-19 and has a dire need for specialist old age mental healthcare services. Overall, the country's mental health manpower is itself grossly inadequate and strengthening primary healthcare services and psychological first aid in psychogeriatric care would represent a first right step in many South Asian nations. The inequalities in older persons have been further widened by COVID. He further stressed the need for individual-based care and treatment, dementia prevention and memory clinics, culturally relevant cognitive assessments, a wider range of geriatric services, coordinated training in mental healthcare among older persons, home-based and institutional services, as well as appropriate caregiver education.

Dr. Saha and **Dr. Prasad Rao** reflected on the various activities organized by the IPS and IAGMH during COVID-19. The IPS has published several manuals (check key references) for psychiatric management, the mental healthcare of general physicians, and the wellbeing of older people in coordination with the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, and the Ministry of Health and Family Welfare (MoHFw), Government of India. Besides, the landmark Telepsychiatry and Tele-psychotherapy guidelines have recently been jointly released by the IPS and NIMHANS, Bangalore, which marks a paradigm shift towards the "new normal" of mental healthcare services during and post-COVID. Tele services are especially relevant for older people in more ways than one, and help in the coverage of wider and remote areas which do not have adequate specialist care. A special IPA Bulletin Issue: Telehealth is dedicated to highlighting global research on digital services in geriatric mental healthcare. However, the implementation, connectivity, and ethical issues still remain a significant challenge, with further training needed among practicing psychiatrists. Also, due to sensory and cognitive deficits, risk of abuse, increased dependency, and poor digital literacy, telecare services also need to be optimized and tailored for older people.

The IPS and IAGMH have coordinated several postgraduate courses on geriatric psychiatry covering dementia, severe and common mental health disorders, grief and loneliness in older people, and psychotherapy in this population. Three-year comprehensive postdoctoral (Doctorate of Medicine) courses already exist in two apex Indian institutes and many more are in the pipeline. This discussion also brought about the need to include human rights, end-of-life, social cohesion, and forensic issues, and preventive aspects in the mental healthcare of older people. Community-based care is the need of the hour, and all the panelists concurred that *"geriatric psychiatry cannot be practiced in a room"*.

ACTION AREAS IN THE MENTAL HEALTHCARE OF OLDER PEOPLE IN SOUTH ASIA

The central themes of the session were the need to implement psychiatric training (inclusive of models of old-age mental healthcare) in undergraduate (MBBS) curricula, community education, and the role of the media in preventing what is currently widely prevalent ageism and, finally, a concerted effort from all the South Asian nations to conduct a systematic survey to explore the post-COVID state of affairs in terms of psychiatric morbidity in older people, their unmet needs, mental healthcare services available, and social service utilization. This will serve as a framework to set up a ground-reality of mental healthcare for older people in these nations, which will in turn enable the development of evidence-based clinical and community interventions. This will also strengthen constructive dialogue with policymakers about the resources and support necessary to promote mental wellbeing among older persons. HelpAge India has very recently published their report *"COVID-19 and the elderly: The silent tormentor"* which reveals a concerning rise of abuse, decreased self-perceived health status, reduced priority for vaccination, low rates of digital literacy, and ageism. Similar core evidence will form the roadmap of both undergraduate and postgraduate training, as well as policy interventions in all the countries. Further cross-nation collaboration is imperative, and Dr. Javed gave the assurance that the WPA will always serve as an encouraging guide for all endeavors related to mental healthcare. The various areas of collaboration are highlighted in Table 2**.**

Telepsychiatric tools need to be utilized to train primary care physicians, grassroot-level health workers, and community health workers, who essentially form the backbone of any nation's mental health infrastructure.

National mental health policies are present in only four countries: India, Nepal, Bhutan, and Pakistan. However, many of these need community integration, amendment, and implementation. Also, related mental health programs that are sensitive to the needs of older people are mandatory. The recently revamped Mental HealthCare Act 2017 (MHCA) passed by India is largely based on the United Nations Convention on Rights for People with Disabilities (UNCRPD), and could serve as a learning anchor for other nations in South Asia, although Dr. Saha and Dr. Prasad Rao both cautioned that the Act is still far from older people-friendly and needs to be further revised to be fully geared toward addressing their wellbeing and needs. Dr. Banerjee added that qualitative interpretative studies are highly valuable in this regard as "lived experiences", and the unheard voices of the service user older people and their families need to form part of both services and policy decisions.

Centralization of mental health delivery systems has been a major drawback in many of these nations, which are now slowly transiting to the community. This is relevant to older people who have been further segregated,

Table 2. Areas discussed for improving mental healthcare for older people under the guidance of the WPA

- Context-specific standard ethical guidelines for capacity assessment
- Community-based mental healthcare models for older people
- Mental health education: involvement of community and the media
- Memory clinics with the help of regional resources (ex: ARDSI)
- Rehabilitation and training subspecialty in old age psychiatry
- Educational content, pedagogy resources, training fellowships for MHP
- Composite UG and PG curriculum inclusion related to old age mental healthcare
- Regional priorities for research, epidemiology of old age mental health concerns, evidence-based interventions
- Cross-nation collaboration and research funds
- Integration of primary-tertiary mental healthcare
- National mental health programs and policies: tailored to the needs of older people
- NGO collaborations
- Optimizing telepsychiatric services and dementia care
- Legal framework for battling ageism and elder abuse
- Rights-based (as opposed to symptom-based) old-age mental healthcare
- Inclusion of lived experiences (service users) in service and policy

Note: ARDSI: Alzheimer's and related Disorders Society of India; MHP: mental health professionals; UG: undergraduate; PG: postgraduate; NGO: non-governmental organizations.

isolated, and lonely due to the pandemic, social distancing, and poor digital literacy. Hence, improving awareness, autonomy, independence, equality, and literacy among older people are key to making the mental healthcare in these nations more friendly towards them.

Resonating the words of Dr. Trivedi and colleagues in their paper in World Psychiatry (2007), the panelists came to the consensus that:

"The organization and coordination of the above-mentioned array of activities related to the development of mental health services need a focal point. Therefore, it is very much appropriate at this juncture to establish an institution which could be developed to be a center of excellence on mental health in the SAARC region."

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Outpatient Services for People with Mental Disorders in the Kyrgyz Republic: What Is Next?

Состояние внебольничной помощи в Кыргызстане: что дальше?

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Short Communication

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ABSTRACT

The outpatient care service for patients with mental disorders in the Kyrgyz Republic is currently experiencing various difficulties. These are largely due to a number of organizational and socio-economic problems at the state level. Treatment of patients with mental disorders is still provided in state mental health centres, while psychosocial services at the community level are only now beginning to be developed. This article describes the directions of mental health care, as well as ongoing efforts to provide outpatient care for people with mental disorders. The actions of a few prolific nongovernmental organizations (NGOs) are proving insufficient to meet the needs of patients. There is currently a gradual and visible movement toward the development of the private sector in the field of mental healthcare. In order to overcome organizational difficulties, support from government structures and certain initiatives to create legislative grounds are needed.

АННОТАЦИЯ

Служба внебольничной помощи пациентам с психическими расстройствами в Кыргызской Республике испытывает определенные сложности. Это во многом объясняется рядом организационных и социально-экономических проблем на государственном уровне. Лечение пациентов с психическими расстройствами по-прежнему осуществляется в государственных центрах психического здоровья, тогда как психосоциальные услуги на уровне сообществ только начинают развиваться. В статье описываются направления развития сферы охраны психического здоровья, а также предпринимаемые усилия по предоставлению внебольничной помощи людям с психическими расстройствами. Действия нескольких плодотворно работающих неправительственных организаций (НПО) недостаточны для удовлетворения потребностей пациентов. Наблюдается постепенное и заметное движение в сторону развития частного сектора в сфере охраны психического здоровья. Для преодоления организационных трудностей необходима поддержка со стороны государственных структур и определенные инициативы по созданию законодательной базы.

Keywords: *mental health; the Kyrgyz Republic; outpatient services; multidisciplinary teams; community-based NGOs*
Ключевые слова: *психическое здоровье; Кыргызская Республика; внебольничная помощь; мультидисциплинарные команды; НПО; внебольничная помощь*

BACKGROUND: PSYCHIATRIC CARE IN THE KYRGYZ REPUBLIC

The Kyrgyz Republic gained its independence from the Soviet Union in 1991, which on one hand led to a national identity crisis [1], and on the other ruined a large number of the establishments that had previously been built [2]. Although the reports by various international organizations described the Soviet healthcare system as “inefficient and over-centralized” [3], there was nevertheless a functioning network of outpatient services that provided regular medical examinations, well-functioning therapeutic workshops (occupational therapy), and home visits to patients with mental disorders.

During the Soviet period, outpatient services for patients with mental disorders operated according to the so-called territorial principle. A doctor and a nurse were assigned to each district of a town or village. The latter was obliged to visit patients discharged from hospital once a week, and, if necessary (for example, should their condition worsen), invite them to see a doctor who might, in turn, make changes to their therapy if needed. As a legacy of the Soviet system, the contemporary Kyrgyz Mental Health Service maintains a centralized treatment system for patients with mental disorders; this, however, results in the stigma of both psychiatric institutions and psychiatrists as professionals, but now without the territorial principle of service provision. A patient’s application for help is either initiated by relatives (the more frequently used option), or by the patient themselves.

According to official data from the statistical committee of the National Centre for Mental Health (NCMH), the incidence of mental disorders in Kyrgyz Republic is 48.1 of new registered cases per 100,000 of the population. By the end of 2021, the NCMH had treated 3,182 patients, 18% of whom presented with schizophrenia and schizoaffective disorders, 21% with mood disorders (including mild depressive disorders), and 17% with anxiety and traumatic stress disorders. Patients with dementia and delirium are more likely to remain at home, especially in rural areas, as cultural traditions discourage taking an elderly relative to a psychiatrist. The high proportion of patients with mental disabilities and mental retardation (33%) among those admitted to hospital for either diagnosis or forensic examination reflects the image of mental disorders in traditional society. To date, residents of rural areas do not consider a person to have a mental disorder if “he/she can speak normally”. Statistics on the prevalence of mental disorders remain unavailable, as patients who seek help at private psychological centres are not recorded in the national statistical system.

There are 153 psychiatrists working in the country that has a total population of 6,636,000 [4]. The availability of psychiatrists by region ranges from one to two per 100,000 inhabitants. The number of psychiatrists working solely in outpatient services in the Kyrgyz Republic decreased from 250 in 2001 to 80 in 2020 against the backdrop of the consequent reduction in psychiatric beds from 2,500 to 1,425 [5]. Day clinics are territorially attached to hospitals, and are typically used for subacute treatment and the selection of supportive treatment for patients who had previously been in acute psychosis wards. Along with the decrease in the number of highly professional specialists, the incidence of mental disorders remains essentially unchanged.

In many districts, there are no psychiatrists and the budgets for such specialists are typically allocated to other doctors available in the particular region in question. It should also be noted that the number of early career psychiatrists has been decreasing over the last 20 years, and the average age of psychiatrists is now 50–55, i.e., most psychiatrists are of preretirement age. The Kyrgyz Republic is still experiencing a lack of well-trained psychiatrists, despite the medical academy in the capital, Bishkek, and two state medical departments in both Bishkek and Osh, which in themselves should be sufficient for a small country. All primary care practitioners, whether trained or otherwise, are responsible for frontline diagnosis, treatment, and prevention of mental disorders, and are entirely funded by the mandatory health insurance fund. In 2020, this payment amounted to 3.2% of the total mental healthcare budget [6].

It is challenging to assess the number of psychologists in the country because there is no professional licensing system in place. A limited number of the private psychological centres function independently and without proper legislative grounding, often not following evidence-based service standards.

The NCMH is still the largest organization to provide mental health services. It has twelve wards, including a day hospital and two wards for psychosomatic disorders. The main wards are the acute psychosis wards that provide care for patients with moderate to severe mental disorders. Should a patient's condition improve, they are transferred to a day hospital for further treatment or otherwise discharged. One of the wards is an outpatient clinic and, according to patient feedback, is the best in the country, being part of the NCMH. It is believed that the best specialists are concentrated in the Centre, where clinicians constantly undergo advanced training.

Two departments at the NCMH accept patients with common mental disorders. Patients with mood disorders, anxiety disorders, obsessive compulsive disorder and certain eating disorders are voluntarily hospitalized in an inpatient setting, while receiving mainly medication therapy. With a caseload of 15–30 people per clinician, there is essentially no time for psychotherapeutic work. Patients with suicidal tendencies are referred to acute psychosis wards, regardless the diagnosis they may have received. It is quite clear that a stay in hospital for a patient with a panic disorder is unlikely to help, just as it is unlikely to help a patient with a generalized anxiety disorder [7].

Reforms and programmes for supporting the mental health care system

None of the three public health reforms, *"Manas", "Manas Taalimi"*, and *"Den Sooluk"*, addressed the needs of patients with mental disorders [8], and not only failed to reduce the cost of treatment for patients with somatic disorders as intended, but ultimately actually increased them.

In 2001, the National Programme "Mental Health of the Population of the Kyrgyz Republic for 2001–2010" was approved by the government [9]. One of the key directives of this programme was the "enhancement of the network of day-care clinics and involvement of primary care physicians in the activities of the mental health service" [9]. Although not all the goals of the Programme were achieved, substantial efforts were invested in the training of primary care physicians for the diagnostics of mental disorders.

Ideally, such specialists would screen patients for symptoms of mental disorders and, if necessary, refer them to a psychotherapist for further outpatient treatment. At the same time, primary care physicians were allowed to prescribe medication and treat anxiety and mood disorders. In practice, patients with mild symptoms continued to be observed by primary care physicians, while those with manifest mental disorders were referred to hospital by the community health centre psychiatrist (*poliklinika*). Thus, whilst out-of-hospital care for patients with mental disorders looked highly effective on paper, in practice the NCMH in most cases turned out to be the primary level care for patients with mental disorders, rather than the tertiary level, as it was originally designed to be [10].

The decentralization of psychiatric services and the transfer of certain diagnostic and therapeutic services to primary care physicians seemed to be beneficial, provided there was good associated funding and that the number of doctors in the field remained essentially stable. In reality, doctors acquired an increased workload without a concomitant increase in salary. The mass exodus of qualified specialists from the profession practically negated the World Health Organization's (WHO) efforts to train therapists in the diagnostics and treatment of mild mental disorders, predominantly those of a depressive nature or on the anxiety spectrum. Medications were often prescribed in an uncontrolled manner by undertrained primary care practitioners, frequently violating treatment regimens and therapeutic doses.

This situation persisted until 2018 when the following national Programme, the "Mental Health of the Population of the Kyrgyz Republic for 2018–2030", was accepted [11]. The Programme promised the provision of qualified, comprehensive, integrated, and responsive mental health and social care at the community level that followed evidence-based approaches.

The implementation of the Programme has already faced a number of significant challenges since 2018, such as a lack of financial support from the government, the persistent migration of well-trained specialists to other countries, and a lack of cooperation between ministries. Some mental health care branches have practically disappeared during this time; for example, there is currently only a limited number of specialists in child psychiatry in the country [12]. Moreover, primary care physicians must now deal not only with eligible patients but, additionally, with a range of other patients with more severe mental disorders. The increased workload has led to even more specialists leaving the profession, causing another wave of migration of qualified clinicians [13].

THE CURRENT STATE OF OUTPATIENT CARE FOR PATIENTS WITH MENTAL DISORDERS IN THE KYRGYZ REPUBLIC

Outpatient care for people with mental disorders is essential to the prevention of relapse in the longer term [14]. The current issues with the outpatient services in the Kyrgyz Republic are the result of a long history of problems across the entire health care system during the post-Soviet period. At the same time, the current mental health care system is the direct descendent of the Soviet psychiatric system. After some years of relatively stable functioning, as fuelled by the remnants of Soviet resources and infrastructure, the mental health care system started to rapidly deteriorate, resulting in the outright neglect of outpatient care on the part of the state. Mental health services are currently funded based on the “residual budget”, which totals about 4% of overall expenditure on health care [15]. Hospitalization is considered the key means of the treatment of patients with mental disorders, even mild ones, and predictably such an illness is highly stigmatized.

There are almost no barriers to establishing a private practice or a mental health centre in the country, except for registering the business with the state fiscal authorities. At the state level, the concept of outpatient mental health services is practically lacking; there are no corresponding laws or regulations, no requirements regarding the professional qualifications of individual psychologists, thus no standards for university programmes based on licensure requirements, and, finally, no requirements for mental health clinics. This has led to poorly formulated requirements for educational organizations, such as degree and certification programmes in the universities. It has also resulted in the growth of educational centres that declare that they can prepare psychologists or counsellors for practice.

From 1996 to 2005, traditional healers and religious figures became extremely popular in the Kyrgyz Republic, essentially replacing psychiatrists and psychotherapists in the outlying regions of the country [16]. These practices were controlled during the Soviet period with some relative success, but which led to an exacerbated interest in these types of services after the collapse of the USSR. Private initiatives in the mental health sphere became essentially absent for several reasons: the sudden decrease of the population’s average income in the 1990s after the break-up of the USSR, the absence of a private insurance system, and the poor preparation of diverse mental health professionals (with the exception of psychiatrists). Similar issues were present in other areas of health care in the Kyrgyz Republic, which survived either at the expense of pharmaceutical companies or by attracting international donors [16].

Another reason for outpatient services being underdeveloped and of low quality in the country is the lack of appropriate legislative attention to the issues of mental health, private services, and the education of mental health professionals, amongst other things. To date, the 1999 “Law of the Kyrgyz Republic on psychiatric care and guaranteeing the rights of persons receiving such care”, signed by the first President of the Kyrgyz Republic and enacted by the Legislative assembly of the Kyrgyz Republic on 25 May 1999, remains the only document defining the key aspects of mental health care in the country [17]. Amendments to this law were introduced in 2017, but the key provisions of the law remain unchanged. According to the law, outpatient psychiatric care for a person suffering from a mental disorder, depending on medical indications, should be provided in the form of consultative care or dispensary observation. In the latest amendments to the law, dated 20 February 2017, this paragraph was left unchanged, and other forms of outpatient care were entirely ignored. When comparing the laws on psychiatric care in other Central Asian republics such as Kazakhstan, Uzbekistan, and Tajikistan, one can see that the associated legislations are largely identical. The differences concern “involuntary dispensary observation”, which is mandatory for the former patients of mental health centres, a clause that is absent in the law of the Kyrgyz Republic.

Community-based mental health services

Despite the many obvious difficulties, there have been several important positive developments regarding a better outpatient care system in the country. One such is the rapidly growing number of non-governmental organizations (NGOs), who are, in fact, the main motivators behind the reform. Multiple NGOs, funded by international donors, are working productively to organize multidisciplinary teams (MDTs) on a community-based level. Twelve MDTs have already been organized to provide community-based outpatient mental health services [18]. Such teams are currently working successfully in several of the country’s major cities. Each team includes a psychiatrist, a psychologist, a home care worker, and a nurse. Such teams provide care to patients through regular home visits. Having a psychiatrist, a psychologist, a home care worker, and a nurse on the team makes it possible to optimize the processes of diagnosis and treatment, to conduct highly accurate integrative assessments of patients' conditions, and to offer a wide range of associated services. Such a multidisciplinary approach allows the interdepartmental barriers that arise to be successfully overcome. Community-based MDTs that provide assertive care directly contribute to a significant reduction in the number of cases and the duration of hospitalizations, resulting in longer at-home periods even among patients requiring multiple hospitalizations. Outpatient services, as provided by MDTs, improve patients' quality of life, alleviate symptoms, and increase social functioning. The mobile team's aim is to integrate patients into society, provide them with problem-solving skills, support them in taking responsibility, and train family members. The only downside of this system is that it is not state-funded, and the sustainability of this productive initiative may be somewhat questionable. Additionally, the manner in which a team is composed makes clients more vulnerable in terms of the ethics of care, such as the collection and storage of information within the team and between the specialists.

Outpatient rehabilitation programmes developed by the NGO "Family and society" aim to support patients in need of mental health care to live independently and with a minimum of medical intervention. Several projects for people with serious mental disorders are currently being carried out by international NGOs with the support of the Soros Foundation Kyrgyzstan, the Mental Health Initiative of the Open Society Institute, and the European Department of Caritas. Within the NMHC, a mobile team provides home care for mental health patients who are unable or unwilling to leave their homes. The recent increase in interest in the WHO's Mental Health Gap Action Programme (mhGAP) and its implementation demonstrates the region's willingness to reduce the treatment gap using evidence-based interventions, with workshops that were held across Kyrgyzstan in 2019.

Some of the types of sociopsychological services for outpatients that are more or less fulfilled by private initiatives and international organizations include services for the most vulnerable population groups: children with special needs, children in the foster care system, older adults (especially those who reside alone or have certain disabilities), female victims of violence, and members of the LGBTQ+ (lesbian, gay, bisexual, transgender, and queer) community. Many of these initiatives have been highly successful and sustainable, providing high-quality outpatient care and engaging qualified clinicians and experts.

Private psychological centres

In general, the situation with private psychological centres in the Kyrgyz Republic is rather ambiguous. Such centres can emerge and disappear rather randomly, as do privately practising psychologists. The private psychological counselling centres, on the one hand, are gradually replacing traditional inpatient care for patients with anxiety and stress-related disorders, but work in an unsupervised and unregulated manner on the other. The absence of a system of control, such as licensure requirements and a professional organization, has led to an increase in the number of self-defined psychologists or counsellors, who often practice without formal education in counselling or psychology, and who may harm patients in various ways. Some attempts to control this sector are being undertaken by individual activists from among the ranks of professional psychologists, who suggest that a professional association be established and suggest a move towards licensure for mental health care professionals. The proposal to adopt the Code of Ethics for Psychologists in Kyrgyz Republic was one such initiative which, whilst it has not been officially approved, is nevertheless widely used by professionals [19].

With only a few exceptions, the growth in the number of psychological centres and private practising psychologists should be viewed as a positive trend in the development of outpatient services.

Outpatient care for children in the Kyrgyz Republic

As for inpatient services for children, adolescents, and adults with autism and intellectual disabilities, which is defined as the medical and nursing care provided in hospital, these are in fact not available in the Kyrgyz Republic, and indeed see little demand from the general population. To undergo an assessment procedure and to receive a diagnosis, parents are often required to leave their children by themselves in the NCMH clinic for two weeks. The majority of parents naturally refuse to leave their children unattended in a psychiatric hospital, but the system is not very flexible with regard to this issue. Moreover, the assessment tools available at the NCMH are outdated and may not provide comprehensive developmental psychological and psychiatric assessments, even during two weeks of observation.

The situation with the public outpatient care for children is even poorer. In general, outpatient care should include a diagnostic, an assessment, and individualized treatment options matched to the intellectual and emotional developmental level of a child, as well as pharmacotherapy, family therapy, or parent training, and educational support for children with special needs. Parents can receive assistance from the state in the form of child psychiatrists and neurologists who provide a diagnosis and pharmacotherapy plan, and from the Psychological Medical Pedagogical Commission (PMPC) in terms of providing children with access to a special or inclusive education [20].

The main challenges to identifying developmental disorders correctly are associated with the lack of specialists trained in the diagnosis of autism or intelligence assessment and a lack of standardized up-to-date diagnostic instruments.

The quality of support in accessing educational goals provided by the PMPC is also questionable. In spite of the fact that many international organizations, in particular the European Union, supported the development of PMPCs by establishing commissions in seven regions and training 72 specialists in assessment [21], these institutions still lack the human, financial, and methodological resources to support children with autism, intellectual, or indeed other disabilities. Furthermore, apparently only two PMPCs in the country work throughout the year, while the remaining 16 do not practice on a regular basis but are rather organized once every six months, mainly to make the decision as to whether a child is eligible for special or regular education, meaning that there is basically no time to conduct an assessment and provide treatment [22]. Moreover, in outlying regions PMPC members are usually lacking in professional education and do not have the skills or qualifications to perform an assessment. Finally, most of the training funded by international organizations is focused on teaching what disability is, the principles and basics of inclusive education, and the United Nations convention of the rights of the child, but does not provide solid training on assessment and the contemporary instrument for assessment and programming early intervention.

At the same time, various new initiatives have been initiated to improve the wellbeing of children with special needs, organized mainly by NGOs, similar to the situation with other mental health patients. For the last decade we have observed a tendency for parent-led organizations to take over state responsibilities and attempt to shift the model of disability from a medical to a social one. Representatives of parent associations encourage parents to minimize medical treatment and instead turn to educational approaches and evidence-based interventions. In the majority of cases, these organizations are founded by prominent and devoted families that completely change their lives to serve children with special needs.

Besides providing outpatient services for children in terms of assessment, diagnosis, programming, and therapy, NGOs are instigating the development of policy documents related to the rights of children with special needs, training family doctors to screen for symptoms of autism, collaborating with child psychiatrists and neurologists, and attracting international donors in the attempt to develop a system of early interventions not only in Bishkek but also in other regions of Kyrgyzstan. Although such initiatives can have a tremendous effect on the lives of children with special needs, their services remain too expensive for many families, are not fully available in the regions, and may lack professionals trained in assessment and evidence-based treatment.

CONCLUSION: WHAT IS NEXT?

Outpatient care in the Kyrgyz Republic is still disconnected from in-hospital treatment and is insufficient both at the conceptual and the practical levels. There is a visible lack of legislature on community mental health care and psychosocial care, in contrast with psychiatric inpatient care, where clear legislation and national programmes exist and, indeed, are regularly updated. The outpatient care initiatives in the country, both public and private, are mostly disconnected from inpatient treatment and public psychiatric services, resulting in a fragmented system of care in the country. A similar situation exists in many post-Soviet Central Asian countries, where mental care is psychiatry-centred and considerably underdeveloped compared to Western countries with regard to other mental health specialities such as psychologists and social workers [6]. Currently, such professions as social workers and psychologists are undervalued and underfunded, resulting in poor-quality services and an imbalance in care in favour of inpatient services. Cases of continuous outpatient care for patients with mental disorders are still the exception rather than the rule. Community psychiatry and psychosocial care is just beginning to develop, and the creation of multidisciplinary teams providing patient care at home is certainly encouraging, but the sustainability of existing initiatives remains questionable.

Perspectives of the development of innovative methods of mental health care are associated with the educational, clinical, and research programmes of the NCMH, the largest professional institution in the Kyrgyz Republic.

The key actions that could currently be taken that should result in a better quality of outpatient care must include the following:

- development of the legislature that would provide the framework for the mental health services as well as defining the governmental position on the issues of public mental health;
- active steps by the professional community towards the creation and development of professional associations and other organizations that would take responsibility for the quality control processes;
- and the active position of universities that could prioritize the research and community service initiatives that influence long-term strategies in the development and popularization of mental health services.

Only the provision of the appropriate legislative grounds, developed in close collaboration with the professional community, would pave the way to better quality and more diverse services. Finally, a more articulated and proactive position on the part of the government regarding issues relating to the mental health care system, and the initiatives to provide better legislative grounds, will promote appropriate outpatient care in the near future.

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Community-Based Mental Health Services in Azerbaijan: a Course Toward Development

Развитие внебольничной психиатрической службы Азербайджана

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Short Communication

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ABSTRACT

Community mental health care in Azerbaijan was established in 2011 in the line with the country's mental health reform. The main directions of the reform, as described in the National Mental Health Strategy, were deinstitutionalization, improving quality of care, integration of mental health into primary healthcare, and implementation of modern community-based services. Over the last decade, the number of beds in psychiatric hospitals has significantly decreased, and many psychiatrists and psychiatric nurses have been transferred to primary care facilities. At the same time, programs focusing on comprehensive care have been implemented in different regions of the country.

Community mental health services currently employ various kinds of mental health professional including psychiatrists, clinical psychologists, social workers, occupational therapists, and nurses to ensure a multidisciplinary approach to care provision. Team-based care may focus on crisis resolution, psychosocial rehabilitation, case management, family support, and early intervention for psychosis.

Among the barriers preventing development of community mental health services, one should note, in particular, stigma belittling the priority of mental healthcare, uncertainty in distribution of authority between the Ministry of Health and the State Agency for Mandatory Health Insurance, and a general scarcity of human resources, especially in the rural regions. Nevertheless, the mental health care in Azerbaijan is continuing its transition from an institutional model to community-based services.

АННОТАЦИЯ

Внебольничная служба психического здоровья Азербайджана была созданы в 2011 г. в рамках реформы системы здравоохранения в области психиатрии. Основными целями реформы, как они описаны в Национальной Стратегии по психическому здоровью, являлись деинститулизация, повышение качества помощи, интеграция психиатрии в систему первичного звена здравоохранения и внедрение современных внебольничных форм помощи. За последнее десятилетие было значительно сокращено число коек в психиатрических больницах и многие врачи-психиатры и психиатрические медсестры были переведены в учреждения первичного звена здравоохранения. Одновременно в различных регионах страны стали внедряться программы комплексной помощи для взрослых и детей.

На сегодняшний день внебольничные службы психического здоровья задействуют различных специалистов, включая психиатров, клинических психологов, социальных работников, специалистов по реабилитации и медсестер для реализации мультидисциплинарного командного подхода в оказании помощи. Работа команд может быть направлена на разрешение кризиса, психосоциальную реабилитацию, индивидуальное сопровождение, семейную поддержку или раннее вмешательство при психозах.

Среди факторов, препятствующих развитию внебольничных услуг, следует отметить стигму, принижающую значение психиатрической помощи, неопределенность в распределении полномочий между Министерством

Здравоохранения и Государственным Агентством Обязательного Медицинского Страхования, а также дефицит кадров, особенно в регионах страны. Несмотря на это, психиатрическая служба в Азербайджане продолжает свой переход от институциональной модели к предоставлению внебольничной помощи.

Keywords: *community care; mental health services; mental health reform; Azerbaijan; multidisciplinary approach; psychosocial interventions*
Ключевые слова: *внебольничная помощь; услуги в области психического здоровья; психиатрическая реформа; Азербайджан; мультидисциплинарный подход; психосоциальные вмешательства*

INTRODUCTION

Azerbaijan is an upper-middle-income country in the South Caucasus region with a population of approximately 10 million and a prevalence of urban residency. The gross domestic product (GDP) per capita in 2020 was US $ 4,214.31, and where 3.5% of GDP was allocated to healthcare [1]. Although mental disorders contribute to 9.1% of Disability Adjusted Life Years (DALYs), mental health expenditure accounts for only 3.4% of the general health budget [2].

The healthcare system is currently in the process of large-scale reform as a result of which the majority of medical services were transferred to State Agency on Mandatory Health Insurance (SAMHI) financing, though certain facilities still continue to be financed by the Ministry of Health (MoH). The consequences of this separation have been most pronounced for mental health services: psychiatric hospitals and specialized outpatient centers are managed by the MoH, and mental health services in general health settings are assigned to the SAMHI. In this regard, mental health care provision has a significant number of conflicting approaches that influence decision-making processes. For example, improved access to community-based services is acknowledged to represent a better alternative to institutionalization; however, only 15% of the mental health budget is allocated to outpatient care. Another example is a general recognition of the need to introduce a multidisciplinary approach in care provision, but rate at which new positions are becoming available for mental health professionals is extremely slow. Development of community-based mental health services requires effective collaboration not only within the healthcare sector, but also with other stakeholders, in particular social welfare and education [3]. Unfortunately, mental disorders and mental disability are still managed from within the framework of a rigid medical-centered model that effectively prevents the delivery of comprehensive care, including psychosocial interventions, sheltered housing, vocational training, supported employment, etc. In the absence of well-developed social services, most people with mental illness have reported unmet needs with regard to their daytime activities, occupations, and socialization [4].

Despite these difficulties, the mental health system's transition from an institutional model to community-based care continues. In recent years, the government implemented important initiatives in mental health to meet modern requirements in care provision.

The aim of this article is to review the transformation of mental health care, describe organizational model in mental health, indicate the advantages and disadvantages of existing services, and discuss the principal lessons learned in the course of such mental health reform.

BRIEF HISTORICAL PERSPECTIVE

The first psychiatric hospital, which consisted of just 30 beds, was opened as a charity initiative in Baku in 1892. In the first half of the 20th century, various attempts were made to open new psychiatric facilities in the framework of the formation of the Soviet healthcare system. However, the establishment of psychiatric hospitals was slow because of a lack of professionals in the field, and hence there were two psychiatric facilities in the capital and a few psychiatric wards scattered around general hospitals in the regions [5].

The introduction of psychopharmacotherapy in the early 1960's resulted in the development of eight new mental health settings (so-called *inter-regional psycho-neurological dispensaries*) providing both in-patient and out-patient treatment. In the 1970s and 1980s, there was a record increase in the number of beds, achieving a maximum of 2265 beds in the largest psychiatric hospital. At the same time, excessive institutionalization in mental health went hand-in-hand with certain destructive effects such as segregation of psychiatric services from general healthcare, patients' isolation from society, deteriorating quality of services, and systematic human rights violations [6].

The restoration of independence in 1991, accompanied by the Karabakh War, resulted in an enormous inflow of refugees, and a severe economic crisis resulted in the collapse of the mental health system in Azerbaijan [7]. Over subsequent decade, these services remained disproportionately institutionalized, over-centralized, underfinanced, and restricted in terms of the available range of services [8].

The adoption of the first piece of legislation on psychiatric care in 2001, and the assessment of the mental health system conducted by the World Health Organization (WHO) in 2007, triggered a broader discussion on the reformation of mental health services in the country [9]. The subsequent decisions mainly affected in-patient facilities through improvements to living conditions, and the supply of medicines and food. In addition, the number of psychiatric beds was reduced from 73.9 to 38.3 per 100,000 [10].

With the view of taking forward the mental health reform, the MoH established a taskforce including mental health professionals, representatives of health administration, and social activists. The taskforce developed the National Mental Health Strategy and Action Plan, which came into effect in 2011 [11]. These documents focused on human rights protection, enhancing governance and intersectoral coordination, building capacities in mental health, improving quality of services, and implementing new services, as well as integrating mental health into general healthcare. In line with these documents, the National Assembly amended the Law on Psychiatric Care to entitle primary care doctors to treat common mental disorders. The MoH developed the relevant clinical guidelines and provided appropriate training for general practitioners.

In addition, with the aim of strengthening psychosocial support in Azerbaijan, the Law on Social Services and the Law on Psychological Care were adopted in 2017 and 2019, respectively. Along with the development of national legislation over the years, Azerbaijan has joined international agreements such as the UN Convention on the Rights of Persons with Disabilities, the WHO Mental Health Declaration for Europe, and the Comprehensive Mental Health Action Plan 2013–2030.

ORGANIZATION OF MENTAL HEALTH CARE SYSTEM

National Mental Health Centre

The National Mental Health Centre (NMHC) was established in 2012 within the framework of the mental health reform. The NMHC structure consists of the Organization and Programs Department, Emergency/Crisis Intervention Unit, Outpatient Unit, Psychosocial Rehabilitation Unit, Child/Adolescent Mental Health Unit, and Daycare Unit.

The NMHC is responsible for the stewardship and coordination of mental health services at the national level. These responsibilities include governance, monitoring and quality assurance for mental health care, as well as analysis of mental health statistics, drafting policy documents (e.g., special programs, practice guidelines, and reports), and providing expert advice for the government. Since a significant number of mental health services are offered by the SAMHI and the Ministry of Labor and Social Protection, the NMHS actively cooperates with these bodies to address mental health issues (Figure 1).

Furthermore, the NMHC develops new approaches to care provision through planning and implementation of community-based services in different regions of the country. Another important activity is the strengthening

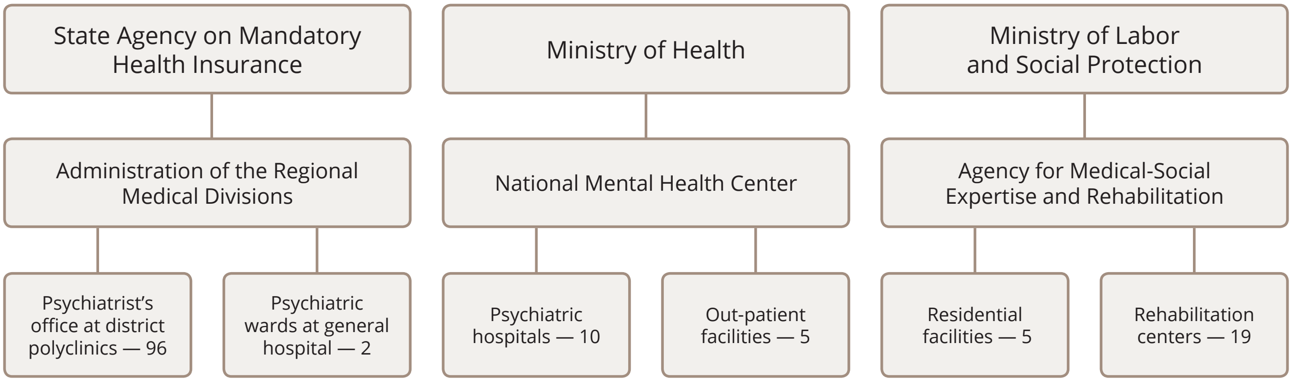

Figure 1. Organizational structure of mental health care in Azerbaijan.

of human resources via educational programs, training mental health professionals, and collaboration with academic institutions and international organizations.

Psychiatric hospitals

Inpatient treatment is provided by ten psychiatric hospitals subordinated to the MoH. Two hospitals are located in the capital, while the others are unequally distributed across the country. The number of psychiatric beds is sufficiently modest at 38.3 per 100,000 (Table 1), as compared to other post-Soviet countries at 79.6 per 100,000 [12].

Most psychiatric hospitals have been renovated or rebuilt as a part of the mental health reform. The average length of stay in the hospital is approximately 60 days, and involuntary treatment makes up 9% of admissions [13]. In 2017, as survey undertaken within the WHO project on adults with mental disabilities living in institutions in the European Region revealed certain deficiencies in psychiatric hospitals [14]. These deficiencies included an absence of any well-defined procedures for discharging patients who have lost family and social ties, a lack of access to free legal representation by a lawyer and/or a social worker, a paternalistic approach (e.g., most decisions are psychiatrist-led rather than patient-led or shared), and insufficient coordination between services beyond healthcare.

Outpatient mental health centers

People with severe mental disorders who do not need acute inpatient treatment receive care at the five outpatient mental health centers available in Azerbaijan's largest cities, where the range of services provided varies significantly from one center to another. Some centers focus on drug treatment and expert examination only, while others offer multiple services including daycare treatment, psychotherapy, and rehabilitation. All outpatient mental health centers are subordinated to the MoH and therefore have a well-established referral system with psychiatric hospitals. Until recently, the centers supervised the work of psychiatrists at district outpatient settings, but subsequent to the division of authority between the MoH and SAMHI, their supervisory functions have gradually diminished.

Psychiatrist's office at district outpatient settings

In 2011, with the aim of integrating mental health services into the primary care system, psychiatric dispensaries were closed, and psychiatrists and psychiatric nurses transferred to primary care facilities. Thus, with mental health services being brought closer to the populace, access for patients with both mental and physical disorders has significantly improved, and the stigma associated with psychiatric treatment has in some way decreased. An psychiatrist's office is now available in almost all outpatient healthcare settings (*polyclinics*) in each administrative district of the country. Since district outpatient settings have been organized on the basis of catchment areas, a psychiatrist's office will typically provide services for 50,000 to 150,000 inhabitants. Just like all other primary health services, psychiatrists' offices fall under the authority of the SAMHI.

Table 1. Mental health resources in Azerbaijan (per 100,000 of population)

Mental health staff	Rate per 100,000 population
Psychiatrists	4.1
Psychiatric nurses	7.8
Psychologists	1.2
Social workers	0.3
Inpatient facilities	
Number of psychiatric beds	38.3
Number of admissions	115
Out-patient facilities	
Number of visits	1964

Residential facilities

The capacity at residential facilities in Azerbaijan is 18.4 per 100,000, which is the lowest amongst all other countries of the WHO European Region [15]. There are only five residential facilities managed by the Ministry of Labor and Social Protection and, according to the existing regulations, they are intended for individuals officially recognized as persons with disabilities. Furthermore, people with mental disabilities are rarely admitted to such facilities due to staff concerns about problematic behaviors and limited opportunities for medical treatment. Therefore, up to 11% of patients lacking family and social ties have to stay in psychiatric hospitals after termination of acute in-patient treatment [16]. Presently the government has initiated discussions to arrange for sheltered accommodation for homeless people with mental illness, allowing for their earlier discharge from hospitals.

Rehabilitation services

Along with rehabilitation programs implemented by the MoH, there are 19 rehabilitation centers within the Ministry of Labor and Social Protection. Fourteen centers intended for adults and five centers for children are located in different regions of the country. Only patients with officially recognized disabilities can be admitted to the centers, and their referrals are coordinated with healthcare settings. Although the centers do not specialize according to form of disability, they employ mental health professionals to provide psychosocial interventions.

DEVELOPMENT OF COMMUNITY MENTAL HEALTH SERVICES

Until 2011, community mental health services were virtually non-existent in Azerbaijan. It may be noted that stand-alone initiatives were run by a number of non-governmental organizations, but which ultimately saw no sustainable success due to termination of their activities as soon as the donor's funding ended. The idea of transition from institutional to community-based care was first mentioned in the National Mental Health Strategy. Chapter III *Strengthening measures on prevention of mental health problems among population* of the Strategy included a paragraph on establishing community mental health services [11]. The follow-up activities marked the beginning of the provision of community care.

Due to the lack of mental health professionals other than psychiatrists and psychiatric nurses, the government created jobs for clinical psychologists, social workers, and occupational therapists at healthcare facilities. In addition, newly recruited specialists were offered the opportunity to undergo professional training, either in the country itself or, indeed, abroad.

Between 2012–2014, the European Union sponsored the *Empowerment of Mental Health Service Users in Five Regions of Azerbaijan* project run by the Lithuanian non-governmental organization, Mental Health Perspectives. The project focused on developing community-based mental health services, psychosocial rehabilitation, human rights, and mental health users' movements. Within the framework of the project, a large group of mental health professionals went to Lithuania to acquaint themselves with community mental health settings. In turn, international experts visited Azerbaijan to promote the development of modern, comprehensive services.

The most important tasks in launching community-based care have been assigned to the NMHC. In recent years, the NMHC dedicated significant effort to the deinstitutionalization of mental health care. It should be noted that the wide range of mental health programs, which included programs on psychosocial rehabilitation, case management, family support, and early intervention, were elaborated upon by the NMHC specialists. Subsequently, these programs have been translated into practice for inpatient and outpatient facilities.

In 2017–18, the MoH established 14 community-based mental health services for children and adolescents. These services were placed at district child outpatient healthcare facilities (*child polyclinics*) in various regions of Azerbaijan. The newly established services utilize a multidisciplinary approach provided by teams consisting of child specialists with a variety of professional backgrounds. Such a team would include a child psychiatrist, developmental psychologist, educational specialist, speech therapist, occupational therapist, and volunteers, who may be also parents of children receiving care.

In 2021, after the second Karabakh War, the government established community-based mental health services for veterans, family members of deceased servicemen, and war-affected civilians. These services were created within general health outpatient settings and mainly employed psychiatrists and psychologists to provide psychotherapy, crisis intervention, and drug treatment for people with post-traumatic stress disorder (PTSD) and other war-induced mental disorders.

Between 2020–2021, COVID-19 seriously affected community-based services in terms of reallocation of funding and restricted access to mental health care. Many outpatient settings were postponed or had their services reduced due to strict quarantine measures. All group activities conducted by mental health teams were canceled. At the same time, mental health services shifted to new modes of care delivery via telephone or online formats. As soon as restrictions associated with the pandemic were eased, these community-based services restored the full range of their activities.

STRENGTHS AND WEAKNESSES OF COMMUNITY-BASED CARE

Despite there being a relatively short history of community mental health services in Azerbaijan, one can see their undeniable advantages over institutional care.

Community-based care seems to be efficient in terms of addressing the populace's needs in ways that are both accessible and acceptable [17]. Patients with severe mental disorders who were being treated in traditional psychiatric facilities had increased the number of unmet needs as compared to patients with the same diagnoses receiving community mental health services [18]. As predicted, patients reported greater satisfaction with mental health services in the community settings, which they found to be comprehensive, person-centered, and recovery-oriented [19]. In recent years, significant progress has been observed in the implementation of psychological interventions and psychosocial rehabilitation. Many people with mild to moderate mental disorders have been able to benefit from counselling sessions, and individual and group psychotherapy, while patients with severe mental disorders have been able to gain access to and participate in rehabilitation programs [20]. There is also evidence to suggest that drug prescription in community mental health settings better meets clinical guidelines than the treatment provided by traditional psychiatric institutions [21].

Although community-based care is considered to be less stigmatizing, that stigma that remains associated with mental disorders still prevents patients from applying for services and contributes to the low priority the government currently assigns to mental health. The above-mentioned distribution of authority in mental health care between the MoH and the SAMHI do not promote community care's ability to address the needs of people with severe mental disorders because of significant differences in the understanding of goals, approaches, and decisions in the field of mental health by each of these authorities. On the one hand, the SAMHI administration is responsible for primary healthcare and interested in preventing most common mental disorders, while treatment of severe mental disorders remains underestimated and unaddressed; on the other, the MoH is mainly responsible for the treatment of individuals with mental disabilities, but have significantly lower financing and other resources with which to establish community-based services. These contradictions may be resolved through certain boundaries determining roles and competencies between the two health authorities, as well as improving their coordination and cooperation.

Due to a shortage of psychiatrists and other mental health professionals, especially in the regions, most mental health services are concentrated in large cities and are barely accessible, or indeed affordable, for people living in rural areas.

Notwithstanding these challenges, development of mental health care is becoming increasingly important, as evidenced by its inclusion in the Principles of the Sustainable Development Goals (SDGs) [22]. Azerbaijan, as a member country, has prioritized SDGs and their targets indicators, including those addressing mental health. In 2021, the government, in cooperation with non-governmental and international organizations, established the Mental Health and Psychosocial Support Technical Working Group. This provided a platform for better coordination and focused inter-agency responses to mental health needs, the implementation of standards of best practice and global interagency recommendations, and the promotion of the quality of psychosocial interventions through joint capacity-building activities.

CONCLUSIONS

The model of mental health services in Azerbaijan represents a quaint combination of institutionalized inpatient care, and outpatient psychiatric counselling and treatment that is semi-integrated into primary healthcare and the recently established community-based mental health services. Due to an absence of a unified systematic approach to mental health services, the community care provided by the healthcare and social welfare systems remains fragmented, poorly coordinated, understaffed, and underfinanced. Nevertheless, we can see a significant shift in paradigm as a result of the increasing attention being paid to mental health issues by policymakers, the media, and the general public. Community-based mental health services have been the subject of discussion at all levels of health and social welfare authority. Moreover, representatives of international organizations in Azerbaijan, such as the WHO, UNICEF, and the International Committee of the Red Cross (ICRC), actively promote programs to develop community-based services for vulnerable adults and children.

At present, one important task facing the healthcare system is the switch from conventional indicators (e.g., the number of inpatient admissions and discharges, number of outpatient visits, etc.) to service outcome indicators (e.g., functioning level, quality of life, and satisfaction with care). In this regard, planning and implementation of mental health policy based on service outcomes opens up vast prospects for the development of community services in Azerbaijan.

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