World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 21, Number 3 *October 2022*

WILEY

NEW IMPACT FACTOR: 79.683

ISSN 1723-8617

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World Psychiatry

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3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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Transforming mental health for all: a critical role for specialists

The *World Mental Health Report: Transforming Mental Health for All* is the World Health Organization (WHO)'s largest review of world mental health in more than 20 years[1]. At its heart lies a call to change how we promote, protect and care for mental health.

The call to transform mental health and mental health care is not new. Mental health advocates and organizations, including the WHO, have been arguing for services reform for decades. Growth in global activism in recent years has focused political attention on the need for quality mental health care. Most recently, the COVID-19 pandemic put both the value and vulnerability of mental health under the spotlight and exposed huge gaps in mental health systems all over the world.

Professionals in multiple sectors, the general public and people with lived experience increasingly recognize the importance of mental health, and more policy makers than ever understand – and publicly support – the imperative for improvement. The appetite for change has arguably never been greater. In 2021, all countries recommitted to the *Comprehensive Mental Health Action Plan 2013-2030*, which provides a roadmap for improved mental health structured around ten global targets[2].

But this type of expressed commitment can only take us so far. Driving the mental health agenda forward to effect meaningful change also requires institutional commitment – policies, plans and programmes to implement the stated intent – and budgetary commitment, which allocates the necessary funds to act. Both are, on the whole, still lacking. In 2020, only 67 countries reported data on mental health spending to the WHO, and those that did only spent on average 2.1% of their total health budget on mental health[3].

The shift to community-based care long advocated by the WHO and others is not happening fast enough, and the wide gap between those needing quality care and those receiving it continues to exist. It has been nearly a decade since countries agreed on the WHO's Comprehensive Mental Health Action Plan, but advances remain few and far between. For most of the world, mental health conditions continue to exact a heavy toll on people's lives, and mental health systems and services remain ill-equipped to meet people's needs.

The new WHO report outlines three key strategies, or "paths to transformation", for moving beyond business as usual and accelerating progress against the Comprehensive Mental Health Action Plan. These focus on shifting attitudes to mental health, addressing risks to mental health in our environment, and strengthening systems that care for mental health.

First, we must deepen the value we give to mental health as individuals, communities and governments; and match that value with more commitment, engagement and investment by all stakeholders, across all sectors. Second, we must reshape the physical, social and economic characteristics of environments – including homes, schools, workplaces and health services – to better protect mental health and prevent mental health conditions. Third, we must strengthen mental health care so that the full spectrum of mental health needs is met through a community-based network of accessible, affordable and quality services and supports.

In this editorial, I direct my words to the readers of *World Psychiatry* and so focus on the role of psychiatrists and other mental health specialists in supporting the actions required. These stakeholders have a critical part to play in enabling each path to transformation. Most specialists are clinicians at heart, motivated by providing care to those in need. This remains a key part of their role, especially to care for people who are presenting with complex problems and who are not recovering in non-specialized care. But, to transform mental health, specialists will have to move beyond being care providers to also serve as advisors, advocates, innovators and educators.

As experts in the field, they can help strengthen institutional and budgetary commitment to mental health through advocacy, by raising awareness of key issues, and advising on and promoting changes in line with the WHO recommendations and the Comprehensive Mental Health Action Plan. They can also help steer policy and practice through research, for example by contributing to the evidence base on which mental health actions have the widest impact for changes. And, as trusted experts, specialists can deepen commitment to mental health across the board by educating policy makers, medical staff and individuals about the intrinsic and instrumental values of mental health.

As mental health leaders, specialists have a major responsibility to strengthen mental health care so that it is respectful, provides dignity, and supports autonomy. Tackling stigma and strengthening rights to eliminate abuse of people with mental disorders within general and mental health services is particularly important. All mental health professionals have a duty to help assure more equitable care for populations who are less likely to seek help or are less likely to be offered quality services, or for whom the risk of missing or misdiagnosing mental disorders is known to be higher than usual. In most countries, these populations include racial and ethnic minorities; lesbian, gay, bisexual, transgender, intersex and queer (LGBTIQ+) persons; migrants and refugees, and persons experiencing poverty and homelessness.

As part of their commitment to person-centred, human rights-based care, all mental health professionals are encouraged to join the WHO in advocating for the development of community-based networks of mental health services and the phasing out of custodial care in psychiatric hospitals as soon as community alternatives become available. At the same time, understanding that the need for mental health care far outstrips supply, mental health specialists should be searching out, adopting and championing innovative tools and technologies that can help scale up care, for example task-sharing, tele-mental health and guided self-help[4-6].

Promoting and facilitating an integrated approach to care is especially important. The evidence is clear that task-sharing can improve health and social outcomes for people living with mental health conditions, especially in low- and middle-income coun-

tries[7]. In all cases, task-sharing relies on mental health specialists leveraging their experience and expertise and supervising, training and mentoring general health workers and community providers to deliver evidence-based care, including psychological interventions and psychosocial supports.

As well as improving care environments, mental health specialists can and should help advocate for action in other environments like homes, schools and workplaces. They can do this by, for example, sharing evidence on the most detrimental determinants of mental health (such as bullying and gender-based violence) and supporting the design and delivery of multisectoral initiatives to address these.

The last time the WHO published a world report on mental health, in 2001, it captured the attention of political and health care leaders around the world and provided the momentum for national and international mental health initiatives to advance. It is our hope that the new World Mental Health Report will similarly inspire and inform all stakeholders to reprioritize mental health and to redouble their efforts to transform mental health. Making change happen is everybody's business. But mental health specialists have a central role to play.

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DOI:10.1002/wps.21030

Psychiatric diagnosis and treatment in the 21st century: paradigm shifts or power shifts?

The paper by Stein et al in this issue of the journal[1] makes a timely and important contribution to our field. In particular, I strongly support the wise counsel to improve diagnostic and treatment systems based upon the foundation of the gradual, careful extension of scientific knowledge. I will focus my remarks upon two specific issues: a) the relationship between deinstitutionalization and the development of community-based services; and b) the involvement of patients/service users in developing and using psychiatric diagnostic systems, and what this tells us in particular about doctor-patient power relationships.

For too long there has been an over-heated debate on a false dichotomy between hospital *or* community care. I have developed with M. Tansella the *balanced care model*, which is an evidence-based model describing the need for *both* services in hospital and the community[2]. It is true, as Stein et al point out, that in many countries which have developed a system of psychiatric hospitals or other large institutions, progress in reducing their size or fully closing them has been slow or haphazard. It is also the case that rushed attempts to shut such hospitals and to transfer patients to poor quality community care have sometimes had terrible consequences, such as the Life Esidimeni case in South Africa[1]. But it is also true that there has been a gradual trend, especially in many middle- and high-income countries, to change the profile of mental health service expenditure from hospital to community-based services and staff, as documented over time in the series of World Health Organization (WHO)'s Mental Health Atlases. Indeed, there are some remarkable national level examples of scaled up community-based care in low- and middle-income countries, such as the 686 Program in China[3].

If I were to bring together my experience of being involved in such policy and practice discussions in many countries around the world with my understanding of all the most relevant evidence, then the following key points strike me as important[4,5]. Almost all the evidence on psychiatric hospital closure is from high-income countries, and there is very little evidence on this question from low- and middle-income countries, some of which have never developed such institutions. We therefore need to be careful not to naively export findings and policy lessons across countries. From the evidence we do have, it is clear that most long-term patients in psychiatric hospitals can be reasonably transferred to community care settings, *if* community care is provided, and *if* the total costs of service investment before and after are about the same. In other words, if hospital "downsizing" or closure is not used as an occasion or excuse for service disinvestment.

Data from high-income countries show that, after substantially reducing long-term psychiatric beds, a mental health system continues to need acute bed provision for admission of severely unwell patients, even in the presence of high levels of intensive community support such as crisis resolution / home treatment teams. There also needs to be hospital provision for discharged long-term patients to be supported from time to time during acute periods of relapse. Overall, evidence is lacking on whether acute psychiatric bed provision is better provided in psychiatric hospitals or in general hospitals. It is likely that this is not so important as long as the services and care provided are accessible to patients and carers, have a decent quality of care and respect for human rights. An asset not used often enough is the value of land of large psychiatric hospitals which are closed or downsized; the resale proceeds of the land sale should be reinvested in mental health services, largely community-based services.

So, in my view, it is right not to choose between hospitals *or* community services, but rather to tailor for each setting the *balance* of hospital and community care that is required. More widely, it is a mistake to confuse specialized mental health services with the wider array of supports and services that are needed for all people with mental health conditions. In most countries, the number of specialist mental health staff is very limited, while the number of primary and community care staff are far greater. The likelihood of being able to substantially reduce the gap between need and treatment for people with mental health conditions worldwide, therefore, rests to a large extent upon training primary and community care staff to be able to recognize, treat and refer patients appropriately, for example using the WHO mhGAP Intervention Guide[6].

I now turn to an issue less well researched: namely, the involvement of patients/service users in developing and using psychiatric diagnostic systems, and what this tells us in particular about doctor-patient power relationships. The advocacy motif of "Nothing about us without us" is a helpful guideline here. Diagnoses are not neutral and can have powerful, indeed life-changing consequences for patients. On the positive side, an accurate diagnosis helps clinicians to know which treatments are most likely to confer benefits to patients. But we also need to keep in mind that diagnoses can also bring harm to patients.

"People's perception of you suddenly shifts as soon as you receive a diagnosis. They are scared to talk to you because they don't know how to approach it or what to say. This makes it even more isolating and a very lonely place". This quotation, from a global survey of people with lived experience of mental health conditions co-ordinated by C. Sunkel of the Global Mental Health Peer Network, suggests that receiving a psychiatric diagnosis can have a profoundly negative impact on people, and can in fact increase stigma and discrimination, both as expressed by others and internalized as self-stigma[7].

In my view, there needs to be much stronger involvement of people with lived experience of mental health conditions in the revision of diagnostic systems in the future, including the naming of conditions, which if poorly phrased may cause misunderstanding or offence[8,9]. I would therefore argue that there is a need for a very specific paradigm shift in psychiatry and mental health: to change the balance of power between patients and psychiatrists and other mental health staff, so as to fully include people with experience of mental health conditions in all the processes, including diagnostic and treatment systems, that are designed to support their intended beneficiaries.

I would like to close my editorial with a quotation from a person with lived experience of a mental health condition who lives in Georgia: "*Even educated people consider schizophrenia a death sentence for the person, like your mind is gone forever, and you have to say goodbye to the person you used to know and care about. In worse cases there are expectations of violence, abuse and some accidents from the person with schizophrenia, there is profound lack of trust and what the person says or does is viewed through the lens of the diagnosis. Friends in many cases just stop understanding and communicating at all"*. We should reflect on these words very carefully.

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The author is supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration South London at King's College Hospital NHS Foundation Trust. The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care. He is also supported by the UK Medical Research Council (UKRI) in relation to the Emilia (MR/S001255/1) and Indigo Partnership (MR/R023697/1) awards.

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DOI:10.1002/wps.21000

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

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

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

(World Psychiatry 2022;21:336–363)

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

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

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

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

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

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

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

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

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

SOCIAL DETERMINANTS OF MENTAL HEALTH IN OLDER ADULTS

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

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

Ageism and stigma

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

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

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

Workforce shortage

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

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

Loneliness and social isolation

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

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

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

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

Wisdom

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

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

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

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

Resilience

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

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

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

Meaning in life

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

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

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

Community engagement

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

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

POSITIVE PSYCHIATRY AND SUCCESSFUL AGING

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

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

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

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

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

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

COGNITIVE AGING

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

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

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

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

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

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

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

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

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

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

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

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

NEUROCOGNITIVE DISORDERS

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

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

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

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

Dementia and mild neurocognitive disorder

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

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

Epidemiology

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

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

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

Risk and protective factors

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

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

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

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

Prevention

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

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

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

mentia, are not yet available.

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

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

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

Neuropsychiatric symptoms of dementia

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

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

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

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

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

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

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

Organization of services

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

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

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

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

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

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

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

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

Specific dementias

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

Table 2 Directions for future clinical practice and research in dementia

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

Alzheimer's disease

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

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

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

Diagnosis and biomarkers

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

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

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

emission tomography (PET) before cognitive symptoms become manifest.

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

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

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

Genetics

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

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

Treatment

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

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

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

Other dementias

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

Table 3 Biomarkers in the diagnosis of common dementing disorders

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

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

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

Vascular cognitive impairment and dementia

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

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

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

Dementia with Lewy bodies

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

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

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

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

Frontotemporal dementia

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

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

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

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

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

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

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

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

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

Delirium

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

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

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

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

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

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

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

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

LATE-LIFE MAJOR DEPRESSION

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

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

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

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

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

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

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

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

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

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

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

Prevention

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

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

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

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

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

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

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

Treatment

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

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

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

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

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

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

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

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

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

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

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

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

Organization of services

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SCHIZOPHRENIA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Treatment: pharmacotherapy

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

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

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

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

Treatment: psychosocial interventions

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

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

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

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

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

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

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

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

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

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

Organization of services

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

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

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

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

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

Successful aging with schizophrenia

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

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

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

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

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

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

SUBSTANCE USE DISORDERS

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

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

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

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

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

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

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

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

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

Screening and diagnosis

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

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

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

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

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

Treatment and organization of services

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ACKNOWLEDGEMENT

The authors would like to thank C. Buchweitz, D. Korzon and S. Dean for their assistance with finalizing the manuscript.

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DOI:10.1002/wps.20996

The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management

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Bipolar disorder is heterogeneous in phenomenology, illness trajectory, and response to treatment. Despite evidence for the efficacy of multimodality interventions, the majority of persons affected by this disorder do not achieve and sustain full syndromal recovery. It is eagerly anticipated that combining datasets across various information sources (e.g., hierarchical "multi-omic" measures, electronic health records), analyzed using advanced computational methods (e.g., machine learning), will inform future diagnosis and treatment selection. In the interim, identifying clinically meaningful subgroups of persons with the disorder having differential response to specific treatments at point-of-care is an empirical priority. This paper endeavours to synthesize salient domains in the clinical characterization of the adult patient with bipolar disorder, with the overarching aim to improve health outcomes by informing patient management and treatment considerations. Extant data indicate that characterizing select domains in bipolar disorder provides actionable information and guides shared decision making. For example, it is robustly established that the presence of mixed features – especially during depressive episodes – and of physical and psychiatric comorbidities informs illness trajectory, response to treatment, and suicide risk. In addition, early environmental exposures (e.g., sexual and physical abuse, emotional neglect) are highly associated with more complicated illness presentations, inviting the need for developmentally-oriented and integrated treatment approaches. There have been significant advances in validating subtypes of bipolar disorder (e.g., bipolar I vs. II disorder), particularly in regard to pharmacological interventions. As with other severe mental disorders, social functioning, interpersonal/family relationships and internalized stigma are domains highly relevant to relapse risk, health outcomes, and quality of life. The elevated standardized mortality ratio for completed suicide and suicidal behaviour in bipolar disorder invites the need for characterization of this domain in all patients. The framework of this paper is to describe all the above salient domains, providing a synthesis of extant literature and recommendations for decision support tools and clinical metrics that can be implemented at point-of-care.

Key words: Bipolar disorder, clinical characterization, phenotyping, subtypes, mixed features, cognition, rapid cycling, trauma, comorbidity, social determinants, stigma, stressors, resilience, bipolar I disorder, bipolar II disorder, mania, depression, personalization

(World Psychiatry 2022;21:364–387)

Bipolar disorder is a common, chronic and highly debilitating condition[1]. Notwithstanding evidence of effective and safe pharmacological and psychosocial treatments, the majority of persons affected by this disorder do not achieve and sustain full syndromal recovery from either a clinician or patient perspective[2]. Multiple modifiable factors contribute to suboptimal outcomes in bipolar disorder, including – but not limited to – the insufficient characterization of the presenting phenotype as well as interpersonal, social and personality factors.

The strategic framework and imperative of personalized/precision medicine posits that biophenotyping an individual can enhance therapeutic outcomes and/or cost-effectiveness by informing bespoke treatment selection[3]. However, notwithstanding the promise of biomarkers/biosignatures as a tactic to assist diagnosis and treatment selection in bipolar disorder, clinical utility is hitherto not established[4]. Consequently, the "near-term" opportunity to improve health outcomes for persons diagnosed with this disorder is deep *in vivo* granular characterization across multiple domains at the point-of-care. It is expected that refining clinical characteristics across multiple salient domains will also inform biomarker research.

It is recognized that bipolar disorder is highly heterogeneous between and within individuals throughout the developmental trajectory. It is also acknowledged that the pleomorphic clinical characteristics of the disorder are moderated by both extrinsic (e.g., social, economic, cultural) and intrinsic (e.g., genetic) factors in dynamic interplay[1]. Moreover, the foregoing domains are also relevant insofar as they moderate illness course and outcomes

Table 1 *In vivo* phenotyping of bipolar disorder: salient domains

1. Psychopathological components of mania/hypomania
2. Psychopathological components of depression
3. Suicidality
4. Clinical subtypes
5. Onset and clinical course
6. Neurocognition
7. Social functioning
8. Clinical staging
9. Temperament and personality
10. Other antecedent and concomitant psychiatric conditions
11. Physical comorbidities
12. Family history
13. Early environmental exposures
14. Recent environmental exposures and relapse triggers
15. Protective factors and resilience
16. Internalized stigma

of the disorder (e.g., higher rate of suicidality in bipolar patients with a history of adverse childhood experiences) as well as inform treatment selection[5,6].

During the past two decades, the number of treatment options proven effective and/or approved by regulators for various aspects of bipolar disorder has significantly increased. Additional treatment options provide opportunity for a more favourable health outcome in bipolar disorder, especially amongst individuals who are motivated to consider further steps when the initial treatment is not found to be helpful[7]. The unavailability of biomarker decision support at point-of-care should not lead to the conclusion that management of the bipolar patient cannot be personalized.

Similar to previously published clinical characterization papers in this journal[8-10], the overarching aim of this report is to identify salient domains for clinical characterization in an individual who is currently diagnosed with bipolar disorder. We have adopted a pragmatic guiding principle insofar as we prioritize domain characteristics that substantively inform case formulation, care planning, and treatment selection (see Table 1).

In addition to synthesizing available evidence across relevant domains, we also provide practical recommendations for measurement-based care and decision support that are scalable, validated and implementable. This paper is not intended to consider bipolar disorder in children and adolescents or in the elderly, as they are comprehensively reviewed elsewhere[11,12]. It is also not aimed to supplant clinical practice guidelines for bipolar disorder, which are considered complementary to the clinical characterization process.

PSYCHOPATHOLOGICAL COMPONENTS OF MANIA/HYPOMANIA

Bipolar I disorder is defined by the presence of at least one lifetime manic episode, whilst bipolar II disorder is defined by the presence of at least one hypomanic episode and one depressive episode. The essential feature of mania as identified by the DSM-5-TR is "a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy", lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary)[13].

Notwithstanding the rich phenomenological literature describing euphoric, expansive, dysphoric and irritable mood states, there is little evidence that further differentiating the foregoing quality of mood, with the exception of identifying mixed features, substantively influences treatment outcomes in bipolar disorder[1].

However, it is probably useful to acknowledge that mood in mania is often also labile (i.e., varying in response to internal or external stimuli). Persistent mood lability can be associated with unpredictably variable behavioural manifestations, including suicidality[14].

The ICD-11 is similar to the DSM-5-TR insofar as not only mood disturbance, but also increase in perceived energy and activity, are regarded as essential features of mania (this was not the case in the ICD-10 and the DSM-IV)[15]. Actually, it has been reported that the inclusion of increased energy along with disturbance of mood enhances the specificity of the diagnosis of mania[16-21], and that speeding of movements, speech and thoughts is even more typical of manic patients than elevated or expansive mood[22].

In both the DSM-5-TR and ICD-11, the diagnosis of mania requires the presence of additional symptoms (at least three – or four if mood is irritable – in the DSM-5-TR; "several" in the ICD-11), including inflated self-esteem or grandiosity, decreased need for sleep, increased talkativeness, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity, and excessive involvement in activities with a high potential for painful consequences. The impulsive nature of reckless behaviour in mania is explicitly mentioned only in the ICD-11. The above symptoms should be present to a significant degree and represent a noticeable change from the individual's usual behaviour. Furthermore, the mood disturbance should cause marked impairment in social or occupational functioning, or necessitate hospitalization to prevent harm to self or others, or psychotic symptoms should be present.

The criteria for hypomania are similar to those for mania with respect to essential and additional symptomatological features. In both the DSM-5-TR and ICD-11, hypomania is differentiated from mania only on the basis of functional outcome, insofar as it is "not severe enough to cause marked impairment", nor does it require hospitalization or include psychotic features.

Clinicians may disagree about whether functional impairment in a patient is or is not "marked", in the absence of further specification (justified by the lack of relevant research evidence). This may contribute to the difficulties recently noted in the differentiation between bipolar I and II disorder[23]. Furthermore, clinical judgement about the degree of functional impairment is likely to be influenced by cultural and even gender considerations, especially when the domain of social relationships is considered. Impairment in work functioning is probably the most reliable indicator in this respect.

There are additional phenomenological domains in mania that are not explicitly recognized in either the DSM-5-TR or the ICD-11 definitions, such as social disinhibition, leading to meddlesome and intrusive behaviour; enhanced perceptions; and impaired insight and judgement[24]. Furthermore, motor symptoms other than agitation may occur in mania: an example is catatonia, which has been reported in some studies to occur in up to one third of manic inpatients and is regarded as an indicator of a poor prognosis[25].

The clinical picture of mania varies from patient to patient and may vary in the same patient from time to time. This heterogeneous, multi-faceted and dynamic presentation invites the need for systematic psychopathological assessment, which is also essential to monitor the effect of treatment. Multiple clinician- and self-rated scales are available.

The most frequently used scale is the clinician-rated Young Mania Rating Scale (YMRS)[26], which takes 15-30 min to complete. The scale includes 11 items, of which four (irritability, rate and amount of speech, thought content, and disruptive/aggressive behaviour) are rated from 0 to 8, and seven (elevated mood, increased motor activity-energy, sexual interest, sleep, language-thought disorder, appearance, and insight) from 0 to 4.

Other available tools are the 44-item Bipolar Inventory of Signs and Symptoms Scale (BISS) (which captures both manic and depressive symptoms)[27], the self-rated 5-item Altman Self-Rating Mania Scale (ASRM)[28], the 16-item Internal States Scale (ISS)[29], the 47-item Self-Rating Mania Inventory (SRMI)[30], and the 9-item Patient Mania Questionnaire (PMQ-9)[31].

Notwithstanding concerns about the validity of self-ratings in mania wherein insight may be compromised, the foregoing self-rated scales have demonstrated sufficient concurrent validity with clinician-rated measures[32]. Shared decision making and patient self-management justify their inclusion as part of the characterization of the adult with bipolar disorder.

In a patient fulfilling the symptomatological criteria for mania, it is imperative to rule out substance abuse or withdrawal, the effects of medications, or a general medical or neurological condition as a possible explanation of symptoms. This is actually recommended by both the DSM-5-TR and ICD-11, but not always implemented in ordinary clinical practice.

It is reported that psychotic symptoms affect from 40 to 70% of individuals during a manic episode. They manifest as delusions (most frequently grandiose or religious, but not rarely paranoid), hallucinations (often of a fragmented and fleeting nature) and/or formal thought disturbances[33,34].

Formal thought disorder has been understudied in mania, but there have been attempts to distinguish it from thought disorder in schizophrenia that may be clinically relevant. In particular, emphasis has been laid on the occurrence in manic patients of "combinatory thinking" (i.e., "the tendency to merge percepts, ideas or images in an incongruous fashion"[35]) as well as the presence of an affective component marked by flippancy and playfulness.

Psychotic symptoms during mania are a medical emergency, indicate greater severity of illness, increase risk for intentional or unintentional harm to self and others, and may lead to inpatient admission. Clinical practice guidelines for adults with mania generally recommend including antipsychotic treatment when psychotic symptoms are present[36-38].

In addition to psychotic symptoms, the presence of mixed features during mania or hypomania should be ascertained[39]. They are defined as three or more intra-episodic depressive symptoms (including prominent dysphoria or depressed mood, diminished interest or pleasure in all or almost all activities, psychomotor retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt; suicidal ideation, attempts or plans)[39,40]. The frequency of mixed features in mania has been variably reported between 20 and 80%[41,42].

The impetus to identify mixed features within mania is provided by observation of the higher risk of suicidality, psychiatric and physical comorbidity, functional impairment, post-mania depression, and chronicity in bipolar patients with these features[43]. Discontinuation of antidepressants in an individual with mania and mixed features is essential, as is the discontinuation of illicit substances and alcohol[39].

The acute efficacy of valproate in mania with mixed features is reported to be higher than lithium[44]. There is no compelling evidence that the presence of mixed features attenuates antimanic efficacy amongst first- and second-generation antipsychotics[45].

Anxiety symptoms are also often observed during mania[46]. "Anxious mania" was described by Kraepelin[47], but does not appear as a codified diagnosis in the DSM-5-TR or ICD-11. Instead, the DSM-5 introduced the specifier "with anxious distress", which may apply to mania or hypomania[13].

Anxious distress is defined as the presence of two or more of the following symptoms: feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen, or feeling that the individual might lose control of himself or herself[13]. The DSM-5-TR uses an ordinal schema wherein severity of anxiety is rated mild to severe as a function of the number of symptoms. The ICD-11 also includes the qualifier "with prominent anxiety symptoms", which can apply to both mania and hypomania[15].

It has been reported that anxiety affects at least 25% of persons during a manic episode[22]. Patients presenting with mania and mixed features are more likely to show anxiety symptoms, which predict longer time to recovery. Moreover, anxiety symptoms during mania are associated with a higher risk of suicidality and aggressive behaviour[48,49]. Anxiety is observed to fluctuate in severity and is frequently a residual symptom after resolution of mania (post-mania anxiety)[46].

Rating scales for anxiety are the 14-item clinician-rated Hamilton Anxiety Rating Scale (HAM-A)[50], the 14-item clinician- and/or self-rated Hospital Anxiety and Depression Scale - Anxiety (HADS-A)[51], the 7-item Generalized Anxiety Disorder (GAD-7)[52], the 40-item self-rated State Trait Anxiety Index (STAI)[53], and the 21-item Beck Anxiety Inventory (BAI)[54].

There are no randomized trials specifically targeting anxiety in an individual presenting with mania. If anxiety is severe, clinical wisdom suggests the use of verbal de-escalation techniques and short-term benzodiazepines (e.g., sublingual lorazepam) or rapidly acting second-generation antipsychotics. The adjunctive

use of anticonvulsants with anxiolytic efficacy may also be considered (e.g., gabapentin). For persistent anxiety symptoms in bipolar disorder, manual-based psychoeducation and cognitive behavioural therapy (CBT) are treatment considerations[55].

A "delirious" variety of mania has been classically described[56], marked by a profound clouding of consciousness. Kraepelin also noted that some manic patients appear "stupefied, confused, bewildered"[47]. Modern descriptions of this variety of mania[57] also exist, emphasizing the sudden onset; the poor orientation for place, date and time, as well as restlessness, fearfulness, confabulation and paranoia. Although this form of mania may be now rare, clinicians should be alerted to consider it in the differential diagnosis with delirium and some substance-induced states of excitement, confusion and agitation, especially in emergency settings.

PSYCHOPATHOLOGICAL COMPONENTS OF DEPRESSION

The DSM-5-TR and ICD-11 provide identical diagnostic criteria/requirements for a depressive episode, with the exception that the ICD-11 also includes "hopelessness about the future" among the symptoms that can be considered (five out of nine are required for the diagnosis in the DSM-5-TR; five out of ten in the ICD-11)[15]. There are no features of depression in the DSM-5-TR or ICD-11 that distinguish and/or are pathognomonic of bipolar disorder. Notwithstanding, replicated evidence indicates that bipolar patients are more likely to manifest atypical, melancholic, psychotic as well as mixed features during a depressive episode when compared to those with major depressive disorder[58,59].

For example, hyperphagia, hypersomnia and profound fatigue are more commonly reported in bipolar depression, and may be associated with obesity and binge eating behaviour[60,61]. Melancholic symptoms during depression in bipolar patients frequently manifest as psychomotor disturbance, anhedonia and non-reactive mood. The psychological component of psychomotor disturbance is generally expressed as inattentiveness, or subjective "fogginess" with difficulty in registering and retaining information. The motor component usually comprises aspects of retardation and/or agitation[62].

Those with psychomotor retardation almost invariably affirm anergia (most commonly evidenced by physical difficulty in getting out of bed), and move and speak minimally and/or slowly. Those with psychomotor agitation generally have epochs of pacing, rubbing their hands, showing facial apprehension or a furrowed brow (the "omega sign") and, in severe instances, stereotypic movements (e.g., hand rubbing, skin picking) and importuning (with a characteristic repeated coda of "What's going to become of me?" that is resistant to reassurance).

Similar to a manic episode, psychotic symptoms are not infrequent during a depressive episode, and influence treatment selection and patient care planning. Delusions are commonly weighted to themes of guilt, but nihilistic or penury themes may be present, as well as somatic ones, with the often associated constipation providing a nidus to develop a delusion of bowel cancer. Delusions are best identified by the clinician inquiring about "guilt" and whether the patient has any sense that he/she "deserves to be punished". Hallucinations are less common (although they may occur in the absence of delusions), being most frequently experienced as a voice telling the individual that he/she deserves to die or would be better off dead. Illusions are common (e.g., seeing a silhouette on the wall), but alone do not establish a diagnosis of psychotic depression. Non-psychotic suprasensory phenomena (e.g., accentuated smell, taste or hearing) may occur.

Mixed features during a depressive episode (i.e., intra-episodic manic symptoms) affect 20-80% of persons with bipolar depression, depending on definitions[39]. They often co-occur with anxiety, agitation, irritability, indecision and insomnia, and are frequently a focus of clinical attention[1]. The foregoing features are not included in the DSM-5-TR mixed features specifier criteria, whereas the ICD-11 lists irritability and increased activity among common contrapolar symptoms in mixed depression[15,63,64].

Individuals presenting with mixed features during a depressive episode are less likely to achieve full syndromal recovery, show higher health service utilization, and frequently manifest treatment-emergent mania when exposed to conventional antidepressants[65]. If depression is severe, a subtle fluctuation in activation or the emergence of racing thoughts may trigger suicidality.

Multiple clinician- and self-rated scales for the assessment of depressive symptoms in adults with bipolar disorder are available, including – but not limited to – the 21-item Hamilton Rating Scale for Depression (HAM-D)[66], the 10-item Montgomery-Åsberg Depression Rating Scale (MADRS)[67], the 21-item self-rated Beck Depression Inventory (BDI)[68], the 20-item Center for Epidemiological Studies - Depression (CES-D)[69], the 16-item Quick Inventory of Depressive Symptoms Self-Report (QIDS-SR-16)[70], the 30-item Inventory of Depressive Symptoms (IDS)[71], the 20-item Zung Self-Rating Depression Scale (SDS)[72], the 20-item Bipolar Depression Rating Scale (BDRS)[73], and the 9-item Patient Health Questionnaire (PHQ-9)[74].

A self-report measure of DSM-5 mixed features during depression – the Clinically Useful Depression Outcome Scale - Mixed features specifier (CUDOS-M)[75] – has been validated and demonstrated high internal consistency and test-retest reliability, as well as high correlation with self-report measures of mania and depression.

The common presence of atypical symptoms in bipolar depression underscores the importance of prioritizing treatments less susceptible to induce weight gain, somnolence or sedation[76]. Psychotic symptoms invite the need for integrating antipsychotic medication as part of the treatment regimen. Long-standing injunctions about not using antidepressants for treating bipolar depression now appear less absolute: in severe bipolar depression, the initial use of an antidepressant (while warning the patient to be aware of switching and mixed states), in conjunction with a mood stabilizer, may be actually needed. Any current mood stabilizer should be reviewed in terms of dose, serum level and adherence, to determine whether it should have its dose adjusted or a different medication should be introduced.

Mixed features identify a subgroup of patients who should not be prescribed conventional antidepressants during the depressive episode, as they increase the risk for treatment-emergent mania[39]. Observational data indicate that anxiety symptoms,

which are often associated with mixed features and frequently occur during bipolar depression, often lead to the prescription of antidepressants, which is not recommended[77].

Relatively few treatment options have proven efficacious for managing anxiety symptoms during bipolar depression. They may include psychological interventions (e.g., CBT), second-generation antipsychotics and, in some circumstances, gabapentin[78].

SUICIDALITY

Psychological autopsy studies have determined that approximately 50-66% of all suicides involve persons affected by a mood disorder[79]. A separate study determined that, among individuals who completed suicide during a depressive episode, 53% had a diagnosis of major depressive disorder and 47% of bipolar disorder[80]. It is estimated that up to 19% of bipolar patients die from suicide, and up to 60% report at least one suicide attempt during their lifetime[80].

In a 40-year follow-up study of 406 patients with bipolar I or II disorder, 11% died from suicide[81]. The risk of suicide is 10-30 times greater for individuals affected by bipolar disorder relative to the general population[82]. Psychological autopsy studies have determined depressive episodes to be more frequently associated with suicide than mixed episodes, while suicide during euphoric mania or euthymia is less common[83].

A rapid-cycling course and a depressive polarity predominance are both associated with a higher suicide risk in persons with bipolar disorder[84]. Some studies report that bipolar II disorder carries a higher risk of suicide than bipolar I disorder[1]. In a 9-year follow-up study of 163 bipolar patients who had been hospitalized, 6% of those with bipolar I and 18% of those with bipolar II disorder died from suicide during the follow-up period[85]. Agitated depression, comorbid anxiety disorders, and a predominant depressive course of illness are characteristic of bipolar II disorder which may account for the elevated suicide rate.

Serious suicide attempts have been reported to be more common early in the course of the illness, especially during the first depressive episode[86]. An early onset of illness also seems to be associated with a higher suicide risk[87]. Recent discharge from hospital is also a risk factor.

A genetic contribution to suicide risk has been reported, and a significant association has been found between first-degree family history of suicide and suicide in bipolar disorder[88]. Twin studies confirm that there is an estimated heritability of approximately 40% for suicide[89]. Studies which have aimed to identify associations between suicidality and specific genes and/or neurobiological substrates have been inconclusive to date.

Socio-demographic factors contribute to suicide insofar as the risk is relatively greater for individuals in both the youngest and oldest age groups. Social isolation or being single/divorced are both associated with a higher suicide risk[90]. Other risk factors include history of childhood abuse, family history of mental disorders, exposure to suicide attempts or completions, traumatic loss of people (e.g., death of a family member), ill health, employment and/or financial insecurity. All the foregoing risk factors should be evaluated in any person with bipolar disorder presenting for care.

Multiple screening and rating instruments for the assessment of suicidality are available for implementation at point-of-care, including the Beck Scale for Suicidal Ideation (BSS)[91], the Beck Hopelessness Scale (BHS)[92], the Columbia Suicide Severity Rating Scale (CSSRS)[93], the InterRAI Mental Health Assessment Tools: Severity of Self-harm Scale (interRAI SOS)[94], the Suicidal Behaviors Questionnaire (SBQ)[95], and the Suicide Intent Scale (SIS)[96].

The clinical management of patients at risk for suicidal behaviour is a challenging task for health care professionals. Risk factor modification should be a priority therapeutic objective in any person with bipolar disorder. Along with assuring safe environment, access to emergency services as needed, and supportive interpersonal contacts, a strong perceived meaning of life and hyperthymic temperament have been linked with reduced risk of suicide, as has receiving active treatment for the disorder.

Currently, there is no proven anti-suicidal effect of antidepressants in bipolar disorder, and some studies have even reported an increased risk of suicidal ideation associated with antidepressant use, although this trend is not observed for completed suicide[82].

Lithium is a mainstay of treatment for bipolar disorder which has been reported to lower the risk of life-threatening attempts and death from suicide by as much as 60-80%[97], although large prospective controlled trials are still needed. Notably, the anti-suicidal effect of lithium has been also demonstrated in patients with otherwise poor treatment response[98]. Preliminary evidence suggests that the anti-suicide effect may not be found in those with low serum lithium levels[99]. The anticonvulsants valproate and carbamazepine have in some studies demonstrated reduction in suicidal ideation, but not in the rate of completed suicide. Antipsychotics, including clozapine, have not been proven to reduce suicide risk in bipolar disorder[1].

Ketamine has been studied primarily in major depressive disorder, where a short-term reduction of suicidal ideation has been reported. Preliminary evidence suggests that similar effects can occur in adults with bipolar disorder[100], although further research is needed in this respect[101]. Electroconvulsive therapy has been found to be effective in treating acute suicidality[82]. Although CBT has been shown to reduce suicidal behaviour in major depressive disorder, such effects are not established in bipolar disorder[102].

Suicidality should be assessed in all individuals with bipolar disorder at initial consultation as well as throughout the illness course. Locus of care is guided by ongoing assessment, especially as it relates to the risk of imminent harm. Clinicians are reminded that suicide risk is increased across all ages in bipolar patients, and that it should be a prioritized part of the assessment during both acute and maintenance treatment phases.

CLINICAL SUBTYPES

The DSM-5-TR and ICD-11 provide diagnostic criteria/requirements for both bipolar I and II disorder. Although bipolar II disorder has been conceptualized as a less severe phenotype, extant evidence suggests that its chronicity and severity are similar to bipolar I disorder. As stated earlier, some evidence indicates that

bipolar II disorder is associated with a higher suicide risk[103,104].

While some debate has occurred regarding the validity of the concept of bipolar II disorder, the weight of evidence supports it as a valid subtype within the bipolar spectrum. Its course of illness is similar to bipolar I disorder, with the distinction that it shows a greater predominance of depression, especially during the early trajectory of illness[105].

The predominance of depression invites the need to assess all persons presenting with depressive symptoms in clinical settings for the possibility of an underlying bipolar II disorder. In probing for a history of hypomania, it is advisable to focus more on hyperactivity than on mood change, and to collect information from people who know the patient well, because patients may not identify the hypomanic periods as pathological.

Treatment considerations in bipolar I and II disorders overlap, but have points of dissimilarity. For example, recent studies suggest that antidepressant monotherapy may be an effective and safe treatment for depression (in the absence of mixed features) in some persons with bipolar II disorder[36,106,107]. Clinical practice guidelines are limited due to the paucity of controlled trials. Quetiapine and lumateperone have demonstrated acute efficacy via replicated studies including subpopulations with bipolar II disorder[108,109], while there is less strong evidence for lithium, lamotrigine and antidepressants[36].

Further clinically relevant subtypes of bipolar disorder are those marked by anxiety and panic attacks, mixed presentations, psychosis, peripartum mood changes, seasonality, and unipolar mania. As reviewed earlier, anxiety is codified by an anxious distress specifier in the DSM-5-TR, which can apply to mania, hypomania or depression. The ICD-11 includes an anxiety qualifier as well as a separate qualifier for panic attacks. The latter should be used only if the panic attacks have occurred specifically in response to depressive ruminations or other anxiety-provoking cognitions[15].

The DSM-5-TR and ICD-11 have taken different approaches on how to define mixed presentations, though both recognize the existence of mixed symptoms in bipolar disorder. The DSM-5-TR includes a specifier "with mixed features" applicable to manic, hypomanic and depressive episodes, whereas the ICD-11 differentiates mixed episodes from mania and depression, consistent with the ICD-10 and the DSM-IV[15].

Mixed states are usually treated with a second-generation antipsychotic as either monotherapy or in combination with a mood stabilizer. Valproate and carbamazepine are effective in mixed episodes, whereas the efficacy of lithium is questionable[110].

A separate subpopulation of persons with bipolar disorder are women with peripartum mood changes. It is of critical importance to screen for mood symptoms in pregnant women and new mothers, to ensure the health of both the mother and the baby[111]. It is well recognized that persons with established bipolar disorder have greater risk for relapse during pregnancy and the peripartum period, and the risk may be higher in women with bipolar II disorder[112-114]. Some women who have experienced prior depressive episodes may develop a first manic episode following childbirth[115,116].

The use of pharmacological treatment is critical in many cases during pregnancy and, if discontinued, should be reinitiated immediately after, or even before, parturition[112,117]. The evidence unequivocally indicates that the use of medication during the peripartum period significantly reduces relapse vulnerability in women at risk for peripartum depression[117].

The seasonal subtype is estimated to affect 15-25% of persons with bipolar disorder[118,119]. It is defined by a regular seasonal pattern of at least one type of episode (mania, hypomania or depression) during the last two years[13]. The most frequent variety is marked by depressive episodes beginning in fall or winter and remitting in spring, often characterized by hypersomnia and overeating.

The seasonal pattern may be more common in females, patients with bipolar II disorder, and those with a family history of bipolar disorder[118,120-122]. It has been reported that bipolar individuals with a seasonal pattern have a higher rate of overweight and obesity when compared to those with a non-seasonal pattern[123].

It is relevant to identify a seasonal pattern insofar as it invites the need for alteration of treatment intensity during periods at higher relapse risk. The additional risk for some comorbidities (e.g., obesity) as well as suicidality is a further rationale for characterizing the seasonal pattern. A validated measure of seasonality in mood disorders is the Seasonal Pattern Assessment Questionnaire (SPAQ)[124]. There is no convincing evidence that any specific treatment modality (including light therapy) is uniquely effective in seasonal bipolar disorder[36].

In addition to the foregoing classic subtypes of bipolar disorder, some additional ones have been proposed. For example, unipolar mania (defined as mania without history of depressive episodes) is a subtype described in both contemporary and classical writings on bipolar disorder[125]. It is estimated that approximately 5% of persons with bipolar I disorder experience this condition[125,126].

Taken together, the subtyping of bipolar disorder, especially the differentiation of bipolar I vs. II disorder, is essential for patient care planning and treatment selection.

ONSET AND CLINICAL COURSE

The onset of bipolar disorder usually occurs in late adolescence or early adulthood, with more than 75% of affected persons exhibiting clinical characteristics of the disorder before the age of 25[1,127]. According to a recent meta-analysis of 40 cohort studies, the modal age at onset of bipolar disorder is 19.5 years[128].

The age at onset of the disorder is clinically relevant, insofar as it affects the clinical presentation, pattern of comorbidity, illness course trajectory, and possibly response to treatment. In particular, a younger age at onset has been found to be associated with a higher prevalence of mixed and rapid-cycling presentations, a greater frequency of family history of the disorder and of substance abuse comorbidity, a higher risk for suicide attempts, and lower levels of treatment response[129-132].

The age at onset of bipolar disorder differs depending on whether the illness is defined by the initial presentation of symptoms, the first onset of functional impairment, the first contact

with health services, or the first codified diagnosis and/or initiation of treatment. Moreover, a proportion of persons affected with the disorder manifest clinically significant psychopathology as a phenomenological antecedent to an index depressive, manic and/or hypomanic episode[133-138]. For example, learning disorders, externalizing behavioural disorders – such as attention-deficit/hyperactivity disorder (ADHD) and substance use disorders – and anxiety disorders frequently manifest prior to initial mania[133,139-145]. The foregoing observation raises a fundamental conceptual and clinical question as to whether such disturbances are "comorbidities" or represent heterotypic continuity of bipolar disorder[146].

Replicated evidence indicates that depressive symptoms/episodes are the most common initial presentation of bipolar disorder[134,147-154]. A separate observation is that a large percentage of persons with the disorder manifest "prodromal" symptoms prior to the initial or subsequent mood episode. For example, a meta-analysis of 11 studies (N=1,078) reported that prodromal symptoms were observed for an average of 27.1±23.1 months prior to an initial mood episode and 1.0±0.9 months prior to a recurrent mood episode[150]. Commonly reported prodromal symptoms are largely consistent with a subthreshold presentation of the subsequent mood episode[150]. Identifying and addressing prodromal symptoms may contribute to preventing episodes, and working collaboratively to identify prodromes can increase mastery of the illness by the patient and engagement of key relatives.

Some rating scales have been developed and validated to specifically assess and quantify prodromal manic or hypomanic symptoms. The Bipolar Prodrome Symptom Interview and Scale - Prospective (BPSS-P)[155] has demonstrated good internal consistency, convergent and discriminant validity, as well as interrater reliability. In addition to the foregoing clinician-rated scale, the BPSS Abbreviated Screen for Patients (BPSS-AS-P)[156] has been developed and validated as a simple self-administered screening tool.

A clinically relevant course feature in bipolar disorder is the predominant polarity of the mood episodes. Predominant polarity has been defined as a >2:1 ratio of either depressive episodes (depressive predominant polarity) or manic episodes (manic predominant polarity)[157,158]. The proportion of bipolar patients in whom the predominant polarity can be ascertained has been variously estimated from 28 to 100%.

Clinical correlates of manic predominant polarity include – but are not limited to – male gender, longer duration of mania, residual manic symptoms, longer duration of euthymia, cyclothymic or hyperthymic temperament, irritability, and cognitive impairment. Clinical correlates of depressive predominant polarity include – but are not limited to – female gender, bipolar II disorder, traumatic events, mixed episodes, higher number of prior mood episodes, and residual depressive symptoms[157,158].

The clinical relevance of predominant polarity is incompletely established[159,160]. Nevertheless, extant evidence indicates that some treatments for bipolar disorder are more effective at preventing and/or forestalling mania (e.g., lithium), whereas other agents are more effective at preventing and/or forestalling depression (e.g., lamotrigine)[129,161]. For antipsychotics proven effective in bipolar disorder (i.e., quetiapine, cariprazine, lurasidone, lumateperone, olanzapine-fluoxetine combination), it is not known if they are preferentially effective in persons with depressive vs. manic predominant polarity.

A separate but related issue is the polarity sequence – i.e., mania-depression-free interval (MDI) vs. depression-mania-free interval (DMI)[162]. The MDI sequence and absence of rapid cycling have been identified as significant predictors of lithium response[132], whereas the DMI sequence may be associated with a higher risk of treatment-emergent mania when exposed to conventional antidepressants[163].

Persons with an MDI pattern should be carefully monitored for the emergence of depression following resolution of a manic episode. There is evidence that conventional antipsychotics are associated with a higher risk for post-mania depression when compared to lithium or atypical antipsychotics[164].

Rapid cycling is defined as four or more acute mood episodes within the past 12 months. Although this pattern is transitory for some individuals, for others it is a more enduring longitudinal course feature[132]. Establishing the presence of rapid cycling is clinically relevant insofar as it is associated with mixed symptoms, suicidality, comorbidity (e.g., substance use disorder), history of adverse childhood experiences, greater risk of treatment-emergent mania with antidepressants, greater psychosocial impairment, and suboptimal pharmacological treatment response[132,165-167].

In addition, individuals with a rapid-cycling course pattern should not be prescribed conventional antidepressants and/or stimulants, as they can accelerate cycling rate. Although the conceptual framework of kindling posited that anticonvulsants may be preferred in individuals with rapid cycling, there is no compelling evidence that either valproate or carbamazepine are more efficacious than lithium in rapid-cycling bipolar disorder.

The systematic assessment of the course of bipolar disorder is advisable in ordinary clinical practice. The Life Chart Method[168] is a flexible and easily usable approach for mapping the course of the disorder, facilitating capture of episodes that might be missed. The assessment may be retrospective or prospective or both, and information may be collected from patients as well as key relatives (with the patient's permission).

NEUROCOGNITION

Despite the use of the term "dementia praecox" by Kraepelin to differentiate schizophrenia from manic-depressive (bipolar) illness, the presence of neurocognitive impairment across different mood states was identified by the end of last century as a core feature of bipolar disorder[1].

Cognitive disturbances may be present during manic, depressive and mixed states, as well as during periods of remission[169]. They may include deficits of attention, learning and memory, executive functions, and processing speed, amongst other domains[170]. Cognitive functions may improve in some affected persons, whereas in others impairment may persist and progress.

Cognitive deficits in bipolar disorder are moderated by multiple variables, including – but not limited to – number of prior episodes, chronicity of illness and exposure to psychotropic agents[171].

There is considerable heterogeneity across persons with bipolar disorder with respect to the type and magnitude of cognitive deficits. For example, 2-40% of patients display global cognitive deficits, 29-40% show selective decline in attention and psychomotor speed, and 32-48% are cognitively intact[172,173]. Cognitive problems are common in both bipolar I and II disorder, with a greater degree of cognitive impairment reported in the former condition, particularly among persons with psychotic symptoms[174,175].

The clinical relevance of assessing cognitive impairment in bipolar disorder is mostly due to its direct mediational effects on patient-reported outcomes (e.g., quality of life, psychosocial functioning)[176]. Some individuals with bipolar disorder may be more insightful than others about their cognitive problems. Therefore, the correlation between objective and subjective deficits is relatively weak[177].

The assessment of cognitive impairment is imperative in bipolar patients. The Screen for Cognitive Impairment in Psychiatry (SCIP)[178] can be recommended as a brief measure of objective deficits, and the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) for subjective deficits[179]. It should be noted that the foregoing assessments do not replace a full neuropsychological battery, but are applicable to clinical practice due to their relative brevity and ease of use. When formulating a personalized management plan, it is advisable to assess objective and subjective cognition when persons are not acutely ill.

The presence of cognitive impairment may be influenced by several modifiable factors. For example, it is often recognized that many persons with cognitive dysfunction also have subthreshold depressive symptoms. Hence, treating these symptoms when present is the first priority towards attenuating cognitive deficits[180].

Moreover, targeting comorbidity is critical, insofar as many types of physical and psychiatric comorbid conditions are also associated with cognitive impairment. Substance abuse, anxiety disorders, ADHD, as well as physical disorders – including obesity, diabetes mellitus, hypertension and hypothyroidism – may adversely affect cognitive performance in adults with bipolar disorder[181-183].

It is well established that persons with bipolar disorder exhibit unhealthy behaviours with respect to lifestyle and diet. Insufficient or poor sleep quality, sedentarism and a suboptimal diet can be addressed, and this may benefit cognitive performance[184]. In addition, many psychotropic agents prescribed to bipolar patients (e.g., topiramate, anticholinergic agents, anticonvulsants, D2 binding agents, benzodiazepines, lithium) may exert adverse effects on cognition[185].

It is well recognized that cognitive deficits are progressive in several bipolar patients[186]. Conceptually, the foregoing observation is hypothesized to reflect a neurodegenerative process.

When cognitive deficits are identified and quantified, and potentially treatable causes are addressed, patients who fail to achieve full functional recovery may benefit from specific interventions. The management of cognitive deficits in individuals with bipolar patients includes cognitive and functional remediation, aerobic exercise, as well as possibly neuromodulation techniques and chronotherapeutic approaches[180,186-189].

SOCIAL FUNCTIONING

Bipolar disorder has a modal onset during late adolescence or young adulthood, affecting the ability to achieve education, obtain a job, and create long-lasting interpersonal relationships and overall settling in life[190].

Social functioning is often impaired in bipolar patients during and between episodes. In a recent Danish nation-wide population-based longitudinal register study, social functioning and interpersonal relationships were systematically investigated in 19,955 bipolar patients, their siblings, and gender, age and calendar matched control individuals from the general population[191]. Compared to individuals from the general population, persons with a diagnosis of bipolar disorder had lower odds of having achieved the highest educational level (45% vs. 54%, odds ratio, OR=0.75); were less often employed (58% vs. 88%, OR=0.16); less often achieved the highest category of personal income (55% vs. 71%, OR=0.33); less often resided with others (36% vs. 54%, OR=0.44); and less often were married (37% vs. 49%, OR=0.54). Bipolar patients demonstrated a substantially decreased ability to enhance their socio-economic status during the 23-year follow-up period when compared to controls[191].

The Global Assessment of Functioning (GAF)[192] is the most frequently employed scale for the assessment of social dysfunction in psychiatric patients, but its scores have been found to correlate more with symptom severity than functional impairment[193]. The Functional Assessment Short Test (FAST) is currently recommended as the standard scale for assessing social functioning in bipolar disorder[194]. It involves a simple 20-30 min interview specifically designed to assess functioning both globally and across six domains previously identified as the most impaired in bipolar patients (i.e., autonomy, occupational functioning, cognitive functioning, finances, interpersonal relationships, and leisure time)[194].

All FAST items are rated from 0 (no difficulties) to 5 (severe difficulties). The instrument has a high test-retest reliability and has been validated against the GAF. Due to its brevity and ease of use, it has been widely adopted in clinical settings[195].

A systematic review of clinical studies investigating social functioning in individuals with bipolar disorder using the FAST demonstrated global and broad functional impairment that often persists during periods of remission[193]. The prevalence of functional impairment in euthymic persons with bipolar disorder has been reported as follows: global, 58.6%; occupational, 65.6%; cognitive, 49.2%; autonomy, 42.6%; interpersonal relationships, 42.1%; leisure, 29.2%; and financial issues, 28.8%[193]. Residual depressive symptoms are the most frequently cited mediational variable associated with functional impairment, followed by impaired cognition[193].

Marriages of untreated or treatment-refractory bipolar patients are often turbulent. Both patients and their spouses regard violence as the most troubling manifestation of mania, and suicide

threats and attempts as the most worrying aspects of depression. Furthermore, they both complain about financial difficulties, unemployment and social withdrawal due to depression[196].

Most interventional studies in bipolar disorder have primarily aimed to alleviate acute symptoms, as well as to prevent recurrence of illness. Relatively fewer studies have primarily sought to determine whether an intervention can improve functional outcomes. Functional remediation, comprising neurocognitive training, psychoeducation and problem-solving, has evidence of being effective in bipolar patients[188].

The perniciousness of social dysfunction in bipolar disorder invites the need for early detection and intervention. It has been reported that early diagnosis and treatment may prevent aspects of social impairment, with an improved functional trajectory as evidenced by greater education attainment, gainful employment in early adulthood, and economic security[197,198].

There is an unmet need for large-scale early intervention studies in bipolar patients with social functioning as a primary outcome measure, including real-world data on education, employment, income, and interpersonal relationships (i.e., cohabitation, marriage). Furthermore, it is important to address, both at the individual and societal levels, the psychological and social barriers that bipolar patients encounter in their daily lives, which contribute to problems in social functioning[199].

It is recommended that bipolar patients have, as part of their clinical characterization during acute as well as maintenance phases of treatment, their overall functioning assessed by using the FAST. Furthermore, initiatives and behavioural steps to improve daily and social functioning should be integrated into clinical treatment plans. Functional remediation, including occupational and cognitive rehabilitation, should be implemented more broadly in clinical care, providing the basis for these persons to have more fulfilling lives.

CLINICAL STAGING

Clinical staging originated in psychiatry as a conceptual framework for schizophrenia, but has been extended to bipolar disorder, with several overlapping proposed staging models[200-205]. These models have generally adopted the numerical system used in medical staging, with stage 0 defined as an at-risk stage, stage 1 as the prodrome, stage 2 as the first episode, stage 3 as single or multiple recurrences, and stage 4 as chronic or refractory disease[200].

These models capture the aggregate evolution of bipolar disorder, but some bipolar patients may have a severe and deteriorating presentation and course from the beginning, whereas others may have an episodic course with full inter-episode recovery. A linear stepwise progression may not be applicable to all bipolar patients[200]. Furthermore, the diagnosis of bipolar disorder requires the occurrence of a manic episode, but substantial depressive morbidity may precede the first episode of mania.

There is some evidence supporting the construct validity of clinical staging in bipolar disorder. First, there is strong evidence that cognitive impairment is associated with the number of episodes of illness[206]. In a prospective cohort study, patients who had a recurrence within the year after a first manic episode continued to show cognitive impairment, whereas those who remained episode-free had significant improvement in cognition[207]. In another study, patients with a first or second mood episode had relatively preserved cognitive functioning compared to controls, whereas those with three or more episodes had a poorer performance than both controls and early-episode bipolar patients[171]. Finally, cognitive performance was significantly worse than in healthy controls in stage 3 or 4 bipolar disorder, but not in bipolar patients in earlier illness stages[208].

A further evidence is provided by treatment response. Lithium has been found to be more effective earlier in the course of bipolar disorder, while response is poorer in those with multiple prior episodes[209]. A similar pattern has been reported with olanzapine[210] and cariprazine[211]. Lamotrigine has also been found to be less effective as a function of prior depressive episodes[201].

A cross-sectional assessment of prescription patterns in bipolar disorder found that monotherapy or combination of two drugs was common in earlier stages of the disorder, while later stages were characterized by polypharmacy. Social and occupational functioning were inversely correlated with the number of medications[212].

The same pattern of response has been observed in some psychotherapy studies conducted in bipolar patients. For example, it has been reported that manual-based psychotherapy (e.g., CBT) exhibits inferior efficacy in persons with multi-episode (i.e., >12) bipolar disorder as compared to individuals with fewer episodes[213]. However, there is no adequately designed study that has primarily evaluated manualized psychotherapy-based treatment in populations dichotomized as a function of fewer- versus multi-episode bipolar disorder[214].

Some psychoeducation studies found that bipolar patients with the lowest number of prior episodes had the greatest benefit from the intervention[215], while there are data suggesting that functional remediation is effective in individuals with late-stage chronic tertiary presentations of the disorder[216].

Further evidence supporting the clinical staging model is the observation of higher rates of psychiatric and physical comorbidity in individuals with multi-episode/chronic bipolar disorder when compared to individuals who are first-episode. In addition, it is observed that individuals with multi-episode bipolar disorder present lower rates of recovery and quality of life when compared to those with fewer episodes[200]. Multi-episode bipolar disorder has been also found to be associated with progressive brain volumetric changes[217].

Relatively few clinical trials in bipolar disorder have recruited individuals stratified *a priori* using a staging framework. In a first-episode mania study, Conus et al[218] compared chlorpromazine and olanzapine as add-on to lithium and reported a relatively shorter time to acute episode stabilization with the latter. A separate first-episode mania cohort study[219] found that, in patients acutely treated with a combination of lithium and quetiapine, continuation treatment with lithium rather than quetiapine was superior in terms of mean levels of symptoms during a one-year follow-up.

Notwithstanding the conceptual appeal of the clinical staging model in bipolar disorder (as well as the indirect support from cognitive, neurostructural and interventional studies), its clinical application with respect to patient care planning and treatment selection is not sufficiently established. However, the observation that bipolar patients with a higher number of episodes exhibit a more complex illness presentation, higher rates of comorbidity, decreased rates of recovery and quality of life, and diminished treatment responses invites the need for integrated, timely implementation of evidence-based treatments early in the course of illness to positively affect its trajectory.

TEMPERAMENT AND PERSONALITY

Kraepelin operationalized specific affective temperament types, including cyclothymic, dysthymic, hyperthymic and irritable. The Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (TEMPS) questionnaire[220] extends Kraepelin's proposal by adding a fifth type of temperament (i.e., anxious).

The clinical value of measuring temperament is incompletely determined in bipolar disorder. Specifically, there is insufficient evidence that implementing any of the established dimensional quantitative measurements of temperament meaningfully informs illness prognostication or treatment selection.

However, preliminary evidence suggests that quantitative characterization of temperament using the TEMPS may inform suicide risk in bipolar disorder. In fact, risk of suicide attempts in persons with either major depressive disorder or bipolar disorder was associated with elevated scores of four factors in descending order (i.e., anxious, cyclothymic, irritable, and dysthymic) and relatively low ratings for hyperthymic temperament[221,222].

An additional consideration is whether assessing aspects of temperament is relevant to prediction of adherence to treatment. It has been reported that lower rates of adherence in bipolar disorder are associated with higher TEMPS-evaluated cyclothymic and anxious personality dimensions and lower hyperthymic measures[223].

Replicated evidence indicates that the rate of personality disorders in bipolar patients is significantly elevated. For example, approximately 70% of persons with bipolar disorder have traits of borderline personality disorder, with 20% meeting full diagnostic criteria[224]. It is also observed that co-occurring personality disorders in bipolar disorder are associated with a more severe and complex illness presentation, as well as with higher rates of suicidality, non-adherence to treatment, health service utilization, and comorbidity (e.g., alcohol use disorder)[224].

The assessment of personality pathology (as well as temperament) in bipolar patients should be conducted during euthymic periods, taking into account the overlap between several symptoms of bipolar disorder – in particular affective instability, exaggerated emotional expression and intense irritability – with histrionic and borderline personality pathology.

The hazards posed by comorbid personality disorders in bipolar patients justify the careful clinical assessment of these disorders and of maladaptive personality traits at point-of-care. Some evidence suggests that the use of a self-reported screening tool (e.g., the McLean Screening Instrument for Borderline Personality Disorder, MSI) may help identify borderline personality disorder in a person with a diagnosis of bipolar disorder[225].

For individuals with borderline personality disorder, psychotherapeutic approaches (e.g., dialectical behavioural therapy) are considered the cornerstone of treatment, and can be integrated with evidence-based treatments for bipolar disorder[226].

OTHER ANTECEDENT AND CONCOMITANT PSYCHIATRIC CONDITIONS

Persons with bipolar disorder have high rates of psychiatric comorbidity[227]: up to 90% of them meet criteria for one other comorbid condition, and approximately 50% for two or more comorbid conditions[228-231]. However, there is significant under-recognition and, consequently, under-treatment of this comorbidity, reflecting the insufficient characterization of the bipolar patient in ordinary clinical practice.

Population-based and clinical studies indicate that, in many circumstances, co-occurring conditions are antecedent to a first lifetime episode of mania. These antecedent conditions may contribute to bipolar disorder risk. For example, cannabis consumption and other illicit drug utilization may predispose and portend earlier age at onset of bipolar disorder[232]. Preliminary evidence also suggests that antecedent substance use disorder in bipolar patients identifies a different subpopulation (illness presentation and course trajectory) when compared to persons whose substance use disorder is coterminous or follows the onset of bipolar disorder[233].

The presence of comorbidity in bipolar disorder is associated with a younger age at onset and a worse long-term outcome, including increased suicidality and self-harm, a poor adherence to treatment and a less favourable response to lithium. The rate of psychiatric comorbidity is higher in persons with multi-episode bipolar disorder and possibly in persons presenting with the depressive predominant polarity pattern[234].

Clinically significant anxiety disorders are commonly encountered, often antecedent, comorbid psychiatric conditions in bipolar patients[235]. Generalized anxiety disorder, panic disorder and social phobia all differentially affect bipolar patients and are associated with suicidality, greater illness severity and the presence of mixed features. As reviewed earlier, anxiety symptoms at point-of-care can be evaluated with clinician- and/or self-rated anxiety measures (e.g., GAD-7).

Post-traumatic stress disorder (PTSD) also commonly occurs in persons with bipolar disorder. Among the contributing factors are the higher risk of trauma in bipolar patients (mostly due to impulsivity and poor judgement) and the sharing of risk factors between the two disorders. One of the consequences of overarousal in PTSD is sleep disturbance, which can have a direct impact on the course of bipolar disorder. Furthermore, avoidance can lead to social isolation, which may worsen the depressive component of the disorder. The assessment of PTSD at point-of-

care can be made using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[236] or the Davidson Trauma Scale (DTS)[237].

Obsessive-compulsive disorder (OCD) and obsessive-compulsive symptoms are common in bipolar disorder[238]. It has been reported that the course of OCD associated with bipolar disorder tends to be more frequently episodic, and that sexual and religious obsessions may be more frequent, and checking rituals less common[239]. The morbidity associated with OCD warrants direct clinical assessment and initiation of integrated guideline-concordance pharmacotherapy, as well as psychological treatments (e.g., CBT). The assessment of OCD and obsessive-compulsive symptoms can be performed by using the clinician-administered Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[240].

Persons presenting with OCD, PTSD and anxiety disorders are candidates for manual-based psychotherapies. The use of antidepressant treatments to target the foregoing concurrent conditions has to balance the potential benefit with the risk of mood destabilization.

Replicated evidence from both epidemiological and clinical studies has identified an increased prevalence of ADHD in persons with bipolar disorder. As mentioned earlier, ADHD in bipolar patients may be a phenomenological antecedent and is associated with additional comorbidity (e.g., substance use disorder, binge eating disorder)[241]. As the phenomenology of ADHD overlaps with bipolar disorder, careful clinical characterization complemented by informant reports can assist in disambiguating the diagnosis. Also, evaluating ADHD in bipolar patients can be assisted by the use of the Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 (ASRS)[242]. The treatment of ADHD in bipolar disorder integrates CBT approaches along with, in select cases, pharmacological interventions[243].

Approximately 60% of individuals with bipolar disorder meet criteria for alcohol or substance use disorders. Alcohol use disorder is the most common concurrent problem, followed by cannabis use disorder[244]. The assessment of substance/alcohol use disorder in the bipolar patient could include the NIDA Drug Use Screening Tool (NM ASSIST)[245] and/or the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) scale[246].

Despite the common occurrence of substance/alcohol use disorders in bipolar patients, relatively few treatments have demonstrated level 1 evidence (i.e., large rigorous randomized double-blind controlled trials) of efficacy at improving such disorders in these patients[247].

Bipolar patients with concurrent substance/alcohol use disorders should be considered at higher risk for a more complicated illness presentation and a worse outcome, in part related to poorer treatment adherence. The difficulties in personal relationships and occupational functioning related to substance abuse may add to those associated with bipolar disorder, and the effects of the substances may mimic or worsen the side effects of medications, contributing to impair treatment adherence.

A future research vista is to empirically establish whether integrating psychosocial treatments for substance use disorders with guideline-concordant care for bipolar disorder results in improved health outcomes.

Behavioural addictions are reported to be several fold more common in individuals with bipolar disorder relative to controls, with pathological gambling, compulsive buying, sexual and work addictions being the most commonly encountered conditions[248]. The social, legal, occupational and interpersonal consequences of the foregoing addictions are significant. Psychosocial interventions are the treatment of choice for individuals who have behavioural addictions, and should be integrated with the management of bipolar disorder[249].

Eating disorders are frequent, with close to half of bipolar patients reporting significant loss of control concerning food consumption[250]. It is reported that a rapid-cycling course of illness and comorbid substance use disorders are more common in bipolar adults with eating disorders. Preliminary evidence suggests that bipolar II disorder is more likely to be associated with eating disorders than type I disorder. The Eating Disorder Diagnostic Scale (EDDS)[251] can be implemented during clinical assessment to determine whether eating disorders are present and clinical targeting is required.

In addition to the morbidity and mortality associated with eating disorders, they also influence the clinical presentation (e.g., greater complexity of depression), course and outcome of bipolar disorder. Moreover, treatment selection, especially as it relates to pharmacotherapy, may be affected by the presence of eating disorder comorbidities, with some treatments potentially contraindicated (e.g., bupropion in persons with comorbid bulimia nervosa). The treatments for individuals with eating disorders are largely psychological, with an emphasis on CBT.

Tourette's syndrome is estimated to be approximately four times more frequent in bipolar patients relative to the general population[252]. Similarly, impulse control disorders are more common in persons with bipolar disorder, with the overlapping of symptoms being a significant problem for the differential diagnosis. Examples of impulse dyscontrol include fire-setting behaviour, aggressive behaviour, and shoplifting. Targeted psychosocial interventions (e.g., CBT) are indicated in these cases.

Premenstrual dysphoric disorder is reported to be more frequent in bipolar II patients[253]. The assessment of this disorder should be made using the Premenstrual Tension Syndrome Visual Analogue Scale (PMTS-VAS), a validated 12-item scale[254]. The treatment should be based on the cautious administration of a selective serotonin reuptake inhibitor (SSRI) as add-on to the ongoing mood stabilizer.

Taken together, the characterization of the patient with a diagnosis of bipolar disorder in all circumstances should carefully ascertain whether concurrent psychiatric conditions are present. Clinicians are reminded that these conditions may manifest as antecedent, coterminous or later declared disorders. The presence of comorbidity is associated with a more complex illness presentation, greater illness severity (e.g., suicidality), suboptimal response to treatment, and a more unfavourable illness trajectory.

All individuals with psychiatric comorbidity will require either sequential or contemporaneous management of the concomitant condition(s), and it can be anticipated that the longitudinal course of bipolar disorder is more likely to be recurrence prone in the

context of comorbidity.

PHYSICAL COMORBIDITIES

Multiple physical comorbidities occur at a higher rate in bipolar disorder, including – but not limited to – obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease, thyroid dysfunction, and inflammatory bowel disease[255-257]. Moreover, there is increasing awareness of the higher rate of non-alcoholic fatty liver disease in persons with bipolar disorder, which is associated with obesity, exposure to psychotropic medication, and number of prior mood episodes[258].

This higher rate of physical comorbidities is a consequence of risk factor clustering in this population[259-261]. For example, persons living with bipolar disorder often have relatively less access to timely, high-quality, primary and preventive health care. Moreover, they are more likely to report economic, housing as well as food insecurity, each of which is associated with adverse physical health outcomes[262-264]. Adverse childhood experiences, which are reported in a significant percentage of these persons, are associated with obesity, metabolic disturbances and cardiovascular disease[265].

Unhealthy behaviours and psychiatric comorbidities associated with bipolar disorder (e.g., cigarette smoking, substance and alcohol use disorders) are additional risk factors for both non-communicable and communicable physical diseases. Smoking has also been identified as a risk factor for bipolar disorder and a predictor of an unfavourable clinical outcome[266]. Finally, contemporary models of disease pathogenesis in bipolar disorder implicate disturbances in immunoinflammatory systems, insulin signalling, mitochondrial function, autonomic regulation, as well as hypothalamic-pituitary-adrenal axis function, each of which may be causative of comorbid physical disorders[1,267-271].

A separate body of literature implicates bipolar disorder as an independent risk factor for cardiovascular disease[272]. For example, in younger populations with the disorder, an increased frequency of subclinical vascular disease has been found[273]. It is also reported that the disorder is an independent risk factor for immune-based non-communicable (e.g., hyperthyroidism)[274] as well as communicable (e.g., COVID-19 infection)[275] diseases. The relationship between bipolar disorder and thyroid dysfunction is complex and reciprocal; subclinical hypothyroidism has been associated with rapid cycling and treatment-resistant depression. Bipolar patients, in particular women, are more likely to suffer from migraine than the general population.

An established modifiable risk factor for some comorbid physical conditions (e.g., obesity, type 2 diabetes mellitus, dyslipidemia) is exposure to psychotropic medications (e.g., lithium, valproate, second-generation antipsychotics)[276-278].

Bipolar patients with obesity are more likely to present suicidality, impaired reward processing, relapse and chronicity[260,279]. It is also established that obesity and related metabolic disorders in bipolar patients are associated with cognitive dysfunction, mixed features, impaired quality of life and psychosocial dysfunction[261,280-282].

Cardiovascular disease is the most common cause of premature mortality and shortened life expectancy in bipolar patients, with approximately 8-12 years of life lost[283,284]. The shorter life expectancy is not observed in unaffected first-degree relatives of bipolar patients, implicating factors specifically related to the disorder[285].

All bipolar patients should be evaluated for the presence of risk factors for physical comorbidities. Several risk factor calculators are available, which may inform and quantify prognostic risk for cardiovascular disease – e.g., the Framingham Risk Factor for Cardiovascular Disease (FRS-CVD)[286], the Systematic Coronary Risk Evaluation (SCORE)[287]. Some risk calculators are able to prognosticate risk for type 2 diabetes and by extension cardiovascular disease[288].

Emphasis should be given to primary prevention of physical comorbidities, especially in newly diagnosed individuals with bipolar disorder. Lifestyle modification, dietary education, sleep hygiene, and stress management should be components of a larger psychoeducational program for any person diagnosed with the disorder.

It is established that approximately 50-70% of persons with bipolar disorder smoke cigarettes daily or regularly. This is associated with depressive symptoms, suicidality, alcohol and substance use disorder, and shorter life expectancy[289,290]. The foregoing hazards of smoking invite the need for smoking cessation programs.

Available evidence indicates that, although bipolar patients may have higher dropout rates from smoking cessation programs, a considerable proportion of them can reasonably expect abstinence from smoking with concordance to the foregoing treatment interventions[291]. Web-based programs – such as acceptance and commitment therapy combined with WebQuit Plus – have been found to increase the likelihood of smoking cessation when combined with nicotine replacement[292].

As part of a comprehensive assessment, all persons with bipolar disorder should have a physical examination with attention paid to blood pressure, weight, and body mass index. Measurement of waist circumference is also encouraged, as it has greater predictive utility of cardiovascular risk when compared to body mass index[293]. Laboratory tests should include assessment of lipid parameters, cholesterol fractionation, blood glucose, and glycated hemoglobin[1]. The evaluation of the thyroid function is particularly advisable in patients with rapid cycling and treatment-resistant depression.

When comorbid physical conditions are present, they should be managed in parallel with the psychiatric disorder. Care pathways for patients should integrate multidisciplinary expertise and implement best practice recommendations longitudinally. Pharmacological strategies targeting concomitant physical disorders should be adopted with attention to potential for drug-drug interactions. Treatments for the psychiatric disorder that do not adversely influence risk and course of concurrent physical conditions should be prioritized[294].

Available evidence indicates that effective management of physical comorbidities has salutary effects on the clinical course

and outcome of bipolar phenomenology[295].

FAMILY HISTORY

Family history is a critical aspect of diagnostic assessment and treatment selection, as well as being pertinent to the risk of suicide and comorbid conditions in bipolar patients.

Bipolar disorder is highly familial, with heritability estimates of approximately 70%[1]. The risk to first-degree relatives of bipolar probands is approximately 8-10 times higher compared to the general population[296]. In addition to an elevated risk of bipolar disorder, family members are at increased risk of other mental disorders (e.g., major depressive disorder, psychotic disorders)[297]. A number of susceptibility loci for bipolar disorder have been identified via genome-wide association studies, but family history remains the best proxy of the genetic liability to the disorder.

Multiple studies suggest an association between a favourable response to lithium and family history of bipolar disorder. It is reported that response to lithium is higher in bipolar probands who have a family history of lithium-responsive bipolar disorder (i.e., approximately 67%)[298].

The suicide risk in bipolar disorder is among the highest of any medical condition, and results from meta-analysis indicate that suicide clusters in families (i.e., OR=1.69)[299]. This finding, however, may under-estimate the risk, insofar as a separate analysis that included systematic assessments of multiple family members reported a much higher risk of suicide in families of bipolar patients (i.e., hazard ratio=6.6)[300].

The modality by which family history is routinely documented by clinicians may be imprecise and have little clinical utility. Frequently, the history is collected by a few questions such as "Did anyone in your family have any similar conditions?". However, in order to have clinical utility, family history should include additional information such as the specific diagnosis, history of comorbid psychiatric conditions, history of physical disorders, and response to treatment(s) including adverse effects. In addition, features such as the presence of psychosis and rapid cycling should be explored as far as possible.

When assessing family history, a useful approach is to draw the family tree and proceed with collection of information systematically, starting with the patient's parents, siblings and children. Various structured tools – including the Family Interview for Genetic Studies (FIGS)[301], the Family History Research Diagnostic Criteria (FH-RDC)[302] and the Family History Screen (FHS)[303] – can aid clinicians in collecting and documenting patients' family history in a comprehensive and systematic manner.

Reviewing individual family members also provides the clinician with an opportunity to probe about family dynamics and gain insight into how the family views psychiatric illness (i.e., are they supportive, do they aid in maintaining treatment adherence, are they interested in psychoeducation, can they be involved in relapse prevention planning?).

While structured approaches to documenting family history can generate useful information beyond routinely collected data, they remain of limited value in patients who were adopted, those who do not keep in close contact with their relatives, and/or in families which hold negative/stigmatizing views of mental illness. Similarly, the advantage of family history is reduced in small families, due to increased random variation[1].

EARLY ENVIRONMENTAL EXPOSURES

Adverse childhood experiences are common in persons with bipolar disorder. It is frequent for these persons to report multiple forms of abuse (e.g., verbal, physical, sexual, emotional) and/or neglect, and cumulative measures and severity of abuse and/or neglect have been found to be associated with a more complicated course and outcome of the disorder[1]. This includes an earlier age of onset; greater levels of anxiety, substance abuse, and comorbid personality disorder; more episodes and rapid or ultra-rapid cycling; and treatment resistance. Adverse childhood experiences are also associated with the occurrence of more physical illnesses in adulthood[304].

The hazards posed by adverse childhood experiences, as well as their frequent occurrence, provide the impetus for recommending that all bipolar patients be assessed for history of these experiences. A careful clinical history is often sufficient to elicit reports of the experiences. Self-report scales, such as the Childhood Trauma Questionnaire (CTQ)[305], may additionally be used[306]. The type, severity and timing of the experiences should be ascertained and documented.

Available research suggests that physical and sexual abuse, rather than verbal abuse, may have more hazardous effects for persons with bipolar disorder. However, verbal abuse alone (i.e., in the absence of physical and sexual abuse) is reportedly associated with an earlier age at onset and a worse course of the disorder[307].

When there is a convergence of adversity in early childhood and a positive family history of bipolar disorder, the incidence of early onset and suicide attempts is significantly greater relatively to when either risk factor is exhibited in isolation[308]. Several lines of evidence indicate that a history of sexual abuse is associated with the highest rate of subsequent suicide attempts[6,309].

A history of childhood adversity may have a priming or sensitizing effect insofar as experiencing subsequent stressful life events. It has been reported that patients with such a history experienced more stressors (in multiple domains including interpersonal support, economic difficulties, and inadequate access to psychiatric and physical health care) in the year prior to the onset of the first episode of bipolar disorder[310].

There is also evidence for a cross-sensitization between the experience of early adversity, mood episodes and bouts of substance use. Early adversity is associated with an increased proclivity to substance use and abuse, and mood episodes can induce stressful life events and further increase the risk for substance abuse. Thus, the experience of early adversity can precipitate a cascading effect of sensitization to further stressors, mood episodes and substance misuse, each of which further drives illness progression[311].

Persons with bipolar disorder reporting adverse childhood experiences should receive treatment that integrates evidence-based pharmacotherapy with manual-based psychotherapies (e.g., CBT). It is not known whether trauma-focused psychotherapies (e.g., eye movement desensitization and reprocessing therapy) are differentially effective in individuals with bipolar disorder[312].

RECENT ENVIRONMENTAL EXPOSURES AND RELAPSE TRIGGERS

Replicated evidence indicates that recent stressors across the exposome (e.g., environmental, economic, interpersonal, vocational, cultural, and social factors) moderate the presentation, course and outcome of bipolar disorder[313].

Commonly encountered recent stressors in adults with bipolar disorder derive from interpersonal relationships and occupational insecurity. Indeed, bipolar patients report shorter duration of relationships as well as divorce rates 2-3 times greater than the general population[314]. They are also more likely to report maladaptive interpersonal experiences (e.g., bullying) which are associated with symptom intensification, suicide and psychosis, especially in younger populations[315].

Individuals with bipolar disorder are also more likely to report job stress, employment insecurity and dislocation, and need for disability payment when compared to the general population[316]. Moreover, job-related stress is often identified as an antecedent of relapse and chronicity of illness.

Taken together, each of the foregoing stressors should be a focus of clinical inquiry given their established association with illness destabilization.

Social determinants of health (e.g., poverty) are increasingly recognized as modifiable environmental factors that also predispose to relapse in bipolar disorder[317]. In addition, comorbidities (both medical and psychiatric) may also represent recent stressors (as well as chronic stressors) and are reported to be more common in persons with multiple-episode unstable bipolar disorder[227].

Life events that cause disruption to sleep/wake cycles are often associated with recurrences of mania, suggesting the importance of keeping regular daily and nightly routines following a disruptive event[318]. Positive "goal attainment" events, such as getting a job promotion or developing a new romantic relationship, promote drive, ambition and self-confidence in bipolar patients, and may result in excessive engagement in goal pursuit and manic symptoms.

Several scales assessing the presence and magnitude of stressors/life events have been validated. The Longitudinal Follow-Up Evaluation (LIFE)[168] and the LIFE Range of Impaired Functioning Tool (LIFE-RIFT)[319] are examples of scales that identify and measure stressors/life events. At point-of-care, recent environmental stressors in bipolar patients can be evaluated with the Perceived Stress Scale (PSS)[320], a patient-administered, 10-item scale measuring self-appraisal of life stress.

Critical elements when assessing life events are the frequency and the individual perception of impact of the stressor. Evaluating stressors in bipolar patients has conventionally focused on critical time points across the course of illness, such as the premorbid period, the first year of illness, and the most recent episode. The lifetime trajectory approach recognizes that the potential for substance misuse, psychosocial supports, financial/employment difficulties, medical comorbidities, and access to health care may differ across the life span[309].

There is increasing interest in tracking daily behavioural patterns, bipolar symptoms, and exposomic stressors with mobile technology such as actigraphy and ecological momentary assessment devices[321-324]. The foregoing technology is a capability which allows for real-time assessment of illness-related dimensions (e.g., circadian rhythms, psychomotor activity) akin to digital fingerprinting of the disease state[325]. Notwithstanding the promise of this technology, it has not yet been established that it positively affects health outcomes, treatment selection, health service utilization, concordance with best practices, and/or cost-effectiveness of treatment in bipolar disorder[322,326,327].

All individuals with bipolar disorder should be queried about recent stressors across multiple domains of the exposome. Problems with access to timely primary and specialty health care as well as disruption to medication availability represent both intrinsic and environmental stressors that should also be explored. Social rhythm therapy[328] should be considered in patients in whom disruption of sleep/circadian rhythms appears to contribute to relapses.

In addition to the foregoing, all individuals with bipolar disorder should be queried about their economic, employment, housing and food security. Characterization of a patient's socio-economic status, as well as spatial/structural stressors (e.g., racism, residency in a high-crime neighborhood) also add to the characterization of the bipolar patient.

PROTECTIVE FACTORS AND RESILIENCE

Although few studies have systematically examined protective factors or resilience in bipolar disorder, randomized trials of psychosocial interventions have provided some insight.

Patients with caregivers who show low levels of expressed emotion (EE) are at a lower prospective risk for relapse than patients with high EE caregivers[329]. Low EE families are able to curtail negative patient/caregiver interchanges before they become destructive, whereas high EE families are characterized by frequent "point-counterpoint" arguments[330]. Low EE families are also more cohesive and adaptable than high EE ones[331]. Differences among patients may moderate the foregoing associations: those who report less distress when criticized by parents or spouses show lower levels of depression and more days of wellness over one year[332].

Family conflict and relationship quality can be assessed via the Conflict Behavior Questionnaire (CBQ)[333] and/or the Family Adaptability and Cohesion Scale (FACES)[334]. EE among caregivers can be difficult to assess in practice, due to the extensive train-

ing required to administer and score interviews. Proxy measures can be obtained with the Five-Minute Speech Sample (FMSS)[335] or the patient-report Perceived Criticism Measure (PCM)[336], a 10-point rating of the amount of criticism from relatives and the causal degree of distress[337,338].

Family relationships are not static entities, and can change considerably as the patient cycles through recurrence and recovery from episodes. Additionally, family environments are influenced by whether relatives are affected by mood disorders themselves, and whether these disorders are stable at the time of assessment.

The duration of depressive episodes is mitigated by social support networks, an important protective factor in maintaining self-esteem[339]. Patients who are low in rejection sensitivity are also buffered against the effects of negative events[340]. Bipolar patients with better emotion regulation (i.e., ability to reappraise negative situations) are less likely to ruminate about their moods after negative events[341]. Bipolar patients who have difficulties with cognitive flexibility are more likely to use maladaptive regulation strategies (e.g., emotion suppression) in emotionally charged situations compared to healthy controls[342].

Insight – i.e., the recognition that one is ill and needs treatment – has been found to be a protective factor for some outcomes of bipolar disorder and a risk factor for others. Higher insight is associated with better medication adherence[343] and better symptomatic outcomes over 1-2 years[344]. However, among patients who have been highly recurrent, increased illness awareness may contribute to feelings of hopelessness about the future as well as suicidality[345].

Illness literacy – i.e., having an understanding of etiology, prognosis, treatment, and self-management – contributes to resilience in bipolar disorder. In a randomized trial of a brief form of individual psychoeducation, patients with higher post-treatment scores on an illness knowledge test had more weeks in remission over the next year[346]. Patients' health beliefs, such as whether medications are likely to have beneficial or disadvantageous effects on moods or functioning, influence treatment adherence[347,348]. Illness literacy in caregivers is also protective: a longitudinal study found that patients with lower ratings of perceived criticism from caregivers, and more caregiver knowledge of bipolar disorder, were 9.5 times more likely to be free of hospital admissions over 1 year than patients without the foregoing factors[349].

Most adjunctive psychosocial treatments for bipolar disorder have a psychoeducational component, in which patients and/or key relatives explore their beliefs about the illness, learn to recognize prodromal signs of recurrences, and practice preventive strategies (e.g., requesting rescue medications). A network meta-analysis of 39 randomized clinical trials of adjunctive psychotherapy for bipolar disorder indicated that guided practice of illness management skills (e.g., self-monitoring of symptoms), conducted in a family or group format, was associated with lower rates of recurrence over one year than the same practice conducted in an individual format[350]. Thus, involving collaterals in pharmacological or psychosocial treatment sessions often leads to better adherence and outcomes.

Clinicians treating bipolar patients should be aware of the potential role of protective factors in informing the choice of treatments and affecting their success. For example, patients in families with high levels of criticism and conflict show greater responses to family-focused therapy than those in more benign family environments[351]. When psychotherapy is successful in encouraging patients to keep consistent daily routines and sleep/wake habits, recurrences occur less frequently[352]. Brief motivational enhancement therapy – a person-centered approach that addresses illness awareness and readiness for change – has been demonstrated to have a strong impact on pharmacological adherence and depression in patients with bipolar disorder[348].

Absent from the literature are well-operationalized, illness-specific definitions of protective and resilience processes. Patient-centered definitions of recovery (e.g., having a satisfying life despite symptoms or impaired functioning) may be more meaningful than traditional endpoints such as symptom remission[353]. Digital tracking of illness coping strategies and their relationship to symptom fluctuations may help clarify whether protective factors are more important in certain phases of the illness (e.g., during acute episodes vs. recovery periods), or in earlier vs. later stages of the disorder.

INTERNALIZED STIGMA

Internalized stigma is defined as a subjective state "characterized by negative feelings (about self), maladaptive behaviour, identity transformation, or stereotype endorsement resulting from an individual's experiences, perceptions, or anticipation of negative social reactions on the basis of their mental illness"[354].

The magnitude of stigma associated with bipolar disorder is comparable to that reported in persons living with schizophrenia[355]. Stigma is identified by persons living with this disorder and their families as a priority concern and therapeutic target[356].

The need for the assessment of internalized stigma in bipolar patients is underscored by its association with decreased health service utilization and concordance with guideline-recommended treatments[357].

A derivative of stigma related to treatments for bipolar disorder is the perceived impact on self-rated measures of creativity. It is well established that bipolar disorder is more common in individuals who are creative, and the disorder is over-represented among persons in the creative professions[358]. Notwithstanding stigma and patient concerns, there is no convincing evidence that psychotropic agents prescribed to persons with bipolar disorder, as well as other modalities of treatment (e.g., neurostimulation), attenuate aspects of creativity[359].

Further evidence instantiating the clinical relevance of internalized stigma as part of the clinical assessment of bipolar disorder is provided by data indicating that higher stigma ratings are associated with increased symptom severity, reduced functioning, greater concealment of illness, social withdrawal and social anxiety[360,361].

Internalized stigma can be assessed via clinical interview by soliciting feedback from the patient regarding his/her experience of living with bipolar disorder. This clinical assessment can be supplemented by several quantitative measures. For example, the Internalized Stigma of Mental Illness (ISMI) is suitable for use in bipolar patients[362,363]. The ISMI scale is comprised of 29 items and has high internal consistency as well as test-retest reliability.

Evidence suggests that stigma reduction initiatives are more likely to be effective when tailored to the clinical profile of specific conditions, yet few stigma interventions targeted towards bipolar disorder have been developed. Although most modalities of psychotherapy for bipolar patients address aspects of internalized stigma, their anti-stigma impact has not been established[364].

In the interim, the clinical characterization of bipolar disorder should query all affected persons about internalized stigma and its impact on the person's experience of mental illness, overall functioning, concordance with treatment, and motivation to participate in chronic disease management. Moreover, where applicable, an evidence-based conversation with bipolar patients expressing concerns about the adverse effects of medications on creativity should take place.

DISCUSSION

In this paper, we have systematically described salient domains for the clinical characterization of the person with a diagnosis of bipolar disorder, and provided suggestions for clinical metrics that can be implemented in both high- and low-resource environments.

Pharmacological discovery and development across phases of bipolar disorder are primarily designed to seek regulatory approval for subsequent marketing authorization. The treatment development process gives greater emphasis to large, randomized, double-blind, placebo-controlled trials. These trials enroll patients that are often not representative of those encountered in clinical practice, limiting their ecological validity. Clinical practice guidelines in bipolar disorder are thus largely comprised of algorithms based on trials that were not primarily designed to identify differences between pharmacological agents and classes or patient characteristics moderating treatment response. Consequently, treatment choices across acute mania, depression, mixed states and maintenance are often not informed by the multiple clinical characteristics of the person living with bipolar disorder seeking health care.

Taken together, compelling evidence indicates that improving health outcomes from a clinician, patient and societal perspective in bipolar disorder is possible with existing treatments informed by deep *in vivo* characterization across salient domains. However, implementation research indicates that most recommendations for patients with chronic disease are not implemented at the point-of-care[365]. As a derivative of the foregoing observation, clinicians should be familiar with enablers and barriers to implementing evidence-based treatment approaches in ordinary practice.

It is apparent that an asymmetric body of evidence exists with respect to which domains should be priorities for clinical characterization by professionals providing care to a person with bipolar disorder. Compelling evidence exists that subtyping the disorder as a function of types I and II has relevant clinical implications. In addition, the identification of mixed features, and history of trauma/maltreatment have demonstrable impact on treatment selection, illness presentation, course and outcome of the disorder. Suicidality should be assessed in all individuals throughout the illness trajectory, and appropriate risk mitigation strategy implemented in high-risk patients. Despite its conceptual appeal, there is less evidence that staging is a clinically useful construct in bipolar disorder, although individuals with multiepisode disorder generally exhibit less favourable responses to pharmacological treatment when compared to those with single-episode mania.

During the past decade, replicated epidemiological and clinical data have underscored the prevalence and clinical implications of physical and psychiatric comorbidities in bipolar disorder. Moreover, the available evidence indicates that cardiovascular disease is the most common specific cause for premature and excess mortality in bipolar patients[366]. Clinician evaluation of comorbidity and its risk factors should be an integral component of every patient assessment[367]. The elevated risk for COVID-19 infection and its complications amongst persons with bipolar disorder illustrates the confluence of innate and social/economic determinants of medical risk in this population[275]. Health systems and organizations are often not configured to sufficiently address both physical and mental health comorbidities in the adult with bipolar disorder. Notwithstanding, scalable risk factor modification, and medical health education including aspects of diet and lifestyle change are cost-effective and should be part of general education aiming to enhance patients' illness literacy and self-management[368,369].

Despite the plethora of research on temperamental characterization in bipolar disorder, there is limited evidence indicating that quantitative assessment of temperament dimensions can inform treatment decisions or other aspects of clinical care. The high rate of personality pathology in bipolar disorder is a replicated observation. The co-occurrence of bipolar disorder and borderline personality disorder, in particular, is a common occurrence in clinical practice and identifies a subgroup especially at risk for self-harm, comorbidity (e.g., alcohol and substance use disorder), maladaptive interpersonal function, and suicide[224].

Despite the ubiquity of comorbidities in bipolar disorder, there is a relative lack of large randomized controlled trials informing treatment decisions in persons presenting with either psychiatric or physical concomitant conditions. Notwithstanding a large and compelling body of evidence describing disparate aspects of resilience and its relevance to wellness and adaptation, this area has been greatly understudied in bipolar disorder. Validated scales for resilience in bipolar patients are currently available, but implementation research has not documented meaningful effects of their use on health outcome.

Furthermore, the robust literature describing the relationship between interpersonal conflict and the course of bipolar disorder stands in contrast to the lack of data evaluating measures of loneliness in persons with this disorder and whether aspects of loneliness influence the presentation and should be measured at point-of-care[370]. A replicated body of evidence has identified an association between validated measures of loneliness (e.g., the UCLA Loneliness Scale[371]) and risk for depression, anxiety, medical comorbidity (e.g., obesity), cognitive impairment, and decreased quality of life[370]. A separate body of evidence also indicates that higher self-reported loneliness measures are associated with an increase in psychotropic drug prescription (e.g., antidepressants, hypnotics, benzodiazepines) in older populations[372].

Subjective measures of loneliness have been insufficiently applied to adults with bipolar disorder. Preliminary evidence suggests that loneliness in bipolar patients is associated with decreased measures of self-efficacy with respect to managing their illness[373]. It is, however, unknown whether loneliness influences relapse vulnerability, phenomenological presentation, illness trajectory, and/or response to treatment. In the interim, clinicians are encouraged to carefully characterize interpersonal networks and supports in each person presenting with bipolar disorder. Future research vistas should ascertain whether loneliness has to be specifically measured at point-of-care and, if so, what are the appropriate measures and what is the impact on health outcomes and cost-effectiveness of treatment.

A compelling body of literature indicates that clinicians' implicit biases influence diagnostic considerations as well as treatment choices in psychiatry[374]. For example, individuals from ethnic and racial minorities with bipolar disorder are more likely to be misdiagnosed with a primary psychotic disorder[375]. It is also reported that male physicians are more likely to prescribe benzodiazepines to female patients when compared to female physicians[376]. The potential for bias to portend discordance with diagnosis and/or best treatment practices amongst persons with serious mental illness provides impetus for contemplation at point-of-care. Future research should attempt to empirically quantify the extent to which implicit biases as well as aspects of equity, diversity and inclusion moderate health outcomes in persons with bipolar disorder, and what are potential measures and mitigation strategies at point-of-care[377].

Personalizing a management plan for an individual diagnosed with bipolar disorder starts with determining locus of care[378]. Lack of timely access to high-quality, integrated, longitudinal care is a modifiable structural barrier to optimal outcome for a large percentage of persons living with bipolar disorder. Digital psychiatry is an opportunity to address access gaps and possibly assist in momentary assessment of disease activity, "just in time care", suicide risk assessment, and monitoring of psychosocial outcomes and response to treatment, as well as to provide a platform for psychoeducation and peer support[322]. End user satisfaction and clinical outcomes achieved with Internet-based manualized psychotherapeutic approaches for depression are compelling and, in some circumstances, comparable to in-person outcomes[322]. Moreover, Internet-based approaches are potentially more cost-effective and destigmatizing and are especially appealing in low-resource environments with minimal access to timely psychiatric care. It is, however, unknown whether digital capabilities meaningfully influence long-term health outcomes in individuals with bipolar disorder – a further research vista priority[379].

The guiding principle of deep *in vivo* clinical characterization emphasized herein is to be integrated with shared decision making and other aspects of chronic disease management[380]. Research into innovative treatments for bipolar disorder will also benefit from thorough characterization of the phenotype as the field endeavours to identify relevant biomarkers[3,268]. It is additionally expected that the future of clinical psychiatry will use big data and machine learning approaches integrating the characterization of the patient informed by clinical assessment with electronic health records and sensor recordings.

ACKNOWLEDGEMENTS

R. McIntyre has received a research grant support from CIHR/GACD/Chinese National Natural Research Foundation. M. Berk is supported by a National Health and Medical Research Senior Principal Research Fellowship (grant no. 1156072). R.J. Baldessarini is supported by a grant from the B.J. Anderson Foundation.

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DOI:10.1002/wps.20997

Coming out proud to erase the stigma of mental illness

Stigma may harm people with mental illness as much as the symptoms and disabilities of their disorders. This experience is often divided into public stigma (the prejudice and discrimination experienced by people with mental illness when members of the general population endorse stereotypes about them) and self-stigma (the sense of shame that emerges when people with mental illness internalize these stereotypes).

Substantial research has examined stigma reduction strategies by contrasting the effects of education (countering the myths of mental illness with facts) versus those of contact (facilitating interactions between people in recovery and the general population). Findings fairly consistently suggest that contact has a deeper and broader impact on public stigma than education. In fact, education programs that seek to decrease stigma by framing mental illness as a brain disorder actually seem to worsen stigma[1].

Stigmas are marks that signal a "spoiled" identity, with these marks described as obvious (such as skin color leading to racism or body features leading to sexism) or hidden. Stigma related to mental illness falls into the latter category, and in some ways is similar to the kind of stigma experienced by the lesbian, gay, bisexual, transgender and queer or questioning (LGBTQ) community. There are no patently observable marks that unequivocally signal a person as LGBTQ or with mental illness. Hence, people must decide to disclose their experiences if they seek to be an effective contact that is meant to diminish the stigma related to their condition. The LGBTQ community realized this over the past 50+ years by bravely coming out to tell their stories and demand solidarity. I want to explicitly state that comparing the LGBTQ experience to mental illness is not a reiteration of previous harmful ideas that LGBTQ is a mental illness, a particularly troubling part of psychiatry's lore. In terms of the goals of this paper, what I mean is that people may need to disclose their mental illness in order to be effective anti-stigma contacts.

This kind of strategic disclosure not only tears down the public stigma that robs people of rightful opportunities, but also diminishes the sense of shame that describes self-stigma. Being in the closet, hiding one's mental illness, has been repeatedly shown to exacerbate the shame of self-stigma, undermining one's sense of self-esteem and self-efficacy[2]. Strategic approaches to disclosure may provide one way to help people overcome the harmful effects of closetedness.

This might seem counterintuitive, especially when considering impression management strategies which suggest that people should reframe or avoid altogether describing troubling experiences in their past – e.g., poor school performance, dishonorable military discharge – in order to avoid the public stigma that accompanies this knowledge. Proponents of impression management seem to suggest that people should at least distance, if not deny, mental illness-related identities that will be disparaged by the public.

This assertion, however, is contrary to fundamental social psychological research about stigma in general[3], which has shown that people from stigmatized groups (e.g., people of color, women, those from the LGBTQ community) report less stress and more self-esteem when identifying with their group. But does this apply to a group that is defined by illness and disability? In fact, yes: research has shown that people who identify with their mental illness and deny the stigma demonstrate more hope and better self-esteem[4]. Even more, people who then decide to disclose some aspect of their "mental illness" identity report less self-stigma, more personal empowerment, and enhanced well-being[5].

A group of us with lived experience of mental illness developed the Honest, Open, Proud (HOP) program as a way to promote strategic disclosure meant to diminish self-stigma (www.HOPprogram.org). HOP is a group-based program for people dealing with the shame of mental illness, typically led by two trained facilitators with lived experience.

The program consists of four lessons. The first lesson is to consider the pros and cons of disclosing one's mental health experiences. These, by the way, vary by situation: the pros and cons of coming out at work differ from those of coming out with one's faith-based community or among one's extended family. The second lesson is to learn ways to safely disclose one's identity. One way, for example, is to "test" a possible person one might disclose to by asking him/her about general attitudes regarding people who have disclosed: "Hey, did you see Mariah Carey came out with her bipolar disorder? What do you think?". If that person responds negatively ("I hate when people talk about things that should be kept a secret!"), then he/she is probably not a good person to disclose to. The third lesson is how to craft disclosure in ways that are most effective for the individual. The fourth lesson is to use one month follow-up: ask people if they disclosed and how it went.

Let me be clear on the goals of HOP. It is not to convince people with mental illness to disclose their story. Such disclosure has risks, and only the individual, over time, can know whether and where it might benefit him/her. Anecdotally, only about one-third of people at the Lesson 4 follow-up will report having actually disclosed their story to someone. Nevertheless, research has shown that completing HOP has beneficial effects on self-stigma, stigma stress, self-esteem, and recovery, if one actually discloses mental illness[6-8]. As one person put it, "I never knew I had the option of coming out. I thought I was supposed to keep it a secret".

Honest, Open, Proud. What is there to be proud of? After all, isn't mental illness fundamentally some mark of failing – albeit biological failing – which the person wants to overcome and move away from? Pride is a common human response based on accomplishment and essence[9]. In terms of accomplishment, people feel proud in meeting personal goals such as students earning diplomas or runners meeting a faster time. People with mental illness have similar aspirations, which sometimes are even more pride-filled when achieved despite disabilities. But, perhaps even more

so, pride is related to sharing one's essence. People do this ethnically; for example, when I tout being an Irish American. Mental health experiences are part of many persons' perceived essence. Being an authentic person means having the choice on when and what to share from these experiences. Coming out tears down the fabric of societal stigma so that people have the space to be authentic and whole.

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DOI:10.1002/wps.21016

Meaning in life is a fundamental protective factor in the context of psychopathology

In the midst of profound upheavals to the world, the question of what life means feels urgent and acute. Decades ago, the inspiring advocate for the human need for meaning, the psychiatrist V. Frankl, argued that the 20th century was marked by a widespread affliction in which people complained of "the feeling of the total and ultimate meaninglessness of their lives. They lack the awareness of a meaning worth living for. They are haunted by the experience of their inner emptiness, a void within themselves"[1, p.128].

Such words could have been uttered last week. In contemporary life, the haunting inner emptiness that Frankl spoke of seems increasingly accompanied by a haunting outer emptiness, as the world whirs through accelerating technological, social and ecological convulsions. Fortunately, a wealth of empirical research has emerged to provide guidance on how meaning in life may buttress us against such pressures.

Meaning in life has been defined as people's subjective judgments that their lives are marked by coherence, purpose and significance, which emerge from "the web of connections, interpretations, aspirations and evaluations that a) make our experiences comprehensible, b) direct our efforts toward desired futures, and c) provide a sense that our lives matter and are worthwhile"[2]. Thus, coherence is our cognitive capacity to make sense of our lives and perceive predictability and consistency. Purpose is our motivational capacity to strive for long-term aspirations that are personally important. Significance is our evaluative capacity to see inherent value and worth in being alive and recognize that we matter.

Despite this tridimensional conceptualization, the vast bulk of research has been conducted using general "meaning and purpose" measures, such as the Meaning in Life Questionnaire (MLQ)[3]. The MLQ is brief, psychometrically robust, has been used globally, and seems to have helped facilitate an explosion in research on meaning in life. It is no exaggeration that thousands of empirical studies have been published demonstrating that meaning in life is a foundational component of well-being. Meaning in life is thought to support well-being by integrating cognitive and motivational aspects of functional relevance to people, such as identity and self-worth, attachment and belonging, and self-concordant goal-setting and goal pursuit[1-3]. Meaning in life gives people a reason to live and a basis to make sense of their life experiences – past, present and future.

It is encouraging to see considerable research aiming to document how meaning in life relates to and interacts with psychopathology and treatment for mental disorders, particularly psychotherapies. Unsurprisingly, most research shows that people with diagnosed disorders or with elevated symptoms of psychopathology report lower levels of meaning in life and are more likely to score in the "my life is meaningless" range on measures.

Research often finds that meaning in life has especially strong inverse relations with the presence and severity of depression symptoms[4], although studies have also focused on schizophrenia, eating disorders, substance use disorders, anxiety disorders, and post-traumatic stress disorder, with multiple papers published on each of these disorders.

Beyond diagnosis- and symptom-focused studies, research has indicated that meaning in life appears to play a protective role against suicidal ideation, suicide attempts, and non-suicidal self-harm. Among 199 patients surveyed in a psychiatric emergency department in Switzerland, lower scores on the presence of meaning in life scale of the MLQ were related to higher levels of suicidal ideation and suicide attempts over and above sociodemographic variables[5].

This protective role of meaning in life also holds for an array of stressors and mental health challenges, including the psychological strain of the COVID-19 pandemic. Meaning in life scores collected among a sample of university students in China were positively related to prosocial behavior and negatively related to severity of depression, stress, anxiety, and negative emotionality in a survey conducted in February-March 2020, when the initial tumult of the pandemic was mounting fearsomely in China[6].

People need not be left to their own devices in seeking the benefits of greater meaning in their lives. Evidence is abundant that psychotherapies and other treatments are reflected in increased meaning in life[4]. A meta-analysis of 33 randomized controlled trials found significant effects in increasing meaning in life for several psychotherapies, narrative methods (i.e., individuals reviewing and writing about their lives), mindfulness techniques, and psychoeducational approaches[7]. An earlier meta-analysis reinforces these conclusions in a larger body of 60 interventions

that were not limited to controlled trials[8].

Even among patients who are facing long-term mental health challenges, maintaining treatment adherence seems to assist in helping build a sense of meaning in life. In a study of 60 individuals with schizophrenia diagnoses and psychiatric histories at least 5 years in duration, meaning in life was positively related to treatment adherence, in addition to being inversely related to depression symptoms and positively to quality of life[9].

Meaning in life is a construct that is relevant and predictive across the continuum of psychological functioning, from individuals receiving inpatient psychiatric care to those experiencing high levels of well-being. Further, measures with high utility and robust psychometric properties are readily available and are collectively shown to reflect positive treatment progress and outcomes. Incorporating explicitly meaning-focused elements into treatment also benefits patient progress and outcomes.

Paying attention to the meaning of patients' lives would be worthwhile throughout the course of treatment, recovery, and psychological health maintenance. Particularly so in an era of significant psychological stress, when so many feel haunted by inner emptiness.

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DOI:10.1002/wps.20916

A lived experience perspective on the new World Mental Health Report

The new World Mental Health Report by the World Health Organization (WHO)[1] is a landmark document that follows up on the 2001 World Health Report[2]. One could argue that not so much has changed since then but, from our perspective, a very significant change has been actually occurring: the collectively amplified voices of people with lived experience of mental health conditions from all corners of the world. We (people with lived experience) have been speaking publicly about our experiences, our struggles, how we have survived and how we can thrive. Indeed, our realities enable us to be uniquely positioned to provide advice and guidance on policy and service transformation, and to accelerate progress in restructuring mental health care so that it takes on a person-centered and recovery focused approach, as recommended in the report.

The report places a particular focus on the shift towards community-based mental health care and recognizes that mental health is not isolated within the health sector but rather represents an essential element across all areas of life and all life courses. A noticeable improvement in quality of life can be seen when unmet needs of persons with mental health conditions are met within the social domain[3]. The WHO defines mental health as "a state of mental well-being that enables people to cope with the stresses of life, to realize their abilities, to learn well and work well, and to contribute to their communities; it is an integral component of health and well-being and is more than the absence of mental disorder". This definition reiterates that a prerequisite for overall well-being and quality of life is entrenched in mental health, applicable in the presence or absence of a mental health condition. Therefore, a community-based approach is sensible and can make a significant impact at multiple levels (the individual, the community, the country and the world).

Providing services and support in communities, through mainstreaming mental health across sectors, has the potential to enhance personal, community and economic development. The benefits range from long-term economic gains to greater access to care and improved identification of when, where and how someone needs mental health services and support, while appreciating equal human rights and creating stigma- and discrimination-free societies. This, in particular, is what we – as users of mental health care services – have been advocating for over the past decades, with the support of international human rights instruments.

The United Nations (UN) Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health has acknowledged that some advancements have been made in mental health care. However, human rights violations within mental health systems have been poorly addressed. He further noted that this failure reinforces a vicious cycle of discrimination, disempowerment, coercion, social exclusion and injustice; and recommended that mental health be seen beyond a biomedical concept[4].

Ethics-based and evidence-based practices can generate positive outcomes when people with mental health conditions are involved in service development and service delivery[3]. Although there have been advances in involving people with lived experience of mental health conditions in strengthening health systems, progress in this regard has been very limited especially in low- and middle-income countries, where continued stigma and poverty remain the main barriers to inclusion[5].

The undeniable importance of including people with lived experience in decision-making processes and integrating peer-led services within mental health care is well emphasized in the World Mental Health report. More common in high-income countries, peer-led services such as formal peer support work and other related recovery occupations, have become part of mental health

service delivery. Peer-led service providers have an advantage in comparison with other professional services, through having lived experience and practical knowledge of navigating mental health related services and processes, and therefore being in a better position to understand the vulnerabilities and associated needs of peers[6]. Hopefully, the new report's explicit reference to the value of including peer-led services will encourage governments to invest in the inclusion of lived experience service providers into the mental health workforce.

Alongside the evidence-based content and showcasing of best practices, the lived experience narratives from diverse geographical contexts make the report powerful and give a clear message to policy makers that we (people with lived experience) are not silent voices anymore, that we claim our right to speak and share our realities and can contribute practical solutions towards improved mental health care and services for everyone. We are ready to partner and to create change together.

We hope that the lived experience contributions in the report will generate encouragement among governments to authentically and meaningfully involve people with lived experience from the planning to the implementation phase of all new developments in the mental health field. Equally important is for people with lived experience to be integrated within the monitoring and evaluation mechanisms of interventions and service delivery, as well as assessing compliance with local and international human rights instruments.

Going forward, for governments to truly commit to the inclusion of persons with lived experience and their representative organizations, it should be well noted that authentic and meaningful inclusion can only happen when these persons are involved from the very start and not as an afterthought. At the same time, it is critical to consider diversity (gender, race, age groups; lesbian, gay, bisexual, transgender and queer or questioning) when engaging and working with people with lived experience, to ensure that all population groups are able to voice their specific concerns, needs and recommendations.

In conclusion, the launch of the new World Mental Health Report is an exciting moment and represents a welcome step towards pushing mental health to become a truly global priority, making mental health everyone's business. At the very same time, we need to forge a link between mental health, social justice and human rights as an intertwined approach towards successfully implementing the recommendations of the report.

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DOI:10.1002/wps.21031

The World Mental Health Report: transforming mental health for all

It has become clichéd to say that mental health is undervalued, that little is done to promote mental health or prevent mental health conditions from occurring, that mental health services fail to meet need in almost all countries, and that human rights are often abused. However, each of these is not only true, but of such serious concern that failing to change them will have serious future consequences for individuals, families, communities, economies, and the cohesion and prosperity of societies as a whole. Decades of research and data collection, advocacy, as well as recommendations and assistance programmes to countries have had some positive global impact, but mental health around the world remains poor, and services insufficient and inadequate, and for some abusive. The new World Health Organization (WHO)'s World Mental Health Report[1] focuses attention on these matters and creates a compelling and fresh picture of why change is urgently needed. Moreover, without being prescriptive, and recognizing country and cultural differences, it provides clear pointers to the transformation needed, and outlines in broad terms how this can be achieved.

Mental health is defined in this report (slightly modified from previous WHO definitions) as "A state of mental well-being that enables people to cope with the stresses of life, to realize their abilities, to learn well and work well, and to contribute to their communities. Mental health is an integral component of health and well-being and is more than the absence of mental disorder". Other than when reporting on epidemiological data, the report focusses on mental health conditions/disorder and not on substance use, neurological disorders or intellectual disability. While this is possibly a limitation in that all these areas are important, it is a strength in that the report includes detail and analysis that would not have been possible had all areas been included. Moreover, other global reports are available that focus on many of these issues, and there will likely be more such reports in the future[2-4].

No single advocacy enterprise, action plan, journal article or report is likely to suddenly overcome the years of inattention to and disregard for mental health. Notwithstanding, there are decisive moments in public health, and strategic documents that are turning points. This report has been launched at a potentially critical historical juncture where mental health is beginning to receive far more worldwide attention, and it contains sufficiently well-researched information (with over 550 references), epidemiological data, persuasive arguments, innovative approaches and practices, and experiences of users to seriously activate greater mental health revitalization and change.

The WHO report *Mental Health: New Understanding, New Hope*[5] was a landmark in mental health. Launched in 2001, at a

time when burden of disease, rather than mortality alone, was being increasingly recognized and prioritized in health policy and planning, that report drew extensive attention to poor mental health status and services globally and the need for mental health change. Ten carefully selected recommendations were made. Critically, the report was accompanied by an aggressive promotion and marketing strategy. For example, high-ranking WHO officials travelled to many countries to promote the report, and met with mental health policy makers, ministers and even presidents of countries to explain the findings and elucidate what was required to achieve better global mental health. To translate the potential impact of the new World Mental Health Report into real transformation, similar advocacy will be crucial.

The new report does not replace or override the *Comprehensive Mental Health Action Plan 2013-2030* and its various recommendations, but aims to complement and support it. As such, the report does not develop new priority areas for countries to focus on, or set new targets and indicators, but rather aims to "inspire and inform the indisputable and urgent transformation required to ensure better mental health for all". The report rests on three interdependent pillars: mental health value, changing environments for better mental health, and improving mental health services. It is reasoned that, through focusing on these issues, profound mental health transformation becomes possible.

Mental health is highly stigmatized, misunderstood or not well appreciated for either its intrinsic or instrumental value, and this contributes substantially to its lack of prioritization and current neglect. The report argues that individuals, families, communities, governments (including but not limited to health ministries), schools, justice systems, social services and others all need to grasp the centrality of mental health to human, economic and social well-being in a deep and authentic manner. Superficial appreciation is unlikely to change the status quo.

Promoting mental health and preventing mental health conditions is fundamental to the public mental health approach, but this area is under-researched and complex to change. In particular, the extent to which the social determinants of mental health should be approached is often uncertain. The report takes the important step of separating the roles and responsibilities that the health sector may be accountable and responsible for, and those that are critical to improved mental health but that fall within the domain of other sectors. How mental health can be woven into deliberations that plan the mitigation of social determinants such as poverty alleviation and violence prevention is proposed. The report also identifies various vital areas where there is strong evidence for direct promotive/preventive interventions, and encourages concerted actions in these areas.

For many readers, Chapter 7 is likely to be the section they look toward for practical guidance, as it deals with mental health *services* transformation. While this section can be read alone and offers important direction and leadership from WHO for service change, the approach is built on the arguments developed in prior sections, and fully comprehending the approaches taken may require a full read of the report. At the centre of the services approach is community-based mental health care, defined as any mental health care that is provided outside of a psychiatric hospital. The report takes the radical approach (and undoubtedly for some controversial) that *all* long stay psychiatric hospital care should be phased out (or not established) and that comprehensive community care must be developed and expanded. At the centre of the services model is a person-centred and recovery approach within a human rights framework.

The report cuts through the question of whether mental health is best handled within an integrated model with physical health or if mental health services should be provided as a separate specialized service by stating that "service networks for mental health will always include some services that combine physical and mental health care at the point of delivery (integrated services), and some services that are unique to mental health (dedicated services)". Readers are provided with many examples of good practice, while the importance of sectors other than health in care/recovery is emphasized. Also accentuated is the need to move away from coercive interventions.

One of the most important shifts that have occurred in public mental health in recent times, certainly since the previous World Health Report on Mental Health, is how important persons with lived experience are to the planning and policy process as well as to care interventions. The report demonstrates, mainly through personal narratives, why taking lived experiences as a starting point to planning provides the fundamental basis for both policy and service approaches.

While the main audience of this report are people in positions that are able to substantially make a difference in mental health, such as ministers of health and policy makers, everyone with an interest in public mental health is likely to benefit from it. While the report focuses significantly on low- and middle-income countries, there are extensive illustrations from all WHO regions and different economic circumstances, so that each and every country should profit from it.

The report concludes by noting that it will be the combined efforts of numerous stakeholders, including professionals in the field, that will be required to bring about the transformation that is proposed. It is hoped that the leadership taken by the WHO in producing this report and the directions provided will result in all concerned with mental health uniting in action for true global mental health transformation.

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DOI:10.1002/wps.21018

Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration

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Psychiatry has always been characterized by a range of different models of and approaches to mental disorder, which have sometimes brought progress in clinical practice, but have often also been accompanied by critique from within and without the field. Psychiatric nosology has been a particular focus of debate in recent decades; successive editions of the DSM and ICD have strongly influenced both psychiatric practice and research, but have also led to assertions that psychiatry is in crisis, and to advocacy for entirely new paradigms for diagnosis and assessment. When thinking about etiology, many researchers currently refer to a biopsychosocial model, but this approach has received significant critique, being considered by some observers overly eclectic and vague. Despite the development of a range of evidence-based pharmacotherapies and psychotherapies, current evidence points to both a treatment gap and a research-practice gap in mental health. In this paper, after considering current clinical practice, we discuss some proposed novel perspectives that have recently achieved particular prominence and may significantly impact psychiatric practice and research in the future: clinical neuroscience and personalized pharmacotherapy; novel statistical approaches to psychiatric nosology, assessment and research; deinstitutionalization and community mental health care; the scale-up of evidence-based psychotherapy; digital phenotyping and digital therapies; and global mental health and task-sharing approaches. We consider the extent to which proposed transitions from current practices to novel approaches reflect hype or hope. Our review indicates that each of the novel perspectives contributes important insights that allow hope for the future, but also that each provides only a partial view, and that any promise of a paradigm shift for the field is not well grounded. We conclude that there have been crucial advances in psychiatric diagnosis and treatment in recent decades; that, despite this important progress, there is considerable need for further improvements in assessment and intervention; and that such improvements will likely not be achieved by any specific paradigm shifts in psychiatric practice and research, but rather by incremental progress and iterative integration.

Key words: Mental disorder, psychiatric nosology, clinical neuroscience, personalized psychiatry, Research Domain Criteria, Hierarchical Taxonomy of Psychopathology, deinstitutionalization, community mental health care, evidence-based psychotherapy, digital phenotyping, digital therapies, global mental health, task-sharing approaches, paradigm shifts, incremental integration

(World Psychiatry 2022;21:393–414)

Psychiatry has over the course of its history been characterized by a range of different models of and approaches to mental disorder, each perhaps bringing forward some advances in science and in services, but at the same time also accompanied by considerable critique from within and without the field.

The shift away from psychoanalysis in the latter part of the 20th century was accompanied by key scientific and clinical advances, including the introduction of a wide range of evidence-based pharmacotherapies and psychotherapies for the treatment of mental disorders. However, there has also been an extensive critique of pharmacological and cognitive-behavioral interventions, whether focused on concerns about their "medical model" foundations, or emphasizing the need to build community psychiatry and to scale up these treatments globally[1].

In the 21st century, global mental health has become an influential novel perspective on mental disorders and their treatment. This emergent discipline builds on advances in cross-cultural psychiatry, psychiatric epidemiology, implementation science, and the human rights movement[2]. Global mental health has given impetus to a wide range of mental health research as well as to clinical strategies such as task-shifting, with evidence that these are effective in diverse contexts and may be suitable for roll-out at scale[3]. It is noteworthy, however, that global mental health has in turn been critiqued for inappropriate and imperial exportation of Western constructs to the global South[4].

Psychiatric nosology has been a particular focus of both advances in and critique from the field. The 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) was paramount, providing an approach that attempted to eschew different models of etiology, focusing instead on reliable diagnostic constructs[5]. These constructs became widely used in epidemiological studies of mental illness, in psychiatric research on etiology and treatment, as well as in daily clinical practice throughout the world. The most recent editions of the DSM (DSM-5) and of the International Classification of Diseases (ICD-11) by the World Health Organization (WHO) have drawn on and given impetus to a considerable body of work in nosological science[6,7].

Early on, psychoanalytic psychiatry criticized DSM diagnostic constructs for missing core psychic phenomena. With increasing concerns that these constructs have insufficient validity, neuroscientifically informed psychiatry has put forward approaches to assessing behavioral phenomena that emphasize laboratory models[8]. Despite the growing body of nosology science instantiated by the DSM-5 and ICD-11, many have argued for new paradigms of classification and assessment – e.g., the Research Domain Criteria (RDoC), the

Hierarchical Taxonomy of Psychopathology (HiTOP) and other novel statistical approaches, and digital phenotyping.

Where do things stand currently with regard to psychiatry's models of and approaches to mental disorder? What are current clinical practices? What novel perspectives are being proposed, and what is the evidence base for them? To what extent will newly introduced models of clinical intervention, such as shared decision-making or transdiagnostic psychotherapies, and novel approaches in psychiatric research, such as the use of "big data" in neurobiological research and treatment outcome prediction, have transformative impact for clinical practice in the foreseeable future?

In this paper we discuss proposed shifts to clinical neuroscience and personalized pharmacotherapy, innovative statistical approaches to psychiatric nosology and assessment, deinstitutionalization and community mental health care, the scale-up of evidence-based psychotherapy, digital phenotyping and digital therapies, and global mental health and task-sharing approaches. We chose these novel perspectives because they have achieved particular prominence recently, and because many have argued that they will significantly impact psychiatric practice and research in the future.

We consider the extent to which proposed transitions from current practices to these novel perspectives reflect hype or hope, and whether they represent paradigm shifts or iterative progress in psychiatric research and practice. Although the contrast between hype and hope is itself likely oversimplistic, with many newly proposed models and approaches in psychiatry representing neither of these polar extremes, our point of departure is that false promises of paradigm shifts in health care may entail significant costs, while hope may justifiably be considered an important virtue for health professions[9]. We begin with a brief consideration of current models and approaches in psychiatric practice.

CURRENT MODELS AND APPROACHES IN PSYCHIATRY

Current practice in psychiatry varies in different parts of the world, but there are some important universalities. The duration and depth of training in psychiatry during the undergraduate and postgraduate years also differ across countries, but typically a general training in medicine and surgery is followed by specialized training in psychiatry, with exposure to both inpatient and outpatient settings. Globally, inpatient psychiatry focuses predominantly (but not exclusively) on severe mental disorders such as schizophrenia and bipolar disorder, while outpatient psychiatry focuses predominantly (but again not exclusively) on common mental disorders such as depression, anxiety disorders, and substance use disorders. In inpatient settings, psychiatrists are often leaders of a multidisciplinary team, with the extent and depth of this multidisciplinarity dependent on local resources. There are differences in subspecialization across the globe, but in many countries recognized sub-specialties include child and adolescent psychiatry, geriatric psychiatry, and forensic psychiatry[10].

A particularly important shift in the 20th century has been the process of deinstitutionalization, particularly in high-income countries. Thus, there has been a decrease of bed numbers in specialized psychiatric hospitals, but an increase of these numbers in general medical hospitals, with variable strengthening of community services. It has been argued that, when it comes to mental health services, all countries are "developing", since there is a relative underfunding of such services in relation to the burden of disease[1].

Currently, the two major classification systems in psychiatry are the DSM-5 and the ICD-11. The DSM system is more commonly used by researchers, while the ICD is a legally mandated health data standard. The operational criteria and diagnostic guidelines included in the DSM-III, the ICD-10, and subsequent editions of the manuals have exerted considerable influence on modern psychiatry. They not only increase reliability of diagnosis, but also have clinical utility, since they provide clinicians with an approach to conceptualizing disorders and to communicating about them[11,12]. They have also played a key role in research, ranging from studies of the neurobiology of mental disorders, through to studies of interventions for particular conditions, and on to clinical and community epidemiological surveys.

However, there has also been considerable critique of the reliance of modern psychiatry on the DSM and the ICD. The notion that psychiatric diagnosis is itself "in crisis" has come both from within the field and from external critics. Two somewhat contradictory critiques have been that in daily practice the DSM and ICD criteria or guidelines are seldom applied formally by clinicians, and that over-reliance on those criteria or guidelines leads to a checklist approach to assessment that ignores relevant symptoms and important contextual issues falling outside the focus of the nosologies. Additional key critiques have been that psychiatric diagnoses lack scientific validity, and that current nosologies are biased by influences such as that of the pharmaceutical industry[13,14].

When thinking about etiology, many clinicians and researchers currently default to a biopsychosocial model acknowledging that a broad range of risk and protective factors are involved in the development and perpetuation of mental disorders. This model was introduced by G. Engel in an attempt to move from a reductionistic biomedical approach to include also psychological and social dimensions[15]. The model has important strengths insofar as it takes a systems-based approach that considers a broad range of variables influencing disease onset and course, and attends to both the relevant biomedical disease and the patient's experience of illness[16].

Nevertheless, the biopsychosocial approach has received significant critique. In particular, it has been argued that the biomedical model critiqued by Engel is a straw man, and that the biopsychosocial approach is overly eclectic and vague. By saying that all mental disorders have biological, psychological and social contributory factors, we are unable to be specific about any particular condition, and to target treatments accordingly[17,18]. While there are few data available on how rigorously psychiatrists consider the range of risk and protective factors in clinical work, a review of the research literature indicates ongoing work on multiple "difference-makers", distributed across a wide range of categories[19].

Psychiatrists are trained to provide a range of both pharmacological and psychological interventions. However, data from psychiatric practice networks and from epidemiological surveys indicate that there has been a growing emphasis on pharmacotherapy interventions[20], albeit with some exceptions[21]. Furthermore, the number of psychiatrists varies considerably from country to country, and from region to region within any particular country[22]. While primary care practitioners are also trained to deliver mental health treatments, and indeed provide the bulk of prescriptions for mental disorders in some regions, there is considerable evidence of underdiagnosis and undertreatment of such conditions in primary care settings.

Indeed, despite the development of a range of evidence-based pharmacotherapies and psychotherapies in the last several decades, current data point to both a treatment gap and a research-practice gap in mental health. The treatment gap refers to findings that, across the globe, many individuals with mental disorders do not have access to mental health care[23]. The research-practice gap, also known as the "science-practice" or "evidence-practice gap", refers to differences between treatments delivered in standard care and those supported by scientific evidence[24]. In particular, clinical practitioners have been criticized for employing an eclectic approach to choosing interventions, for not sufficiently adhering to evidence-based clinical guidelines, and for not employing measurement-based care.

The treatment gap and the research-practice gap are of deep concern, given evidence of underdiagnosis and undertreatment, of misdiagnosis and inappropriate treatment, and of inadequate quality of treatment[25,26]. There are, however, some justifiable reasons for a gap between practice and research, including that the evidence base is relatively sparse for the management of treatment-refractory and comorbid conditions, the relative lack of pragmatic "real-world" research trials in psychiatry, and the possibly modest positive impact of guideline implementation on patient outcomes[27,28]. Indeed, several scholars have emphasized that including clinical experience and addressing patient values are key components of appropriate decision-making[27,29].

Considerably more research is needed to inform our knowledge of current psychiatric practice and its outcomes. Data from psychiatric practice networks have been useful in providing fine-grained information in some settings, but much further work is warranted along these lines[30]. Data from randomized controlled trials indicate that psychiatric treatments are as effective as those in other areas of health care, but further evidence should be acquired using pragmatic designs in real-world contexts[31]. Epidemiological data from across the globe suggest that individuals with mental disorders who received specialized, multi-sector care are more likely than other patients to report being helped "a lot", but there is an ongoing need for more accurate estimates of effective treatment coverage globally[32].

In the interim, evidence of the treatment gap and the research-practice gap in current mental health services has given impetus to the development of a number of novel diagnostic and treatment models and approaches, ranging from clinical neuroscience through to global mental health. Some of these models and approaches have achieved particular prominence in recent times, with proponents arguing that they will significantly impact psychiatric practice and research in the future. At times advocates for these perspectives and proposals have limited aims, while at other times they speak of paradigm shifts that will drastically alter or wholly reshape current clinical practices[33-36]. We next consider a number of these perspectives and proposals in turn.

CLINICAL NEUROSCIENCE AND PERSONALIZED PHARMACOTHERAPY

A key shift in 20th century psychiatry, at least in some parts of the world, was from psychoanalytic to biological psychiatry. The serendipitous discovery of a range of psychiatric medications in the mid-20th century, and advances in molecular, genetic and neuroimaging methods, propelled this shift. More recently, terms such as clinical neuroscience, translational psychiatry, precision psychiatry, and personalized psychiatry have emerged, helping to articulate the conceptual foundations for a proposed psychiatric perspective aiming to replace or significantly augment current practice[37-39].

The proposed paradigm of clinical neuroscience rests in part on a critique of current standard approaches. First, in terms of diagnosis, it has been argued that the DSM and ICD constructs are not sufficiently based on neuroscience[40]. Thus, for example, particular symptoms, which may involve quite specific neurobiological mechanisms, may be present across different diagnoses. Conversely, research findings demonstrate that there is considerable overlap of genetic architecture across different DSM and ICD mental disorders[41]. If current diagnostic constructs are not natural kinds, then arguably attempts to find specific biomarkers and develop targeted treatments for them are doomed to fail[42,43].

The proposed new paradigm views psychiatry as a clinical neuroscience, which should rest on a firm foundation of neurobiological knowledge[44]. With advances in neurobiology, we will be better able to target relevant mechanisms and develop specific treatments for mental disorders. Neuroimaging and genomic research offer opportunities for personalizing psychiatric intervention: those with specific genetic variants may require tailoring of psychopharmacological intervention, while particular alterations in neural signatures may be used to choose a therapeutic modality or to alter parameters for neurostimulation.

The RDoC project, developed by the US National Institute of Mental Health (NIMH), has provided an influential conceptual framework for this proposed new paradigm[8]. Whereas the DSM-III relied on the Research Diagnostic Criteria (RDC) in order to operationalize mental disorders, the RDoC project emphasizes domains of functioning that are underpinned by specific neurobiological mechanisms. Disruptions in these domains may lead to various symptoms and impairments. Domains of functioning are found across species, and their neurobiological substrates are suffi-

ciently known to allow translational neuroscience, or productive movement from bench to bedside and back. Each domain of functioning can be assessed with specific laboratory paradigms.

The RDoC matrix initially included five domains of functioning and several "units of analysis" for assessing these domains (see Figure 1)[45]. Each domain in turn comprises a number of different "constructs" (or rows of the matrix): these were included on the basis of evidence that they entail a validated behavioral function, and that a neural circuit or system implements the function. Different "units of analysis" (or columns of the matrix) can be used to assess each construct: the center column refers to brain circuitry, with three columns to the left focusing on the genes, molecules and cells that comprise circuits, and three columns to the right focusing on circuit outputs (behavior, physiological responses, and verbal reports). A column to list paradigms is also included.

The RDoC matrix is intended to include two further critical dimensions for integrating neuroscience and psychopathology, i.e. developmental trajectories and environmental effects[45]. Thus, from an RDoC perspective, many mental illnesses can be viewed as neurodevelopmental disorders, with maturation of the nervous system interacting with a range of external influences from the time of conception. Several key "pillars" of the RDoC framework, including its translational and dimensional focuses[8], have been emphasized.

Anxiety, for example, can be studied in laboratory paradigms, and ranges from normal responses to threat through to pathological conditions. Indeed, a clinical neuroscience approach has contributed to the reconceptualization of several anxiety and related disorders[46-48] and to the introduction of novel therapeutic approaches for these conditions[49]. Further, work on stressors has usefully emphasized that environmental exposures become biologically embedded, with early adversity associated to alterations in both body and brain that occur irrespective of the DSM diagnostic category[50,51].

The NIMH has linked the RDoC to funding applications, and this framework has given impetus to a range of clinical neuroscience research. Translational research will certainly advance our empirical knowledge of the neurobiology of behavior and of psychopathology. The RDoC has also prompted conceptual work related to the neurobiology of mental disorders, and the development of measures and methods. Indeed, to the extent that constructs in the RDoC matrix have validity as behavioral functions, and map onto specific biological systems such as brain circuits, the project summarizes key advances in the field, and provides useful guidance for ongoing research.

At the same time, it is relevant to note important limitations of the RDoC approach. First, the RDoC seems less an entirely new paradigm than a re-articulation of existing ideas in biological psychiatry. Certainly, the importance of cross-diagnostic neurobiological investigations of domains of functioning has long been emphasized[52]. Second, the neurobiology of any particular RDoC construct, such as so-

			UNITS OF ANALYSIS					
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social communication								
Perception/understanding of self								
Perception/understanding of others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

Figure 1 The Research Domain Criteria matrix (from Cuthbert[45])

cial communication, may be enormously complex, so that alternative approaches to delineating the mechanisms involved in particular mental disorders may provide greater traction[53]. Third, methods used to measure domains in the RDoC framework may not be readily available to clinicians. The further one moves from academic centers to the practice of psychiatry in primary care settings around the globe, the less relevant an RDoC framework may be to daily clinical work.

Personalized and precision psychiatry are important aspirations of clinical neuroscience. The notion that psychiatric interventions need to be rigorously tailored to each individual patient makes good sense, given the substantial inter-individual variability in the genome and exposome of those suffering from psychiatric disorders, as well as the considerable variation in response to current psychiatric interventions. With advances in genomic methods and findings, and the possibility that whole genome sequencing will become a standard clinical tool, with polygenic risk scores readily available, it is particularly relevant to consider the application of genomics to optimizing pharmacological and other treatments[54].

The Clinical Pharmacogenetic Implementation Consortium (CPIC) has already provided a range of clinical guidelines for drugs used in psychiatry. For example, a CPIC guideline recommends that, given the association between the *HLA-B*15:02* variant and Stevens-Johnson syndrome as well as toxic epidermal necrolysis after exposure to carbamazepine and oxcarbazepine, these drugs should be avoided in patients who are *HLA-B*15:02* positive and carbamazepine- or oxcarbazepine-naïve[55]. The evidence base that pharmacogenomic testing improves outcomes is gradually beginning to accumulate, and recent guidelines have started to recommend a number of specific tests[56].

From an RDoC perspective, particular domains of functioning involve specific neural circuits, which are in turn modulated by a range of molecular pathways. One notable recent development in these fields has been a focus on "big data". Large collaborations in basic and clinical sciences have been established, which provide sufficient statistical power to advance the field in important ways.

Examples of such "big data" collaborations are the Enhancing Neuroimaging Meta-analysis Consortium (ENIGMA)[57], which includes tens of thousands of scans from across the world, and the Psychiatric Genetics Consortium (PGC)[58], which includes hundreds of thousands of DNA samples from across the globe. The work of ENIGMA and PGC has been at the cutting edge of scientific research in psychiatry, and has provided crucial insights into mental disorders. Certain biological pathways, such as immune and metabolic systems, appear to play a role across different mental disorders, and genomic methods have contributed to delineating causal and modifiable mechanisms underlying these conditions[58,59]. At the same time, it must be acknowledged that to date few findings from this work have been successfully translated into daily clinical practice[36,54,60].

In summary, clinical neuroscience provides an important conceptual framework that may generate some useful clinical insights, and that may be particularly helpful in guiding clinical research. This framework has contributed to the reconceptualization of a number of mental disorders, and has on occasion contributed to the introduction of new therapies[61]. As clinical neuroscience generates new evidence, this may be incorporated in nosological systems in the future. There are already good arguments for including advances in this area in the curriculum of psychiatric training, and for updating clinicians on progress in the field[62].

At the same time, there are currently few biomarkers with clinical utility in psychiatry, and methods such as functional neuroimaging and genome sequencing, which are key for future advances in frameworks such as the RDoC, are not readily available to or useful for practicing clinicians[63]. The vast majority of clinical neuroscience publications appear to have little link to clinical practice. At best, therefore, we can expect that ongoing advances in clinical neuroscience will contribute to clinical practice via iterative advances in our conceptualization of mental disorders, and via the ongoing introduction of new insights and new molecules that emerge from laboratory studies.

Indeed, the claim that any particular laboratory, neuroimaging or genetic finding will dramatically change clinical practice should raise a red flag. The neurobiology of behaviors and psychopathology is complex, reproducibility of findings is an ongoing important issue, and clinical neuroscience investigations only occasionally impact clinical practice[64]. Indeed, we should be careful not to be over-optimistic about clinical neuroscience constituting a paradigm shift. Neurobiological research has not to date provided a rich pipeline of accurate biomarkers for mental disorders, nor speedily found new molecular entities that are efficacious for these conditions, and we cannot, for example, expect that the DSM and ICD will be replaced by the RDoC anytime soon.

NOVEL STATISTICAL APPROACHES TO PSYCHIATRIC NOSOLOGY, ASSESSMENT AND RESEARCH

Disease taxonomies are particularly complex, and may not be able to follow historical models of scientific taxonomies, which have defined all elements of a given set. An often-used example of the latter taxonomies is the periodic table of elements. Another venerable example is Linnaeus' *Systema Naturae* and the resulting nomenclature of biological species. The periodic table of elements has the simplicity of small numbers plus the hard and fast rules of chemistry, while the *Systema Naturae*, despite having to deal with an ever-expanding number of entities, is arguably based on direct observation of beings. In contrast, a disease taxonomy deals with thousands of unruly entities (versus 118 elements), which cannot be directly observed, apprehended or dissected (as animals or plants can).

Despite these challenges, disease taxonomies have sought to provide a shared, evidence-based, clinically meaningful, comprehensive classification that is informed by etiology and therapeutics. The notion that underneath the observable syndrome lies a causal entity, that we should investigate and treat, lies at the heart of the prac-

tice of medicine[65]. Such "disease entities" have specific characteristics that make them clear and distinct from others (i.e., presentation, etiology, response to intervention), are transparent to the clinician, and are well-grounded in evidence.

Psychiatry has long faced the challenges of producing a causal nosology that is able to direct treatment[66]. Pinel developed the first comprehensive nosology for people with severe mental disorders, along with moral treatment, the first therapeutic framework of the scientific era[67]. Soon afterward, Kahlbaum, Kraepelin and Bleuler laid a firm groundwork for clinical psychiatry through close observation and systematic documentation of the natural history of severe mental illness. Arguably, Freud further advanced nosology and therapeutics by focusing on a different set of disorders (usually milder but much more prevalent), which he termed *neuroses* (to highlight their difference from *psychoses*), and by developing the concept and practice of psychotherapy. These frameworks gave impetus to subsequent advances in our understanding of and interventions for mental disorders.

Perceptions of insufficiently rapid and robust advances in treatments have led to criticism of current nosology[68]. In particular, the DSM and ICD have been criticized for overly focusing on reliability at the expense of validity. In this view, schizophrenia and bipolar disorder may be genuine disease entities, but our syndromic definition lacks specificity, and there are likely different causal pathways that lead to clinically meaningful subtypes of these disorders. Major depressive disorder, on the other hand, is likely to be a hodgepodge of mood syndromes, some non-dysfunctional (i.e., non-disorders) or non-specific (i.e., combining depressive with anxiety symptoms), including only a few true but potentially diverse disease entities (e.g., melancholia, psychotic depression). And when it comes to, say, personality disorders, the disease-entity concept is even more distant, and the search for new approaches is seen as particularly key.

One such novel paradigm is the HiTOP. This proposes a hierarchical framework that, based on the observed covariation of dimensional traits, is able to identify latent super-spectra and spectra (supra-syndromes), syndromes (our current disorders), and lower-level components[69-72]. In this conceptual framework, a dimension consists of a continuous space in which an element occurs in differences of degree, but not of kind, between the normal and the pathological.

The HiTOP relies on factor analysis and related techniques, which tap into the covariation of observable traits to identify an unobserved, common factor that, once included in the model, explains the covariation[73]. Costa and McCrae's studies leading to the identification of five personality domains were a prime example of this approach. There is a common underlying reason that explains a person's tendency to worry about many things, think that the future looks bleak, be bothered by intrusive thoughts, and be grouchy[74]. That unobserved factor was conceptualized as "neuroticism", and fully explains the covariation of these traits in any given individual. A similar approach to the study of childhood psychopathology led to the binary characterization of an "internalizing" and an "externalizing" dimension to childhood disorders[75].

The HiTOP paradigm seeks to leverage these well-established lines of research to develop a data-driven nosology that is free from the theory-driven dead weight built into current approaches. The key conceptual departure relies on the premise that, since evidence points towards psychopathological dimensions existing on a continuum, disorders should be similarly conceptualized, and nosology should move away from a focus on categorical entities. Instead of insisting on questionable boundaries, this approach proposes dimensional thresholds, which are empirically determined and do not involve any difference "in kind". By grouping co-occurring symptoms within the same syndrome, and non-co-occurring symptoms separately, within-disorder heterogeneity is reduced. And by assigning overlapping syndromes to the same unobserved spectra, excess comorbidity found when using current categories is explained.

The resulting dimensional classification, the proponents of HiTOP argue, is consistent with evidence on risk factors, biomarkers, course of illness, and treatment response[69]. Figure 2 shows a schema of the proposed new nosology. An intriguing element of this approach is what has been termed "p", or general psychopathology factor (at the top of Figure 2). In addition to super-spectra and spectra, factor analysis ultimately points towards the existence of a single latent trait that would explain all psychopathology, comparable to the well-established "g" factor for general intelligence[76,77].

If dimensional nosologies seek to overturn categorical ones, network analysis arguably aims to overturn both, insofar as it posits that the notion of an unobserved underlying construct is unwarranted, be it a categorical disease entity or a dimensional latent factor[78]. The network approach to psychopathology holds that mental disorders can be conceived as "problems in living", and are best understood at the level of what is observable. Rather than by latent entities, disordered states are fully explained by the interaction between signs and symptoms (the "nodes" of the networks). These interactions are themselves the causal elements (i.e., a symptom causes another symptom, then another symptom, and so on), and a disorder is simply an alternative "stable state" of strongly connected symptom networks (as opposed to the "normal" steady state of health).

A conceptualization of disorders as "problems in living" does away with the medical notion of a disease as an underlying causal entity. In this view, deficiencies in our understanding of etiology are not necessarily due to diagnostic limitations or insufficiently accurate models for the unobserved but, on the contrary, may be due to our lack of attention to the surface, i.e. the symptoms themselves, which go about reinforcing each other while we are distracted by peeking behind imaginary curtains.

Unlike dimensional approaches, proponents of network analysis disavow any nosological hierarchy (super-spectra, spectra, disorders, symptoms, etc.), and posit that there is only one level, that of symptoms, which can all cause and reinforce one another. Of note, network analysis posits that symptoms (or interacting nodes) can be activated by disturbances emerging from the "external field" (i.e., "external" to the

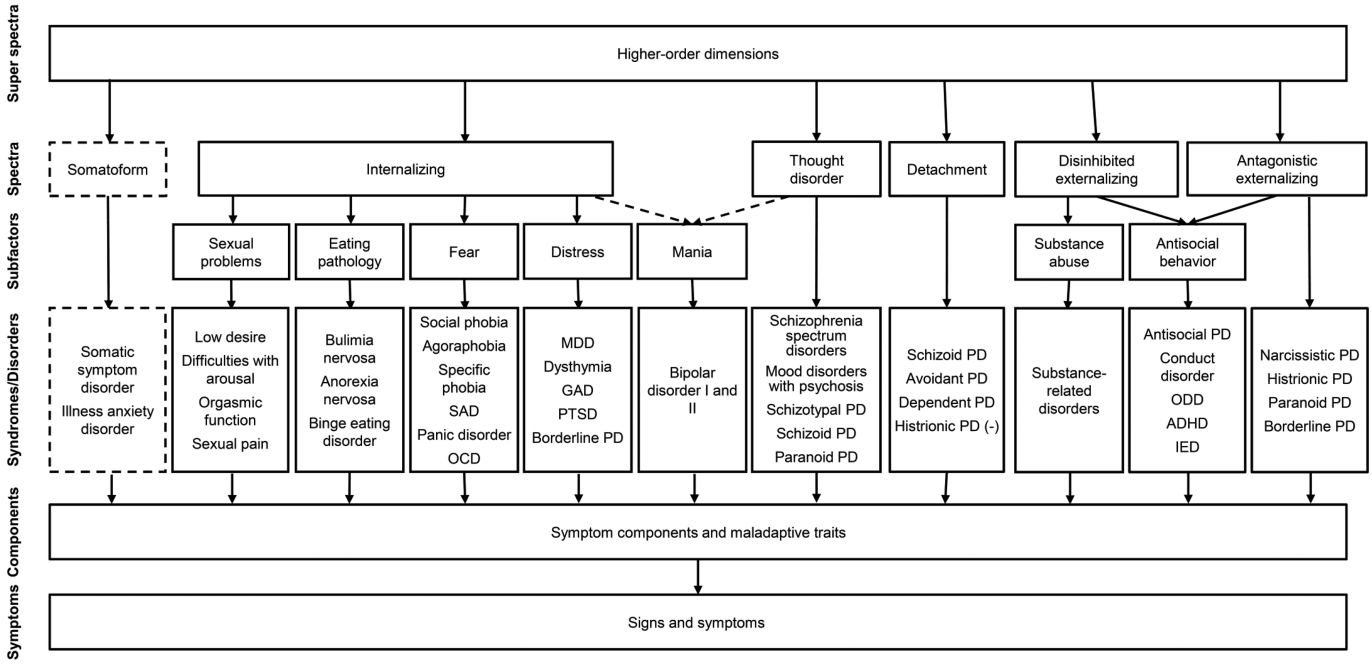

Figure 2 The Hierarchical Taxonomy of Psychopathology (HiTOP) model (from Krueger et al[69])

symptom network, not necessarily to the body or person), such as the loss of a loved one (which may activate the symptom depressed mood, setting in motion the depressive network) or a brain abnormality (which may activate the symptom hallucination, setting in motion the psychotic network).

Whether an individual develops a new strongly connected network of symptoms in the face of a stressor depends on his/her "vulnerability", which is based on the network's connectivity. Given a dataset with symptoms and/or signs for disorders, a network analysis can quantify all relevant nodes and interactions, including the frequency and co-occurrence of symptoms, the strength and number of their associations, and the centrality of each symptom (i.e., the sum of the interactions with other nodes). Empirical work using network analysis potentially provides rigorous accounts of vulnerability to and evolution of mental disorders.

A number of other novel statistical approaches have also been put forward as potentially facilitating paradigm shifts in psychiatry. Psychiatry has long relied on linear models to explore associations and develop theories of risk and resilience for mental disorders. However, causal inference methods have now been developed in statistics, and provide new approaches to delineating causal relationships[79]. In genetics, Mendelian randomization provides an innovative method for addressing the causal relationships of different phenotypes, and has increasingly been employed in psychiatric research[80]. Neural networks and deep learning have played a key role in advancing artificial intelligence, and are increasingly being applied to the investigation of psychiatric disorders, including prediction of treatment outcomes[81-84]. While many view such techniques as allowing iterative advances, some are persuaded that they allow an entirely novel perspective and so constitute a paradigm shift in the field[85].

Work on the HiTOP and network analysis has been important and useful in a number of respects. First, unbiased data-driven approaches have an important role in strengthening the relevant science, whether of nosology, or of areas such as genetics. A focus on fear-related anxiety disorders, for example, offers interesting avenues for research, both from a neuroscience and a therapeutic perspective, and network analysis has contributed insights into the presentation of some disorders[48]. Second, some dimensional constructs, including those of internalizing and externalizing disorders, have clinical utility. The "distress" subfactor reflects the notable overlap between depressive and anxious symptoms, and the association between symptoms from two different disorders (e.g., major depressive disorder and generalized anxiety disorder) may be stronger than associations "within" each disorder[86]. Third, the use of novel statistical methods to draw causal inferences has provided important insights into risk for and resilience to mental disorders[59]. For instance, network analysis offers a nuanced foundation for targeted treatment of the core symptoms of some mental disorders (e.g., reframing specific automatic thoughts through cognitive-behavioral interventions).

At the same time, such approaches have important limitations. Notably, categorical and dimensional approaches are interchangeable: any dimension can be converted into a category, and any category can be converted into a dimension[87]. There is no reason to conceptualize mental disorders as exclusively dimensional. In physics, matter itself is sometimes better conceived in terms of waves (a dimensional concept) and other times in terms of particles (a categorical one). Similarly, in psychiatry, a pluralist approach that allows the employ-

ment of a range of different dichotomous and continuous constructs seems appropriate[88,89].

Remarkably, the HiTOP employs DSM terminology at the disorder level. "Number-driven" psychopathologies and their resulting nosologies may not necessarily lead to a shift in constructs grounded in long-standing clinical practice and research. In the same vein, network analysis offers a useful model to understand the distribution of symptoms, identify therapeutic targets, and explain the effectiveness of symptomatic interventions. However, network analysis does not specify the particular levels of explanation that underlie a network structure; so, while it may be a useful organizing framework, it is unclear that it will provide novel insights into underlying etiological mechanisms.

Consider a set of patients presenting with the following symptoms, among others: headaches, vomiting and seizures. A factor analysis may point towards a latent factor explaining the covariation among them. Any clinician will know that, unless the cause is substance-related, the first thing to rule out in these patients is a space-occupying lesion in the brain, and that this unobserved element is only an intermediary that can itself be caused by multiple disease entities, most notably hemorrhage, infection and cancer. The fact that a latent factor may explain the covariation between anxious and depressive symptoms does not exclude that these symptoms are in fact caused by very different dysfunctions (upstream of the latent factor), and that other accompanying symptoms will hold the clue to the ultimate cause (just as high blood pressure, fever or weight loss would hold clues for a space-occupying lesion syndrome).

Relatedly, consider the focus of the HiTOP on a general psychopathology factor "p". This focus can be countered by a *reductio ad absurdum* argument suggesting that a latent factor "i" explains the covariation of any and all human illnesses. Given some datasets, we may find that the covariation of nausea, hemoptysis, jaundice and myocardial infarction is explained by a latent dimensional trait. We may choose to call this "sybaritism", dimensionally distributed between one extreme (temperance) and another (debauchery). Readers who focus on values-based medicine might well criticize the choice of words here, while those focused on evidence-based medicine are unlikely to be persuaded that an approach that elides disease entities will advance studies of psychiatry, gastroenterology and cardiology[29].

In a latent class analysis of depressive and anxious syndromes, Eaton et al[90] proposed an approach called "guided empiricism", whereby they explicitly imposed a theory-driven structure on various statistical models, compared them, and obtained the best empirical fit. Perhaps using such explicitly theory-driven constraints is preferable to accepting hidden theoretical constructs. For example, rather than assuming that all the DSM depressive and some anxiety/stress related disorders are explained by a latent factor called "distress", itself under a spectrum called "internalizing disorders", a theory-grounded structure can be imposed on the models to try to identify what is driving the overlap. Indeed, it should be emphasized that purportedly "number-driven" nosologies all have built-in qualitative components: from the questions in the scales used to measure traits, to the labels chosen for the latent factors, these classifications are theory-laden.

In summary, the solution to nosologic challenges in psychiatry may not reside in the building of new nosologies or psychopathologies from scratch[91], nor in the banishment of the "disease entity" concept, but rather in continuing the humble, laborious, iterative work of systematic clinical observation, painstaking research, and creative thinking, while purposefully comparing dimensional, categorical and hybrid models applied to the same datasets. The claim that a "quantitative" nosology is somehow "atheoretical" raises a red flag: where theory is seemingly absent, it is often hidden. Instead, we need thoughtful and explicit combinations of theories grounded on clinical practice and confirmatory quantitative evidence. Hypothesis formulation is a qualitative, creative, theory-laden endeavour, while quantitative research helps us discard false theories and refine what we know (by proving hypotheses wrong or quantifying associations).

Similarly, etiological and treatment challenges in psychiatry are unlikely to be addressed merely by the employment of larger and larger datasets, using more and more sophisticated statistical methods. Certainly, big data consortia and sophisticated statistical analyses have yielded valuable insights into the nature of psychiatric disorders. However, it is important to recognize the limitations of any empirical dataset and any analytic method, as well as the value of a wide range of complementary research designs and statistical approaches – including the age-old single-case study, which may sometimes provide clinical insights that outweigh those from big data analyses[92].

Indeed, the claim that a new statistical, bioinformatic or computational method will provide entirely novel insights that enable a paradigm shift in psychiatry should again raise a red flag. Furthermore, where solutions reside within a black box, there is ongoing uncertainty about the extent to which they will be able to provide clinically useful assistance[93,94]. Thoughtful and explicit combinations of existing and novel research designs and statistical methods should be employed, with the aim of achieving iterative and integrative progress in our diagnosis and treatment of psychiatric disorders.

DEINSTITUTIONALIZATION AND COMMUNITY MENTAL HEALTH CARE

The last 70 years have seen a seismic shift in models of mental health care delivery around the world. The first half of the 20th century was dominated by the growth of psychiatric hospitals, particularly in high-income Western countries. By 1955, there were 558,239 severely mentally ill people living in psychiatric hospitals in the US, with a total population of 164 million at the time[95]. In the years that followed, there was a significant reduction in psychiatric hospital bed numbers in many high-income countries, as part of a trend that came to be known as deinstitutionalization. In the UK, the US, Australia, New Zealand and countries in Western Europe, there was an 80-90% reduction in psychiatric hospital beds between the mid-1950s

and the 1990s[96].

Deinstitutionalization refers to the downscaling of large psychiatric institutions and the transition of patients into community-based care. This is said to include three components: the discharge of people residing in psychiatric hospitals to care in the community, the diversion of new admissions to alternative facilities, and the development of new community-based specialized services for those in need[97]. More recently, a focus in community-based care has also been the development of models for integrating mental health into primary care, as well as of shared decision-making and recovery approaches[98]. To the extent that these models propose new ways of addressing mental illness, as well as extensive scale-up of community-based services, many would argue that they constitute a crucial paradigm shift.

Deinstitutionalization was driven by three main forces. First, the introduction of new medications made it increasingly possible for people with severe and enduring mental disorders such as schizophrenia and bipolar disorder to live reasonably well in community settings. Second, the mushrooming of psychiatric hospitals had come with high costs, and deinstitutionalization was seen by many governments as a cost-saving strategy. Third, the growth of the human rights movement in the 1950s and 1960s generated increasing public concern about practices in psychiatric institutions, including involuntary care. Films such as *One Flew over the Cuckoo's Nest* drew public attention to the conditions in those facilities and provided support to the idea that people living with mental disorders should have a choice over the nature and locus of their care. This trend was reinforced by research demonstrating that community-based models of care, including for people with severe mental disorders, could be delivered effectively, in a manner that was more acceptable to service users, and in some cases less costly[97].

However, in many regions of the world, these developments have not actually occurred. Particularly in many post-colonial low-income countries, for example in sub-Saharan Africa and South Asia, large psychiatric hospitals have been left behind by departing administrations, and have remained the main locus of care. In these countries, there has been little substantial deinstitutionalization, and very limited scaling up of community-based and primary care mental health services[22]. In low-income countries, there were 0.02 psychiatric beds per 100,000 population in 2001, and this increased to 1.9 beds per 100,000 population in 2020.

The success of deinstitutionalization programmes in transitioning to community-based care has been highly varied around the world. In some countries, such as Italy, legislation has mandated the establishment of community-based services, and consequently these services have been widely implemented, although with substantial variation across the country[99]. In many other countries, funding did not follow people who were discharged from psychiatric hospitals into community settings. For example, in many parts of the US, deinstitutionalization has been associated with a burgeoning population of homeless mentally ill and mentally ill prisoners[95].

In Central and Eastern Europe, even with recent reforms, studies have criticized the uneven pace of deinstitutionalization, the lack of investment in community-based care, and the "reinstitutionalization" of many people with severe mental illness or intellectual disability[100]. In a tragic case in South Africa, deinstitutionalization of 2,000 people with severe mental illness or intellectual disability from the Life Esidimeni facility into unlicensed and unregulated community organizations led to the death of over 140 people, sparking a public outcry and a national enquiry by the Human Rights Commission[101].

Importantly, deinstitutionalization has been associated with "revolving door" patterns of care, in which people are discharged from hospital after admission for an acute episode, but do not have adequate care and support in the community, and therefore relapse and need to be readmitted. Indeed, readmission rates have been an important indicator for service managers to monitor in the post-deinstitutionalization era, and the focus of several intervention studies[102].

The WHO has advocated for the development of community-based services for mental disorders for many decades. In the early 2000s, it produced a set of guidelines for countries to develop national mental health policies, plans and services[103]. This included the now widely cited "optimal mix of services" to guide countries on how to balance hospital- and community-based care. This model proposed a pyramid structure, in which specialist psychiatric inpatient care represents only a small proportion of services at the apex of the pyramid, and is supported by psychiatric services in general hospitals, specialist community outreach, primary care services, and self-care at the base of the pyramid. Others have developed similar "balanced care" models[104].

The 21st century has also seen the development of models for integrating mental health into primary care, such as collaborative care models[105]. These latter initially focused on managing people with comorbid depression and other chronic diseases. Subsequently this work has been expanded to include other mental disorders, through models in which a mental health specialist provides support to non-specialist health care providers, who are the main point of contact for people needing care. The WHO has endorsed this approach, particularly through its flagship mhGAP programme, which provides clinical guidelines for the delivery of mental health care through non-specialist health care platforms in primary care and general hospital settings[106]. The mhGAP Intervention Guide has now been implemented in over 100 countries.

In parallel, the latter part of the 20th century and early 21st century have seen the rapid development of shared decision-making and recovery approaches to mental health care. Shared decision-making involves clinicians and people with mental disorders working together to make decisions, particularly about care needs, in a collaborative, mutually respectful manner[98]. This approach is consistent with an emphasis on human rights, as well as on the importance of patients' lived experience, explanatory models and specific values, and clearly deserves support[107,108]. Recovery models have challenged traditional roles of "patients" to reframe recovery as a way of living a satisfying, hopeful life that makes a contribution even within

the limitations of illness[109]. The recovery movement has been highly influential, is now incorporated into mental health policies, and has shaped the design of mental health systems in several countries[109].

Yet, despite the strong scientific and ethical principles supporting community-based care, collaborative care and moves towards shared decision-making and recovery approaches, there remain major challenges, and the proposed paradigm shift remains to a large extent aspirational. While community care models have been developed, tested and shown to be effective in landmark studies, there are few cases of countries systematically investing in these models at scale, in a manner that substantially influences the mental health of populations. In addition, although there are apparent advantages to approaches such as shared decision-making, a wide range of barriers across individual, organizational and system levels have been reported[110], and implementation remains limited in mental health care[98].

Indeed, it has been noticed that the agreement about the concept of shared decision-making among stakeholders is only superficial[98]. After all, clinicians may not support this approach if it leads to patients being more empowered, but less adherent to treatment recommendations. This example raises broader questions about community-based care models: is the failure to systematically scale up these models just due to a lack of political will and related scarcity of resources, or are there fundamental concerns with the model? Our view is that both of these may be true.

There is certainly a lack of political will and investment. Despite the courageous campaigning by people with lived experience for their rights to make decisions about their care, together with the robust evidence of improved outcomes associated with community-based collaborative care models, governments often remain indifferent[1]. In 2020, 70% of total government expenditure on mental health in middle-income countries was allocated to mental hospitals, compared to 35% in high-income countries[22]. These differences need to be viewed in the context of massive global inequities in governments' commitments to mental health more broadly. While high-income countries spend US$ 52.7 per capita on mental health, low-income countries spend US$ 0.08 per capita[22].

On the other hand, it may also be the case that community-based care does not go far enough in addressing the social determinants of mental health. While many community-based care models focus on individuals with a mental disorder and their immediate family, very few address the fundamental structural drivers of mental illness in populations, such as inequality, poverty, food insecurity, violence, and hazardous living conditions[111,112]. Successful community-based mental health services arguably require the existence of viable communities.

The strategy of deinstitutionalization was founded on the premise that communities can provide a safe, supportive environment in which people with severe mental illness can thrive. In countries marked by high levels of poverty, inequality, civil conflict and domestic violence, this is certainly not the case. Advocating for community-based care requires addressing the fundamental social injustices which precipitate and sustain mental illness in populations.

Furthermore, community-based service planners may have not gone far enough in considering demand-side drivers of mental health care. For example, in many low- and middle-income countries, traditional and faith-based healers continue to be major providers of care for people with severe mental disorders, due to the scarcity of mainstream mental health professionals, and shared beliefs about the causes and treatments of such conditions.

The effectiveness and cost-effectiveness of collaborative shared care models with traditional and faith-based healers has been documented in Ghana and Nigeria [113]. Similarly, the possibility of addressing demand-side barriers by implementing a community informant detection tool, based on local idioms of distress and vignettes to identify people with various mental health conditions, has been demonstrated in Nepal[114]. These innovations from low- and middle-income countries provide potential lessons for high-income countries in developing collaborative care models that are aligned with the belief systems of mental health care users and address demand-side barriers to care.

In summary, despite the development of community-based services, collaborative care, shared decision-making and recovery models, a paradigm shift towards the implementation of well-functioning and effective community mental health care around the globe has not occurred. A red flag should be raised when plans for community-based services are under-resourced (for example, not providing sufficient human resources to do the work), or are over-optimistic about implementation (for example, overlooking important barriers to shared decision-making)[115].

Nevertheless, community-based models have many strengths, and should be incorporated into attempts to iteratively improve clinical practices and society responses to mental disorder. Indeed, it has been argued that the shift to community-based services has not been a sudden change, but rather the culmination of a slow, gradual, evolutionary development, which has old historical roots and will hopefully continue over time[116]. Efforts to strengthen community-based approaches around the world are needed to consolidate and extend the advances that have been achieved.

Taken together, the slow transition from institutional to community-based mental health care is partly attributable to the failure of governments in low-, middle- and high-income countries to adequately invest in such care – to mandate the funding to follow people with mental disorders into their communities and provide them with the support and choices they need to live productive meaningful lives – and strategies are needed to persuade them to do so. But, perhaps to an equally important degree, there are shortcomings in models of community care, with unrealistic expectations of a dramatic paradigm shift.

CBT AND THE SCALE-UP OF EVIDENCE-BASED PSYCHOTHERAPY

Since its development in the 1970s, cognitive behavioral therapy (CBT) has been

at the core of an important shift in clinical practice towards the use of evidence-based psychotherapies. Hundreds of randomized controlled trials have examined the effects of CBT for a wide range of mental disorders, including depression, anxiety disorders, substance use disorders, bipolar disorder, psychotic disorders, somatoform disorders, eating disorders, personality disorders, and also other conditions, such as anger and aggression, chronic pain, and fatigue[117]. CBT has also been tested across age groups and specific target groups, such as women with perinatal conditions and people with general medical disorders[117].

Several other types of psychotherapy have also been rigorously investigated, and even psychotherapies that had not traditionally been explored using randomized controlled trials, such as psychoanalytically oriented therapies and experiential therapies, have now also been tested using such methods[118-120]. Nevertheless, CBT is by far the best examined type of psychotherapy and therefore dominates the transition of the field towards the use of evidence-based psychotherapies[121].

CBT is highly consistent with a neurobiological model of mental disorders, insofar as it focuses on symptom reduction, improvement in functioning, and remission of the disorder. Furthermore, the literature on the neurobiological bases of behavioral and cognitive interventions has become increasingly sophisticated[122,123], and a more recent literature on process-based CBT aligns well with the focus of RDoC on transdiagnostic mechanisms[124]. CBT can therefore be readily combined with neurobiologically oriented approaches, especially pharmacotherapy.

However, despite the strength of the evidence and its compatibility with other evidence-based interventions, CBT has not been integrated into mental health systems globally. In many countries, it is still often seen as a reductionist approach that does not tackle the real underlying problems. Psychoanalytic approaches remain dominant, for example, in France and in Latin America[125].

In low- and middle-income countries, psychotherapies in general are often not available for people suffering from mental disorders, due to lack of resources and trained clinicians. Even in high-income countries such as the US, the uptake of psychotherapies has declined since the 1990s[20], while the use of antidepressant medication has increased considerably[126], despite the fact that most patients prefer psychotherapy over pharmacotherapy[127].

In most treatment guidelines, CBT is recommended as a first-line treatment for several mental disorders. However, the actual implementation of such guidelines in routine care has been consistently shown to be suboptimal[128-130]. In addition, when CBT is employed, it is unclear whether therapists actually use it as detailed in standardized treatment protocols, or whether they combine it with other approaches.

The Increasing Access to Psychological Therapies (IAPT) program in the UK represents the most ambitious attempt to address the barriers faced by evidence-based psychotherapy, with scaling up of CBT across an entire country. The main goal of the program was to massively increase accessibility to evidence-based psychotherapies for individuals suffering from common mental disorders, such as depression and anxiety disorders.

An important argument for massively scaling up evidence-based therapies was economic. Depression and anxiety disorders often start during the working age, and therefore the economic costs associated with them are large, due to production losses and costs of welfare benefits. If these conditions are treated timeously, costs of treatment are balanced by increased productivity and reduced welfare costs[131]. A global return on investment analysis confirmed this assumption cross-nationally, indicating that every invested US dollar would result in a benefit of 2.3 to 3 dollars when only economic costs are considered, and 3.3 to 5.7 dollars when the value of health returns is included[132]. Hence, the hope was that IAPT would pay for itself.

The IAPT model has a number of key features[133]. First, patients can be referred by a general practitioner or another health professional, but can also be self-referred. People with depression, generalized anxiety disorder, mixed anxiety/depression, social anxiety disorder, post-traumatic stress disorder (PTSD), panic disorder, agoraphobia, obsessive-compulsive disorder, and health anxiety receive a person-centered assessment that identifies the key problems, and an agreed-upon course of treatment is defined[131].

Second, IAPT works according to a stepped-care model. Patients are first treated with an evidence-based low-intensity intervention, typically a self-help intervention based on CBT. Only if this is not appropriate or patients do not recover, they receive a high-intensity psychological treatment. Low-intensity therapies are delivered by "psychological well-being practitioners" who are trained to deliver guided self-help interventions, either digitally, by telephone, or face to face. High-intensity therapies are delivered by therapists who are fully trained in CBT or other evidence-based interventions.

Third, the therapies offered by IAPT are those recommended by the UK National Institute for Health and Care Excellence (NICE). When the NICE recommends different therapies for a mental disorder, patients are offered a choice of which therapy they prefer. This means that IAPT does not only deliver CBT, although a recurring criticism has been that the program is overly focused on that type of psychotherapy.

Fourth, outcome data are routinely collected in IAPT. Patients are asked to fill in various validated questionnaires before each session, so that clinicians can review the outcomes and use them in treatment planning.

Between April 1, 2019 and March 31, 2020, 1.69 million patients were referred to IAPT, of whom 1.17 million started treatment, with 606 thousand completing treatment, and 51% of them reporting recovery. The proportion of those recovered, however, is substantially lower (26%) when it is calculated based on those who started treatment (assuming that dropouts did not recover), and it has been argued that IAPT outcomes have been reported in an overly positive way[134,135].

An important issue is that the outcomes vary considerably across IAPT services. In 2015/2016, the lowest recovery rate was 21% and the highest was 63%. There is some evidence that recovery rates are higher with an increasing number of sessions and more patients stepping up to more in-

tensive therapy[136]. Other variables that are associated with better outcomes include shorter waiting times, lower number of missed appointments, and a greater proportion of patients who go on with treatment after assessment[137].

A recent systematic review and meta-analysis of the IAPT program identified 60 open studies, of which 47 could be used to pool pre-post outcome data[138]. Large pre-post treatment effect sizes were found for depression (d=0.87, 95% CI: 0.78-0.96) and anxiety (d=0.88, 95% CI: 0.79-0.97), and a moderate effect for functional impairment (d=0.55, 95% CI: 0.48-0.61).

The IAPT program arguably represents the state-of-the-art for implementation of evidence-based psychotherapy in routine clinical care. Indeed, it has served as a model for the development of similar programs in other countries[138], including Australia[139], Canada[140], Norway[141], and Japan[142]. More broadly, IAPT indicates recognition of the importance of mental health and of the allocation of sufficient resources to treatment of mental disorders, as well as acknowledgement of the importance of psychotherapies and their role in addressing mental disorders.

There are other large scale implementation programs of CBT, especially in digital mental health care. For example, Mood GYM[143], an online CBT program for depression, had acquired over 850,000 users by 2015. Psychological task-sharing interventions developed by the WHO, especially Problem Management Plus, have been tested in several randomized trials and are now being implemented in low- and middle-income countries on a broad scale[144,145]. However, the IAPT program is still the largest systematic implementation program of psychotherapies across the world.

Given the ambitiousness of IAPT, with extensive and rigorous roll-out across an entire country, it seems reasonable to raise the key question of whether this program has had real-world impacts, including a reduction in the disease burden of mental disorders. A first issue, however, is that comparison of IAPT with other treatment services would require a community intervention trial in which people are randomized to either IAPT or "regular" mental health care. Such a trial has not been conducted and probably never will be. Thus, although it is possible to claim on the basis of outcome data from routine care that other services are as effective as IAPT[146], or that IAPT services may not provide interventions that match the level of complexity of the problems of patients[147], it is difficult to validate such claims.

A second issue is whether any mental health treatments, including IAPT, are truly capable of reducing the disease burden of mental disorders. A key modeling study has estimated that current treatments only reduce about 13% of the disease burden of mental disorders at a population level[148]. In optimal conditions, in which all those with a mental disorder receive an evidence-based treatment, this percentage can be increased to 40%. So, even under optimal conditions of 100% uptake and 100% evidence-based treatments, reduction of disease burden is not expected to be more than 40%. This is true for IAPT as well as other programs disseminated on a broad scale.

The limited ability of current treatments to reduce the disease burden of mental disorders raises the so-called "treatment-prevalence paradox"[149]. This refers to the fact that clinical treatment rates have increased in the past decades, while population prevalence rates of mental disorders have not decreased. Increased availability of treatments could shorten episodes, prevent relapses, and reduce recurrences, in turn leading to lower point prevalence estimates of depression, but this has not transpired. Most meta-analyses indicate stable prevalence rates or even small increases in prevalence, despite increased uptake of services[150] and the demonstrated efficacy of psychiatric treatments[31].

There are several possible explanations for this "treatment-prevalence paradox"[149]. First, it is possible that prevalence rates of depression have dropped, but that at the same time incidence has increased due to societal changes. Second, it is possible that prevalence rates have dropped, but that emotional distress has been more often diagnosed as a depressive disorder over the past decades, thereby masking the drop. Third, it is possible that prevalence rates have not dropped, because treatments may not be as effective as the field would like[151]. Indeed, treatment effects may be overestimated in trials due to publication bias, selective outcome reporting, use of inappropriate control groups, or the allegiance effect. Moreover, treatments may not benefit chronic depressive patients, or treatments may have iatrogenic effects that block natural recovery and prolong depressive episodes[152].

Taken together, the development of evidence-based psychotherapies has been a remarkable step forward for psychiatry, and the scale-up of such effective psychotherapies in IAPT and other large-scale implementation programs has contributed to consolidating this advancement. That said, the several criticisms of IAPT suggest that it is by no means a panacea. Instead, the implementation of evidence-based psychotherapies is arguably best conceptualized as representing incremental progress. The impact of evidence-based treatments on the disease burden of mental disorders currently appears to be modest; and the time horizons for introduction of interventions that are notably more successful is unclear.

DIGITAL PHENOTYPING AND DIGITAL THERAPIES

Rapid technological advances and the expansion of the Internet have spurred the development and widespread use of a host of digital devices with the potential to transform psychiatric research and practice[153]. Indeed, the fourth industrial revolution and the nudge towards telepsychiatry by the COVID-19 pandemic have already revealed that digital technologies provide novel opportunities to improve psychiatric diagnosis, expand the delivery of mental health care, and collect large quantities of data for psychiatric research[154,155].

There are many examples of how these advances have enabled digital solutions in psychiatry[156,157]. To name a few, virtual reality can facilitate exposure therapy for phobias and PTSD[158], chatbots can deliver remote CBT anonymously day-and-night[159], computer analysis of closed circuit television (CCTV) images can identify suicide attempts in progress at suicide hot-spots[160], voice and facial recognition

software may enhance psychiatric diagnosis[161,162], wearable devices may enable real-time monitoring and evaluation of patients[163], analyses of human-computer interaction may detect manic and depressive episodes in real-time[164], and suicide risk may be assessed by analysis of social media posts[165].

Furthermore, the widespread use of digital medical records, the collection of vast quantities of data from individuals via smart devices, the ability to link multiple databases, and the use of machine learning algorithms have redefined the use of big data in psychiatry with the promise of overcoming the failures of conventional statistical methods and small samples to capture the underlying heterogeneity of psychiatric phenotypes[81-83]. The ability to access, store and manipulate data, together with the use of machine learning algorithms, promises to advance the practice of individualized medicine in psychiatry by allowing matching of patients with the most appropriate therapies[81-83].

Smartphone use is now ubiquitous even in remote and resource-constrained environments across the globe[166], making these devices a powerful medium to improve access to psychiatric care[167]. Smartphones are already being used to deliver interventions for common mental disorders[168-171], and more than 10,000 mental health apps are available in the commercial marketplace[172]. There is considerable potential to turn smartphones into cost-effective and cost-efficient treatment portals by literally placing mental health interventions in the hands of the 6,378 billion people who own these devices (i.e., 87% of the world's population), many of whom do not currently have access to mental health care.

As communication devices, smartphones can be used to facilitate peer support, deliver personalized messages, provide access to psychoeducational resources, and facilitate timely referrals to appropriate in-person clinical care[153]. The communication capabilities of smartphones have enabled the expansion of telepsychiatry via high-quality low-cost voice and video calls[173], with evidence indicating that the use of video conferencing is not inferior to in-person psychiatric consultations[174].

Because smartphones are equipped with a range of sensors and the ability to store and upload data, they can be easily used to collect real-time active data (i.e., data which the user deliberately and actively provides in response to prompts). Active data collected via smartphones are already being used in psychiatry for ecological momentary assessments, cognitive assessments, diagnosis, symptom monitoring, and relapse prevention[175,176]. Beyond these clinical applications, smartphones are also powerful tools for data collection in psychiatric research[177,178].

Digital devices, including smartphones and wearables, can also collect and store a host of passive data (that is, data generated as a by-product of using the device for everyday tasks, without the active participation of the user) with near zero marginal costs. These passive data have been likened to fingerprints or digital footprints. They provide objective continuous longitudinal measures of individuals' moment-to-moment behavior in their natural environments and could be used to develop precise and temporally dynamic markers of psychiatric illness, a practice known as digital phenotyping[155,179].

If digital phenotyping delivers on its promises, it will enable continuous inexpensive surveillance of mental disorders in large populations, early identification of at-risk individuals who can then be nudged to access psychiatric treatment, and early identification of treatment failure to prompt timely individualized treatment decisions[180]. These potential applications are important, given the dearth of accurate real-time psychiatric surveillance systems in many parts of the world, individuals' reluctance to seek treatment at the early stages of psychiatric illness, and the high rates of treatment failure which necessitate timely adjustments to management.

Identifying digital markers for mental disorders is, however, not without potential pitfalls, that will need to be mapped and navigated before digital phenotyping can realize its full potential. There are still unanswered questions about the sensitivity, reliability and validity of smartphone sensors for health monitoring and diagnosis[181]. Furthermore, there appears to be a bias in measurement of everyday activities from smartphone sensors, because of variations in how people use their devices[182]. It still remains to be seen if actuarial models developed from population level digital footprints are clinically useful at the level of individual patients, as well as how digital phenotyping can be meaningfully integrated into routine clinical practice, and how patients will respond to and accept passive monitoring of their day-to-day activities[180,183].

Digital solutions are not without shortcomings, and a digital intervention is not necessarily better than no intervention [184-186]. Reviews of the quality and efficacy of mental health apps indicate that there is often little evidence to support the effectiveness of direct-to-consumer apps[184-186]. Even when mental health apps seem to be useful, data indicate that many of them suffer from high rates of attrition and are not used long enough or consistently enough to be effective[187].

Concerns about data privacy and security are a significant obstacle to expanding the use of digital technologies in psychiatric practice and research[188,189]. Psychiatry is often concerned with deeply personal, sensitive, and potentially embarrassing information, that requires secure data storage and stringent privacy safeguards. The risks associated with collecting and storing digital mental health information need to be clearly articulated in terms that patients understand, so that they can provide informed consent. Privacy policies in digital solutions such as smartphone apps are unfortunately often written in inaccessible language and "legalese", making them incomprehensible to many users[189], and there is as yet insufficient regulation of mental health apps and no minimum safety standards[188].

While digital technology use has increased across the globe, there are ongoing inequalities in the access to these technologies within and between countries[166]. The rapid digitalization of psychiatry may unintentionally exacerbate health inequalities if digital mental health solutions cannot be shared[190]. Psychiatry will need to grapple with thorny questions about how to share digital technologies with those most in need of access to mental health care, and how to develop digital solutions for culturally diverse resource-constrained environments.

High data costs, unstable Internet connections, and bandwidth limitations can create logistical constraints on the utilization of digital mental health solutions in low-income countries[191].

The development of digital mental health solutions has typically been driven by the information technology industry and commercial interests[172]. On the other hand, the demand for mental health apps has been largely driven by consumers through social media, personal searches, and word of mouth, rather than professional recommendations[192]. Commercialization of health care and the repositioning of patients as customers has certainly created some efficiencies in health care delivery[193]. However, the profit motive is not always aligned with good patient care, as illustrated by the recent opioid crisis[194].

Ensuring that clinicians are part of the process of digitalization of psychiatry will entail training them to understand, use and develop digital technologies; establishing ethical guidelines for the use of these technologies; ensuring independent evaluation of the effectiveness of digital interventions by researchers who have no commercial interest in the products; and protecting patient safety by ensuring that the claims made about the benefits of digital solutions are supported by robust evidence.

Emerging evidence suggests that screen time may be associated with mental health problems, although most of the work in this area focuses on children and adolescents[195-197]. While research is mostly cross-sectional, there are a small number of longitudinal studies showing that screen time has small to very small effects on subsequent depressive symptoms, and that these associations depend on device type and use[198,199]. If screen time is bad for mental health, would it be wise to promote the use of digital mental health interventions that entail more time online or in front of a screen? This is not an easy question to answer, and the answer is likely not a simple yes or no.

The challenge is to think about how digitizing psychiatry can be balanced with a careful understanding of the potential for digital devices to harm mental health. Few interventions in psychiatry are without potential side effects, and it would be naïve to think that digital ones are different. As with any psychiatric treatment, the prescription of digital interventions needs to be accompanied with consideration of the contraindications, advice about how to use the intervention to its maximum benefit, and warnings about potential side effects and how to manage them. To enable this we require data, which we do not yet have, about the contraindications and side effects of digital interventions[188].

We already have evidence to show that digital technologies can be at least as effective as traditional practices in making a psychiatric diagnosis, identifying appropriate individualized interventions, and teaching psychological skills such as mindfulness and attentional training[180,200,201]. Yet, most clinicians would likely agree that psychiatric practice is fundamentally relational and that most mental illnesses have an interpersonal dimension. The increasing use of technology in psychiatry will change the relationship between physician and patient in ways that we probably do not yet understand and cannot anticipate.

How technology is utilized in psychiatry will be a function of how central we think relationships are in diagnosis and treatment, and whether or not we see digital technologies as primarily a tool to enhance the therapeutic relationship, or simply a conduit to deliver content or collect and process information[202]. Theories will need to be developed to conceptualize and understand the digital therapeutic relationship, while we hold in mind the potential to harness technology to deepen the relationship between clinicians and patients. Indeed, evidence suggests that digital interventions are most effective when they have at least some person-to-person interaction[179,200].

Digital technologies may change the way psychiatry is practiced, but to date much of the research in this area has been experimental, with proof-of-concept and clinical trials in highly controlled settings using very small samples[172]. The translational potential of these technologies has not yet been realized, and we still have some way to go to bring digital advances in mental health "from code to clinic"[172]. There are relatively few examples of digital technologies other than teleconferencing being used routinely in everyday real-world psychiatric practice, and there is an urgent need for pragmatic trials and translational research to understand the barriers to adoption and implementation of new technologies[203]. The attitudes of clinicians and patients towards digital solutions in psychiatry and their perceptions of the effectiveness and safety of these devices are important determinants of how widely new technologies will be adopted.

Taken together, the science is still too young to let us know the extent to which the introduction of digital technologies will truly constitute a paradigm shift in psychiatric diagnosis and treatment, and whether these technologies will deliver on their promise to reduce the burden of disease caused by mental disorders. The available evidence gives cause for optimism and suggests that these technologies could assist in iteratively progressing the science and practice of psychiatry. However, there are many red flags when it comes to digital psychiatry, including overpromising with regards to efficacy and overlooking the human relationship. In order for iterative progress to happen, we will need continuous critical reflection, with an ongoing emphasis on equitable access, appropriate regulation, and quality assurance[204].

GLOBAL MENTAL HEALTH AND TASK-SHARING

The concept of global health emerged in the aftermath of World War II, when cross-national organizations were needed to coordinate health efforts, particularly against infectious diseases[205]. The WHO was established in 1948, and became a key advocate for global health, exemplifying the key pillars of this approach, including the recognition that health is a public good requiring support from all sectors of the governments, that health involves a continuum ranging from wellness to illness, and that the determinants of health are biological, sociocultural and environmental[206]. Global health saw the protection of human rights as a central concern of all action concerning health, and expected that action to improve health in-

cludes the formulation of working policies addressing upstream social determinants of health, and a strengthening of health services[207].

With growing recognition of the burden of non-communicable diseases, including mental, neurological and substance use disorders, global mental health became an important focus. B. Chisholm, a psychiatrist who was the first WHO Director General, introduced the mantra "No health without mental health"[208]. An early 4x4 model of non-communicable diseases emphasized the comorbidity of cardiovascular diseases, diabetes, cancer and respiratory diseases with tobacco use, unhealthy diet, physical inactivity and harmful alcohol use as risk factors for these conditions. A later 5x5 approach has emphasized that these non-communicable diseases are commonly comorbid with mental disorders, and that childhood adversity is an important common risk factor[209].

Over the past several decades, global mental health has become a significant discipline, with specific departments established at several leading universities, textbooks and journals devoted to the subject, and significant support for research obtained from funders[210]. In addition to a focus on mental health as a public good and human right, on mental health as entailing a continuum and a life course approach, on the importance of social determinants of mental health, and on the need of strengthening mental health services, work in global mental health has emphasized the efficacy of task-shifting interventions, the importance of addressing stigma, and the value of including service users' perspectives in research and planning[1,2].

Early work by the WHO, and subsequent work by others in global mental health, has led to important contributions. A first key contribution has been the recognition of the burden of mental disorders, and advocacy that this burden needs to be urgently and appropriately addressed. There are far too few mental health clinicians in low- and middle-income countries, where the vast majority of the world's population resides[22].

A second key contribution has been a focus on addressing mental health in primary care. In the 1970s, the WHO conducted a multinational collaborative study demonstrating the feasibility and effectiveness of offering community-based mental health care, delivered by primary health care workers, in developing countries[211]. A few years later, in 1978, the Primary Health Care Conference in Alma Ata, composed of representatives of almost all countries in the world, included the promotion of mental health into the list of essential components of primary health care.

Nevertheless, global health in general and global mental health in particular have faced many challenges. Early hopes were that globalization would entail a border-free world with easy communication, trade, and mutual support. However, globalization has also arguably allowed unidirectional unloading of products of the North to the less industrially developed South, and a simultaneous migration of many individuals, including health professionals, from the global South to the North. Colonial practices, including large psychiatric hospitals, have remained in existence in many low-income countries. Rapid urbanization and breakdown of traditional communities, which provided some support to vulnerable individuals, have further complicated the provision of health care. The introduction of digital technologies – which has been considered as a potential equalizer – also runs the risk of creating a new divide, the digital divide.

In terms of the clinical practice of psychiatry, while the numbers of psychiatrists and other mental health care workers has significantly increased across the globe, their inequitable distribution has not significantly improved[22]. There are still many countries with only a few psychiatrists, and the brain drain – the movement of fully trained psychiatrists from the global South to the North – continues[212]. Training programs which can be used for primary health care providers in mental health have been produced by the WHO and other agencies, and the situation has improved in some countries, but the numbers of those left with no adequate care remain high. Primary care practitioners are not always willing to accept responsibility for the treatment of mental disorders, and many well-trained psychiatrists have continued to work in private health care services that reach only a minority of those who need help.

Earlier sections of this paper considered some of the concerns about current psychiatry nosology raised by neurobiologically-focused and "number-driven" researchers. But even from a public health perspective, application of key aspects of the chapter on mental disorders of the ICD rises problems[213]. First, most practicing clinicians feel that in daily work the number of diagnostic categories proposed for use should follow the number of options for therapeutic interventions, and so ICD approaches may be too complex. Second, reporting about inpatient mental health services to national authorities in most instances follows the guidelines provided by hospitals, which do not allow for the collection of sufficiently detailed or validated data. The interpretation of findings may be made even more difficult by the fact that in federal countries the rules of reporting to the central authority differ from area to area.

Global mental health has been crucially important in putting forward a number of innovative models and approaches. At the same time, critics might suggest that the strategies of global mental health are not so much an entirely new paradigm but instead a re-packaging of long-standing ideas in the field, and that each of these strategies has important limitations which deserve emphasis.

First, global mental health has focused on the notion of "task-shifting". This involves the use of non-specialized health care workers, who are trained and supervised by mental health specialists. Systematic reviews have concluded that there is now considerable evidence for the efficacy of this approach[3,214]. Nevertheless, this strategy is not a panacea. There are limits to what can be done by untrained personnel. The treatment of more complex conditions, such as treatment-refractory mental disorders, requires well-trained clinicians. Moreover, significant supervision and monitoring may be required, and this entails human and financial resources. There is now interest in how to assess therapist competence in task-shifting trials[215,216]. Finally, there is a difference between demonstration projects conducted by academic

researchers and real-life scale-up projects undertaken by governments. Pharmacotherapy outcomes are worse in real-world pragmatic trials than in academic-centre explanatory trials, and we might expect that the same will hold true in the case of task-shifting research.

A second important strategy of global mental health has been to build the investment case for mental health, demonstrating the return on investment for countries scaling up community-based care. As noted earlier, this gave key impetus to the implementation of psychotherapies in the UK. However, a number of challenges remain. Many economic returns accrue to sectors outside ministries of health, which traditionally hold mental health budgets. Economic returns on scaled-up mental health care are likely to accrue through improved labour market participation, reduced homelessness, and savings to correctional services and police services, and not necessarily to the health sector. Moreover, such savings might only be realized at some time in the future, creating what has been termed pernicious "diagonal accounting"[217]. Finally, it must be conceded that not all investment in mental health – for example, care for those with severe neurodevelopmental disorders – will yield significant economic returns.

A third key strategy of global mental health has been to focus on building stronger, better coordinated advocacy, with partnerships between people with lived experience and clinicians to campaign for better and more resources for mental health care. It has been argued that ongoing dialogue between the various stakeholders involved in community-based care is essential to reach common ground on service development priorities. This should also include maximizing opportunities for leadership from people with lived experience, to address demand-side barriers to community-based mental health care. Nevertheless, there are key barriers to advocacy work, including low mental health literacy of policy-makers, and a gap in frameworks linking research to policy[218].

A fourth key strategy of global mental health has been to focus on stigma reduction strategies. Certainly, reducing stigma and discrimination against people living with mental illness is vital if we are to promote care in the community. Furthermore, there is a growing evidence base for the positive impact of stigma reduction campaigns for mental health, such as the World Psychiatric Association's "Open the Doors" program. At the same time, there are important challenges to acknowledge. Much more needs to be done to both improve the effectiveness of these interventions and extend stigma reduction programmes to a range of different countries[219]. Stigma reduction strategies should not deny the dysfunction that accompanies severe mental disorders (services for such conditions remain sorely needed), and they need to also highlight that individuals suffering from psychiatric disorders have "responsibility without blame"[220]. Finally, it is notable that, in some contexts, providing neurobiologically focused information increases rather than decreases stigma[221].

A fifth key strategy of global mental health is to address social determinants of mental disorders. Governments need to address fundamental social injustice such as rampant inequality, high unemployment, civil conflict and violence, particularly gender-based violence, that drive mental disorders in populations[222]. That said, the evidence base for population-level interventions to address the social determinants of mental health is rather sparse and of low quality[223]. Ironically, global mental health has been accused of ignoring key contextual data[224], and of perpetuating some of the sociopolitical inequities it critiques[225]. Less contentiously, while some clinicians may well contribute to efforts focused on social determinants, the majority will focus on providing direct clinical care. Public mental health skills are needed to supplement, rather than replace, standard clinical training.

Taken together, it is clear that the concepts and methods of global mental health have many strengths, have contributed to important advances, and should be incorporated into further attempts to incrementally improve health policies as well as clinical practice. As always, discourse about a paradigm shift and over-optimism about the extent of envisaged change raise red flags. Indeed, the key strategies of global mental health that may facilitate ongoing incremental progress may themselves require iterative attention: we need to continue to be innovative about task-sharing, to gradually strengthen the investment case, to steadily develop better advocacy strategies, to further reduce stigma about mental disorders and increase mental health literacy, and to better address social determinants of these conditions.

DISCUSSION

Kuhn's notion of scientific paradigms has been extraordinarily influential[226]. He argued that most of science is "normal": scientists have a particular conceptual framework, with various exemplars that are key for the field, which allows them to address a range of relatively minor "puzzles"[227]. However, from time to time, there is a paradigm shift, with an entirely new conceptual framework and new exemplars coming to fore and causing a "crisis", and so entailing a major revolution in the field. Thus, for example, at one point *phlogiston* was thought to explain combustion, but this paradigm was replaced by one that emphasized the importance of oxygen, providing an entirely new perspective. Notably, from a "critical" perspective, scientific paradigms are incommensurable; those who adopt different paradigms are really talking past one another, and the shift from one paradigm to another happens not because of scientific advancement, but rather due to a sociopolitical shift in the field[228,229].

From this perspective, psychiatry has been characterized by a history of continual paradigm shifts, with the field lurching over time from one set of models to another, with no substantive scientific advances in our knowledge, but rather merely a responsiveness to the prevailing sociopolitical winds of the day[229]. Thus, as noted earlier, psychiatry has seen movements from psychodynamic approaches to neuroscientific ones, and from institutional care to community-based care. While a good deal of the critique of psychiatry has come from external fields, there is a significant contribution from within the discipline, with proponents of new paradigms at times being very critical of current practices.

The idea that psychiatry is in crisis seems to be prevalent and persistent in both the professional literature and in social media[230-234].

We would argue strongly against this view of psychiatry. This is not to disagree that there have been important shifts in the field over its history: there certainly have been. Nor is it to disagree with the valid points that sociopolitical and sociocultural factors are key to such issues as determining budgets for mental health services, and in influencing the experience and expression of mental disorders[235]. Nor is to deny or downplay the many crucial challenges that continue to face psychiatry as a profession, and psychiatrists as practitioners[236,237]. And perhaps most importantly, it is not to ignore or to minimize the enormity of the treatment and the research-practice gaps discussed in detail earlier in this paper. Clearly, considerably more needs to be done to improve mental health care services, and to effectively address the burden of disease due to mental disorder.

However, we wish to emphasize that there has been a gradual accretion of knowledge about mental disorders, and that our understanding of their causes and our ability to manage them has significantly increased over time. We also wish to argue that the different proposals for the field discussed in this paper are not necessarily incommensurable paradigms, but rather are important perspectives that can productively be drawn on and integrated into contemporary practice[238]. The integration of clinical neuroscience and global mental health, for example, may facilitate advances in precision public mental health[239]. Space precludes a detailed consideration of a range of other innovative perspectives that may also contribute to the incremental and integrative advance of psychiatric practice, including collaborative care[240], preventive psychiatry[241], evolutionary psychiatry[242], positive psychiatry[243], intergenerational psychiatry[244], and welfarist psychiatry[245].

Perhaps most importantly, we would wish to problematize the notion that psychiatry is in perennial and perpetual crisis. Tools provided by "critical" authors, who emphasize the sociopolitical aspects of science and medicine, may be in fact be useful in investigating why psychiatry is so often viewed in this way, and why a view of psychiatry as steadily accreting knowledge and improving clinical practices is less often put forward than seems reasonable, even from within the field. Are there specific interests that stand to gain from negative views of the psychiatric profession? What are the benefits to particular authors of being overly critical of existing practices and of promising entirely novel or disruptive solutions? What can be done to encourage those without and within the field to emphasize that scientific progress is often iterative and incremental, with gradual consolidation of knowledge, with inclusion and integration of a range of different models and approaches?

We have noted in this paper a number of red flags, which seem indicative of overly optimistic promises of a paradigm shift in psychiatry practice and research, and that may inadvertently even support an anti-psychiatry position that discourages patients from seeking sorely needed professional care, or policy-makers from funding desperately needed mental health care services. A few of these red flags deserve particular emphasis here.

First, given the complexity of mental disorders, and the need to avoid both a brainless and a mindless psychiatry[246], various forms of reductionism serve as red flags, whether these involve neuro-reductionism (e.g., mental disorders are merely brain disorders) or culturalism (e.g., mental disorders merely reflect social inequalities). As a field, we should promote the breadth and depth of psychiatric concepts and findings, emphasizing that psychiatry builds bridges across biological, psychological and social domains, and that – despite the complexity of mental disorders – this has allowed important insights into their phenomenology and etiology, and has facilitated the development of a broad range of different evidence-based treatment modalities and types of intervention. The complexity of mental disorders may, however, mean that there are few "silver bullets" in psychiatry: any individual mental health intervention may have only modest effect sizes, and reduction of disease burden due to mental disorders is a massive goal, likely requiring a broad range of interventions[247].

Second, economic over-optimism may be a red flag: bringing new drugs to market requires significant financial investment, deinstitutionalization is not an inexpensive option, and it is a challenge to demonstrate that large-scale implementation programs such as IAPT save money. While a range of different metaphors may be useful in describing psychiatric work, and in encouraging policy-makers to fund mental health services, we need perhaps to be particularly careful of seeing patients as merely consumers, and psychiatry as simply providing a return on investment. Similarly, while a collaborative relationship between professional clinicians and patient partners may be useful in encouraging shared decision-making, this metaphor of psychiatric work and mental health services may miss some aspects of the clinical encounter. The metaphor of clinicians providing care is a crucial one, and we need to call for more such care, even if at times it is somewhat expensive[115].

Third, calls for a radical transformation of psychiatry's research agenda are a red flag. Hubris may result in downplaying what has already been achieved over decades, or in overly focusing on one or other favoured perspective. A more humble position that emphasizes how difficult is to know what approaches and models will lead to the largest advances, that encourages a broad range of promising work, that insists on principles of reproducible science including the common metrics agenda, and that acknowledges the key role of serendipity, is appropriate[64,248,249]. Analogously, calls for a radical transformation or narrowing of the training curriculum also constitute a red flag: psychiatry trainees need exposure to a broad range of concepts and methods, including neuroscience, statistics, evidence-based psychotherapy, digital psychiatry, and public mental health. The field needs well-rounded graduates who are able to access and employ the full range of concepts and findings from our rich discipline.

How can we facilitate an ongoing focus on incremental advances in clinical practice, with integration of a range of different perspectives and findings? It may be useful to approach the issues discussed in this paper with a particular knowledge of how

science works, and with a particular attitude towards progress.

From the perspective of knowledge, it seems useful to emphasize that concepts of scientific crisis and paradigm shifts often serve as rhetorical devices, that in sciences ranging from physics to psychiatry multiple approaches and models are potentially useful, and that in psychiatry there is a particular need for pluralistic and pragmatic approaches that integrate a range of different concepts, methods and findings[229,250]. From the perspective of attitude, we would emphasize the value of staying hopeful, avoiding hype, and committing to the important work of closing the treatment gap as well as the research-practice gap.

Thus, in terms used earlier in this paper, the solution to challenges in psychiatric diagnosis and treatment is unlikely to lie in entirely novel paradigms, but rather in the humble, laborious, iterative work of systematic clinical observation, painstaking research, and creative thinking. In the case of psychiatric assessment, for example, we have elsewhere argued for the need for more work on post-diagnostic assessments and measures that are consistent with measurement-based care and that promote personalized psychiatry[251-253]. In the case of psychiatric treatment, addressing the treatment and the research-practice gaps will require more attention to expanding innovative delivery models that will reach more people in need[254], systematic adoption and roll-out of integrated evidence-based interventions[255], and an iterative discovery-confirmation process to assess and improve efficacy[256].

In conclusion, this review of a range of proposed approaches to and models of diagnosis and treatment of mental disorders suggests caution in concluding that we are facing a crisis in psychiatry which necessitates a disruptive transitioning from traditional to new practices. We argue instead that an approach which emphasizes paradigm shifts should be replaced by one that focuses on the importance and value of incremental and integrative advances. In particular, we caution against an advocacy for paradigm shifts that inadvertently represents a disguised manifestation of anti-psychiatry, and we instead suggest the need for a position that emphasizes both the accomplishments and limitations of psychiatric diagnosis and treatment, and that is cautiously optimistic about their future.

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DOI:10.1002/wps.20998

Incremental advances in psychiatric molecular genetics and nosology

I begin my commentary on Stein et al's impressive, in-depth and balanced paper about the current status of psychiatric research and practice[1] with a few general thoughts, and then dig more deeply into two main points to further explicate what for me is a central theme in the paper.

In my view, the authors are exactly right to seek to discredit the frequently repeated claim that psychiatry is in crisis. At the same time, they provide a healthy skepticism of the claims, long echoed in our field, that major breakthroughs are "just around the corner". They instead advocate for a far more realistic projection of modest incremental advances.

At a different level, I also applaud the authors' commitment to explanatory pluralism. Nearly all psychiatric disorders are highly multifactorial. Despite the appeal of monocausal models, which have over history been repeatedly proposed for psychiatric disorders (and were correct for one – general paresis of the insane), they have, with this one exception (plus perhaps a small number of severe, rare forms of autism) represented false hopes. At a deeper philosophical and historical level, I also believe that the history of psychiatry has been defined by a joint commitment to brain and mind which has led to endless controversies but also a rich tradition of attempted integrations[2]. Abandoning either of these approaches would lead to an impoverishment of our field.

In the spirit of Stein et al's paper, I want to comment in more depth about two areas with which I am familiar: psychiatric genetics and psychiatric nosology. They illustrate in different ways the failure of overly-enthusiastic paradigm shifts in the field of psychiatry and the success of slow incremental advances.

With the advent of molecular genotyping methods in the 1980s, and the early successful mapping of the Mendelian locus for Huntington's disease, the psychiatric field, with more exuberance than was justified by the available data, yearning for a dramatic paradigm shift, sought, with poorly powered samples, single major genes for schizophrenia and bipolar illness. The result was painful and predictable – dramatic false-positive findings followed by the inability to replicate.

Then came the ill-conceived candidate gene era, where the field flaunted well-understood rules of multiple testing. Furthermore, it was imagined that genes involved in the structure of neurotransmitter receptors and/or the uptake or degradation of these neurotransmitters were true candidate genes. However, these genes were not involved in the etiology of the disorders but in the action of pharmacological treatments – a classic category mistake. In a triumph of exuberance over common sense, these studies also yielded almost entirely false-positive findings.

Then came the more mundane and much more effortful brute force method of genome-wide association studies (GWAS). This humbler method was based on the fact that, for psychiatric disorders, we knew next to nothing about specific etiologic mechanisms of illness. The field properly did its multiple testing homework. What was unknown was the expected effect sizes of the risk alleles. Not surprisingly, initial estimates here were far too optimistic. The first studies with sample sizes thought to be adequate were entirely negative. Then something unexpected happened. The field abandoned important parts of the more typical academic model of inter-group competition for a model of inter-group cooperation, forming the Psychiatric Genomic Consortium[3]. Positive results, that have replicated well, finally began to flow in, first as a trickle and then as a cascade[4].

As genotyping costs fell, samples of exome sequence became large enough to also begin to yield positive results – this time identifying specific biological processes, and not the statistical signal of a genomic region that is obtained from positive GWAS results[5]. This is only a start. The pathway from genetic variants to pathophysiology, let alone to druggable targets, will certainly be long and complex, and success is by no means certain. Like many of the chronic diseases of humanity, we now know that psychiatric disorders suffer from the "curse of polygenicity".

I next want to turn to psychiatric nosology with some comments complementary to those provided by Stein et al, and with an apology for a parochial emphasis on the US perspective. The Feighner criteria represented a major break with the "Great German Professor Principle" whereby the influence of a psychiatric nosology was based largely on the reputation of the proposer. By contrast, the Feighner criteria grew out of a journal club run by S. Guze and E. Robins at Washington University St. Louis that tried to develop criteria from the then rather skimpy empirical literature, inevitably complemented, when data were lacking, by clinical experience[6]. We might call this an "empirically aided expert consensus" model.

This model was applied with only modest changes for the Research Diagnostic Criteria, the DSM-III and the DSM-III-R, the last of which I was able to observe personally. Literature was discussed, but largely to support clinical opinions, with some growth during the process of the importance of having at least some research basis for proposals for change. Systematic literature reviews became much more common in the DSM-IV, although they varied widely in quality, and the idea of trying to systematically evaluate a set of validators was not widely adopted.

The DSM-5 was initially conceptualized by its leaders as a paradigm shift in nosology, in particular with the intention of moving from descriptive to etiologically based diagnoses. However, when the work groups for DSM-5 began meeting, none of them felt that the available data were adequate to support such a change. Although several had approached the DSM-5 leadership to develop a clear set of guidelines for changes in DSM-5, these requests were not acted upon[7]. However, in the middle of the DSM process, the DSM leadership requested such a document, that was developed quickly by a small group. While widely disseminated, the recommendations were not systematically adopted by all work groups.

With rising concerns about the heterogeneity of the approach across the work groups, the leadership of the American Psy-

chiatric Association requested the formation of a Scientific Review Committee which, building on the previously proposed criteria, further developed them in a conscious attempt to move the process from an "empirically aided expert consensus" model to a more empirically driven process in which the focus would shift from personal expert opinion to systematic review of research evidence for validity and reliability[8].

This is a very challenging process, and will never be as simple as the evaluation of efficacy of a drug treatment, which can focus largely on results from randomized controlled trials and reports of side effects. What we see in the DSM-US based psychiatric nosologic process is a gradual shift from an expert consensus to a more data-driven decision making, in line with the developments of the broader medical field[9].

I am convinced that a move toward etiological diagnoses in psychiatry will result from incremental advances, not one dramatic change. The DSM-5 already contains an etiologic diagnostic criterion for narcolepsy – evidence for a hypocretin deficiency. In the coming years, if genetic risk factors (e.g., polygenic risk scores) or imaging findings can add to the diagnostic validity or reliability of specific diagnostic categories, then they can be added with the usual diagnostic review process. Eventually, psychiatric diagnostic criteria may come to resemble those seen in other areas of medicine, for example, rheumatology, where the operationalized criteria are a mix of symptoms, signs, course of illness, and specific biological findings.

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DOI:10.1002/wps.20999

Incremental integration of nosological innovations is improving psychiatric diagnosis and treatment

Stein et al[1] present a perspective on the many forms of ferment and creative activity in contemporary psychiatric research and scholarship. Their paper articulates an appealing basic stance toward these developments: rather than calling for a revolution or paradigm shift to realize the clinical applications of recent research advances, their view is that such advances can be integrated incrementally. The breadth and scope of the paper is indeed impressive, covering numerous generally insular literatures, and successfully articulating a truly international perspective on developments in psychiatric research and practice.

A focus on incremental integration provides an appealing stance, because paradigmatic disruption can be difficult to navigate in an ongoing enterprise such as psychiatric care. As Hyman points out[2], it can be difficult "to repair a plane while it is flying". Many contemporary scholars call for fundamental shifts in psychiatric thinking, but, as we incorporate novel approaches, we must still attend to the structures in which current care is embedded. This is because ongoing patient care depends on those extant structures.

Although the basic stance of incremental advances has pragmatic appeal, there are also some aspects of the arguments offered by Stein et al that may benefit from further thought and discussion. Specifically, their stance involves defining a threshold for the distinction between "incremental integration" and "paradigm shift". The basic concern voiced by the authors is that paradigm shifts are disruptive and therefore problematic and suboptimal, whereas incremental integration is desirable and of course part and parcel of the history of medicine. But how should we distinguish between incremental integration and disruptive paradigm shifts, in incorporating novel evidence and approaches?

My impression is that constructive evolution in the field is happening within normal channels, thereby suggesting that important improvements do not require disruptive paradigm shifts. Moreover, this type of progression is obviously necessary if the goal of psychiatry is to base practice on research. This is because research aims to challenge tradition by its very nature as a creative and forward-thinking enterprise. Impactful medical research strives toward continuously improved understanding of the world, with direct implications for patient care.

Consider for example the assertion that "categorical and dimensional approaches are interchangeable: any dimension can be converted into a category, and any category can be converted into a dimension"[1]. This statement, although appealingly ecumenical, may be scientifically misleading. Fortunately, the burgeoning literature comparing categorical and dimensional approaches directly is impacting psychiatry not through disruption, but via the normal interdigitation of science and practice.

Categorical and dimensional models are routinely contrasted and compared directly in their ability to account for data, and these direct empirical comparisons help to distinguish various conceptions of psychiatric signs and symptoms. There is a vast literature on this topic and, when such comparisons are undertaken, dimensional models tend to fit data better than cate-

gorical ones[3-5].

This body of evidence is shaping psychiatric thinking not via disruptive paradigm shifts, but through incremental integration. One area where this is abundantly evident is that of personality disorders (PDs). Few sections of classical diagnostic manuals have proven as problematic as that on PDs, because the vexing conceptual problems of comorbidity and within-category heterogeneity are particularly acute when conceptualizing cases in terms of classical PD categories[6]. As noted by Stein et al, "when it comes to, say, personality disorders, the disease-entity concept is even more distant, and the search for new approaches is seen as particularly key".

For these reasons, contemporary PD models in diagnostic manuals are transitioning to dimensional approaches. For example, the ICD-11 model is based on the empirical dimensional structure of PD variation, and is now officially in use[7]. Is this an example of a paradigm shift, or of incremental integration? Inasmuch as research influenced the structure of the evolving and established ICD nosological endeavor (vs. dispensing with the ICD altogether), this provides a compelling example of a much needed and welcome incremental integration. The general point is that progress does not require disruption in all instances; existing structures and mechanisms (such as the ICD revision endeavor) can often support constructive forms of progress.

Importantly, whether such progress is seen as paradigm shifting or as incremental integration may be in the eye of the beholder. For example, to maintain conformity with the international psychiatric community, the DSM's approach to PDs will need to shift toward the ICD-11 approach, which is highly similar to the DSM-5 alternative model of PDs (as opposed to the DSM-5 PD categories reprinted from DSM-IV in the categorical diagnostic section of the manual). Whether this inevitable evolution is perceived as disruptive or as incremental will depend on the perspectives of the scholars contemplating these changes. Nevertheless, the general point is that PD nosology is shifting based on evidence, within the pages of stalwart diagnostic manuals. Progress is being incrementally integrated through normal channels and is achieved without needing to dispense entirely with the ICD and DSM. Indeed, to maintain scientific viability, the ICD and DSM will need to continue to integrate dimensionality more thoroughly and not just for PDs, given the state of the extensive literature on empirical classification of psychopathology[8].

Innovations in PD classification are also beginning to impact thinking about effective approaches to intervention, through incremental integration. Sauer-Zavala et al[9] provide a compelling example of framing such approaches as transitional, via modules aimed at unpacking heterogeneity in the classical category of borderline PD. Rather than reifying this category, they embrace the heterogeneity of presentations within it, by parsing it in terms of modern dimensional approaches. They show that borderline PD heterogeneity can be effectively conceptualized by tailoring interventions to specific dimensional sub-elements, shifting treatment to more directly address the features delineated in the DSM-5 alternative model (e.g., tailoring treatment for more antagonistic vs. more disinhibited presentations). This type of perspective shows that innovation can make its way into front-line practice not by demanding abandonment of classical diagnostic labels, but by showing how modern dimensional research can help to improve case conceptualization, focusing interventions on specific presentations.

In sum, Stein et al are to be commended on a thorough and forward-thinking review of the numerous developments at the cutting edge of psychiatric research and practice. Their call to incorporate these advances is indeed welcome. Nevertheless, whether the incorporation of advances is seen as disruptive as opposed to integrative is often tied to the perspective of the observer, and the previous investments and traditions embraced by that observer. The good news is that many creative and novel ideas from the research realm are making their way into practice through normal channels, even if some are afraid that innovation may be unnecessarily disruptive.

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DOI:10.1002/wps.21001

The future of CBT and evidence-based psychotherapies is promising

Stein et al[1] point out that, while evidence-based psychotherapies and particularly cognitive behavioral therapy (CBT) represent a "remarkable step forward", their implementation in mental health systems globally is "arguably best conceptualized as representing incremental progress".

Modest implementation is tied to several factors, including incompatibility with other psychotherapeutic models, frequent departure from evidence-based guidelines in routine care, and lack of trained clinicians. Further, even with embedded training in evidence-based therapies, as exemplified by the UK Improving Access to Psychological Therapies (IAPT) program, the authors report that rates of clinically significant improvement are estimated at only 26% when assuming poor treatment response among dropouts[1].

In line with 2004 modeling to suggest

that universal provision of evidence-based practices will reduce the global disease burden by only 40%, Stein et al[1] raise the specter that the burden of mental disorders will never be significantly reduced. In further support of this bleak outlook, they refer to the treatment-prevalence paradox of increased treatment uptake without corresponding reductions in population prevalence rates (as documented for depression).

Herein, I argue that a more promising future of CBT and other evidence-based psychotherapies is achievable through: a) more mechanistically targeted interventions, that b) are personalized or matched to individuals and c) are scaled with fidelity by harnessing technology.

The majority of randomized controlled trials (RCTs) to date evaluate CBT packages of multiple elements (e.g., cognitive restructuring, relaxation, exposure), designed for individuals classified according to diagnostic nosologies. Yet, within a set of therapeutic elements, some are likely to be more effective than others for a given individual, increasing the risk of iatrogenic effects, inefficiency, and treatment dropout. Moreover, diagnostic categorization for treatment selection ignores the substantial heterogeneity within diagnoses (e.g., within post-traumatic stress disorder, some people experience numbing and dissociation whereas others suffer from heightened emotional arousal). Transdiagnostic symptom dimension models, such as hierarchical latent structural models and symptom network approaches, promise greater precision in personalization of mental health care. Shifts towards treatment elements rather than packages, and symptom dimensions rather than diagnoses, will enable more targeted interventions that are more effectively matched to individuals. Evidence in support of prescriptive matching to specific treatment elements is beginning to emerge[2].

A treatment elements approach also aligns with targeting specific dysregulations in physiology, cognition, behavior or emotion that correlate with or contribute to psychopathology. Exemplars include advances in neuroscience and behavioral science of fear extinction, that have led to refinements of exposure therapy for fear and anxiety symptoms[3]. Corresponding advances in the area of reward processing have led to treatments that target reward hyposensitivity for anhedonia symptoms across anxiety and depressive disorders[4]. Feedback from evaluation of target engagement can then inform iterative intervention refinement.

With moderated mediation approaches, we may further learn that mediators (as measures of purported mechanisms) have differential relevance across persons. As an illustration, prediction error generalization may be a stronger driver of exposure therapy effects for some people, whereas reappraisal of feared outcomes may be more relevant for others, such that different versions of exposure therapy may be tailored for each individual. Consequently, theoretically relevant features of responding could be matched to targeted interventions more precisely and thereby more effectively, as a step beyond moderation based on standard features of clinical presentation (e.g., symptoms and functioning).

Advances in the mechanisms contributing to psychopathology, continuing development of intervention elements that specifically target mechanistic features, along with prescriptive algorithms for selecting the right intervention for a given person, represent an enormous research agenda, but one that is nonetheless underway, with the US National Institute of Mental Health's emphasis upon experimental therapeutics for clinical trials and the recent Wellcome Trust initiative of "Finding the next generation of mental health treatments and approaches".

Alongside the development of more targeted and personalized intervention elements, technologies can facilitate screening and triaging to the type of care predicted to be most effective, with rapid adaptation of care as needed, for more scalability and more effective outcomes.

Online screening and tracking of mental health status and related variables is suitable for large scale deployment, particularly adaptive testing which increases measurement precision and minimizes participant burden relative to traditional fixed length instruments[5]. Automated feedback from scoring algorithms can then guide treatment selection. Prescriptive treatment selection algorithms generated from machine learning or other modeling of an array of relevant data may improve overall outcomes relative to standard clinical decision making, as has been demonstrated when selecting between low-intensity versus high-intensity care within IAPT using a limited range of predictive variables (i.e., symptom severity, impairment, personality traits, employment status, race/ethnicity)[6]. As mentioned, theoretically relevant variables (e.g., emotion regulation, response inhibition, and threat expectancy) may enhance accuracy of treatment response prediction for specific treatment elements (versus levels of care).

Rather than adapt level of care after a patient shows non-response or prematurely discontinues treatment (as is typical in stepped care models), ongoing predictive modeling can facilitate adaptation to higher levels of care or to different therapeutic elements before failure occurs. This just-in-time treatment approach has the potential to improve effectiveness and reduce attrition, as patients may be more engaged in treatment when they are receiving what they need most at the time they most need it. Adaptive interventions can also increase the efficiency of service delivery and reduce downstream service costs. Furthermore, adaptation extends to maintenance goals, so that care can be rapidly reinitiated upon signs of symptom worsening to prevent full relapse.

Task-sharing through non-specialized providers is a cost-effective strategy for scalable mental health care[7], but is challenged by scalability of training and supervision and by fidelity assurance (adherence and competency). Digital tools can address these issues, such as training courses with interactive feedback for skill development and ongoing competency evaluations, as well as computerized session guides to maintain fidelity[8].

Digital CBT and other evidence-based psychotherapies via phone, computers and other electronic devices increase access to care, and overcome barriers of stigma, financial difficulties, time constraints, and location of services. The available evidence clearly supports their efficacy, although more research is needed in low- to middle-income countries. Digital thera-

pies are particularly suited to the research agenda of prescriptive algorithms for selecting specific intervention elements most likely to benefit an individual. Yet, user uptake, engagement and dropout are problematic, especially in routine clinical care settings. Since human support mitigates these concerns[9], models that combine nonspecialist providers with digital interventions have unique potential to expand reach, engagement and effectiveness.

Mechanistically targeted and personalized intervention elements that are matched to individual needs and adapted as needs change over time, delivered digitally or by clinicians, that can be scaled up through online tools and artificial intelligence technologies, offer a future in which delivery of evidence-based care will reduce the global disease burden of mental health by more than 40%. Challenges include the enormous research agenda for developing mechanistically targeted interventions and their prescriptive matching to individuals.

Implementation will continue to be challenged by transportability of digital technologies into under-resourced areas, lack of resources for the most severely ill, and cultural adaptations to avoid simple exportation of Western constructs. Whether systems will choose to endorse evidence-based psychotherapies, in spite of the view that they are overly reductionistic or do not address complex refractory or comorbid cases, will most likely depend upon the success of that implementation.

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DOI:10.1002/wps.21002

A path towards progress: lessons from the hard things about digital mental health

Discerning hype from hope in psychiatry remains challenging, as Stein et al[1] demonstrate in reviewing if promising perspectives and methods may launch a paradigm shift. Their conclusion that the path forward is incremental progress and iterative integration instead of a single transformative breakthrough is well argued. Perhaps nowhere else is this conclusion truer than for digital phenotyping and app-based digital mental health. Thus, focusing less on the well-known potential of these technologies, but instead on the current challenges can highlight the incremental and integrative advances Stein et al call for.

The current state of smartphone apps and digital mental health can be approached from many perspectives, but the paper published in this journal in 2019[2], promoting a consensus around evaluation, offers a very useful starting point. Briefly, the areas covered in that paper are: data privacy and safety, app effectiveness, user experience/adherence, and data integration. Considering selected examples of some of the actual hardest challenges in each of these areas can help highlight the real work towards the progress of more equitable access, appropriate regulation, and quality assurance for digital health, as noted by Stein et al. This focus on negative examples is not to detract from the true potential, but rather to identify tangible targets for necessary next steps.

Focusing first on data privacy and safety, digital mental health continues to lack trust. In March 2022, the US-based Crisis Text Line was found to be sharing users' personal text messages with a for-profit company. Days later, the same concerns were raised about a UK-based crisis text line service, Shout, highlighting the global nature of this challenge. While academic research continues to undercover many technical risks around medical app security[3], the cases of Crisis Text Line and Shout stand out, as they were legal under current regulation. They will both likely serve as the spark for regulatory changes, since patients, clinicians and the public have lost faith in self-regulation. Thus, the most important and necessary innovation for digital mental health may be identical to what it was half a decade ago – transparency and trust[4]. Legislation affording app users guaranteed protections for their data is not as flashy as cloud blockchain solutions for privacy, but it is the necessary and incremental work critical to improving the field.

The second incremental step involves proving app effectiveness. On the surface, this seems like an area of more progress compared to data privacy and safety. Today, terms such as digital therapeutics are commonly used, and regulatory agencies are granting approval or clearance to some apps. But looking beyond the hype reveals a different picture. Digital therapeutics is an industry-created term that has little grounding in either health care regulation or research. The term is actually confusing, as it is very hard to evaluate the entire evidence base for mental health apps. A 2022 systematic meta-review of 14 meta-analyses of randomized controlled trials for smartphone-based interventions failed to find convincing evidence in support of any mobile phone-based intervention on any outcome, because of the overall low quality of studies[5]. That is not to say that apps cannot

be effective, but that higher-quality studies are necessary. A case in point is the March 2022 study comparing a proposed digital therapeutic app to a control app which was little more than a count-down timer. While the use of the proposed digital therapeutic app was associated with improved symptoms, the study found the surprising result that the use of the count-down timer was equally effective[6]. Before creating new names, the field needs to do better science. Digital control groups may not make for an inspiring investor pitch, but they are the necessary and incremental work critical to improving the field.

Building off the first two steps, digital mental health must be engaging. Metrics of patient interest in mental health apps or the number of potential users as measured by smartphones are no longer useful. Instead, the question must be around digital literacy and whether people have the knowledge, skills and confidence to equitably benefit from innovation. This question is too rarely asked until it is too late. The complexity of engagement and its challenges are exemplified by the city of Reno, Nevada, and the contract they signed with the digital mental health company Talkspace to provide remote therapy during the height of COVID-19 pandemic. While details are not public, news reports suggest that the actual use of Talkspace was so low that the contract was not renewed[7]. A July 2021 interview with the founder of Talkspace suggests that, of the 55 million people who have access to the service, only ~0.1% (60,000) actively use it[8]. This example serves to counter the notion that industry can solve health engagement challenges. The reality is that no one has solved this challenge and that it will require solutions beyond gamification or better design. The recent push for coaches to support digital mental technology is promising, but brings with it new risks that need to first be addressed under the first and second points of this framework (privacy/safety and evidence). Solutions such as task sharing suggested by Stein et al may also improve engagement, but the investment in such efforts only makes sense for tools that are truly effective and not, for example, digital clocks.

The last step, data integration, also only makes sense in terms of the other three. How can the digital health data be used to improve outcomes or the treatment integrated into a complete management plan? The point is moot if users do not trust the tool, the tool generates nothing of clinical value, or users do not engage with it at all. But, assuming progress in these steps, digital integration presents a new frontier for psychiatry. Vast amounts of new patient data generated by technology, combined with constant care through synchronous and asynchronous telehealth, require new clinical workflows, practices and training for true integration[9]. There is no artificial intelligence algorithm for retooling a field, but this investment in people expected to integrate and facilitate digital mental health may be the most valuable of all. While this step is often ignored with the assumption that high user engagement will make it unnecessary, now in 2022 it should be apparent that ignoring any of the above four steps is perilous.

Just like Stein et al do not forecast any immediate paradigm shift but rather the need for incremental progress, digital mental health must follow the same route. Rather than a harbinger of a paradigm shift, there is an urgent need for iterative improvements around data privacy and safety, app effectiveness, user experience/adherence, and data integration. While this selective review took a purposely pessimistic view, focusing on harsh realities is necessary for a field where the hype is so amplified. These harsh realities also underscore how incremental progress can actually be transformational for digital health, and justify why we need to do the hard work instead of just the glamorous.

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DOI:10.1002/wps.21003

Systems-based approaches to mental disorders are the only game in town

Stein et al's paper[1] provides an excellent overview of current directions in psychiatric diagnosis. The paper makes clear that, although there has been considerable work investigating novel approaches to psychiatric nosology, psychiatric diagnosis has in practice changed relatively little in recent decades. Mental disorders are defined and diagnosed today in pretty much the same way they have been for many years: as sets of symptoms that tend to cluster in somewhat reliable ways. Hallucinations are often accompanied by delusions; sad mood by self-reproach; anxiety by avoidance. Thresholds based on such symptom clusters are typically used to operationally define mental disorders, and the presentation of symptoms in a person is phenomenologically matched to these definitions to arrive at a diagnosis that guides treatment.

In recent years, much research operated under the assumption that, under the hood, psychiatric disorders are brain disorders[2], and that advances in neuroscience and genetics would reveal "what mental disorders really are". It is evident that no such breakthrough has materialized. It seems that most mental disorders simply lack central pathogenic pathways. Instead,

they have turned out to be massively multifactorial in causes and constitution, involving a highly complicated and barely understood interplay between genes, neural processes, behavior, environment and culture. Symptoms of different disorders often overlap; many disorders exhibit exceptional levels of comorbidity; and transdiagnostic factors and processes are the norm rather than the exception. For these reasons, the separation of mental disorders into distinct disease entities often appears artificial, and the diagnostic categories used in the DSM and ICD can be a Procrustean bed when applied to individual cases.

Given this massively multifactorial background, the biopsychosocial model has the best cards as a framework for understanding mental disorders. After all, the scientific evidence shows that: a) factors at societal, psychological and biological levels are involved in mental disorders; b) these factors interact across different time scales and levels of analysis; and c) interactions between factors feature nonlinearities (i.e., factors do not combine in a simple additive fashion). However, as Stein et al note, unless one answers the question of *how* psychological, biological and social factors interact to cause and maintain mental disorders, the net theoretical content of this model is close to zero. How then shall we address this question in the next century of research on psychiatric diagnosis and treatment? We suggest that, in this respect, a systems-based approach is the only game in town.

A systems-based approach, as practiced in other domains of science, allows us to explicitly model the interactions among a set of components across time scales and levels of analysis. These models, in turn, allow us to investigate those systems and evaluate how they give rise to the phenomena of interest. In the domain of mental health, a systems-based approach allows us to take the compelling but vague biopsychosocial framework and make it concrete, positing the precise system that gives rise to the etiology, maintenance and recovery from a mental disorder. The past decades have seen massive advances in methodology and modeling strategies suited to study complex systems[3]. If humanity can build climate models to project the effect of political interventions on global temperatures, it should also be possible to build models that can project the effect of therapeutic interventions on mental disorders.

Central to a systems-based approach are models that express our theories about how components of a system interact in the language of mathematics or computational programming. Such mathematical or computational models are *generative*, which means that they allow us to simulate the etiology and maintenance of mental disorders. For instance, our group has used very simple network models to show how interactions between symptoms could lead people to get "stuck" in an episode of depression[4]. Generative models also allow us to make changes to the system and thereby simulate treatment interventions. For instance, in a network model, one can simulate shocks to network elements or the effect of breaking links between them[5,6]. This procedure has already been used to mimic existing interventions[7], and could be used to discover new ones.

It is this ability to precisely deduce what our theories predict about etiology and treatment that make mathematical or computational models so crucial to the future of psychiatric diagnosis and treatment. It is all but impossible to intuit the behavior of complex systems through mental reasoning alone. Indeed, the complex systems literature is replete with examples of even relatively simple systems behaving in chaotic and unpredictable ways (e.g., the simple Lorenz equations giving rise to the famous butterfly-shaped strange attractors). Given the heterogeneous and multifactorial nature of mental disorders, it will be all but hopeless to advance our understanding of these disorders without the assistance of formal models.

Importantly, generative models are different from the data-analytic models in which mental health researchers are primarily trained. Data-analytic models can be estimated from a single dataset and represent patterns in the data. In contrast, generative models are developed by integrating empirical findings from many studies with different data on different levels of analysis (e.g., neuroscientific and behavioral) and creating a model that represents the real-world system that gave rise to those empirical findings.

How to best use empirical research to inform a generative model is an open question and an important area of research, though potential approaches already exist in the mental health literature[8,9]. For our purposes here, the key is that generative models provide a tool that is distinct from the data-analytic models that dominate much of psychiatric research. Critically, this means that future generations of modelers should focus on building generative models *alongside* data-analytic ones. Theory building skills will be as important to the future of psychiatric research as empirical research skills, and the curriculum we offer students should reflect that.

The models that have been developed in early efforts to adopt a systems-based approach in psychiatric research are relatively simple and, in most cases, best seen as toy models. However, the fact that it has been possible to construct these models gives rise to a modest hope. It is important to emphasize the word "modest" here. Examples spanning from pandemics to financial crashes and from climate change to polarization have taught us that the behavior of complex systems is extremely difficult to predict and control, even with the assistance of formal models. We should not expect magic bullets or free lunches. Similar to Stein et al, we believe that understanding mental disorders will require an integrative and iterative process of systematic clinical observation, painstaking research, and creative thinking. The value of a systems-based approach is that it provides a framework for organizing and tools for promoting the accumulation of knowledge through this iterative process and equips us to better leverage that knowledge to improve psychiatric care.

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DOI:10.1002/wps.21004

Psychiatry in the 21st century: the glass is half full

The paper by Stein et al[1] has prompted me to reflect on my remarks to this year's incoming class of psychiatry residents, as it outlines many of the factors that make psychiatry one of the most interesting, rewarding and challenging specialties for a new physician to pursue.

During its relatively short history, psychiatry has experienced a succession of different paradigms, explanations of what constitutes and causes mental illness, diagnostic and therapeutic approaches. These diverse paradigms and their proponents have at times competed fiercely, drawn vocal criticism from inside and outside our field, and made it challenging for us to have a coherent narrative about our work.

Like many other branches of medicine, we do not have a complete understanding of the illnesses we treat. We are beginning to understand the complex circuitry of the human brain, a 3-pound organ made up of roughly 100 billion neurons and glial cells, and some 100 trillion connections. We are coming to appreciate how social determinants such as poverty, unstable housing, and incarceration contribute to such problems as anxiety, depression and substance use, and we are working to understand why some people experiencing traumatic events develop crippling post-traumatic stress disorder while others become seemingly more resilient. We are far from cracking the enigma of mental illness, but we have a multitude of sophisticated approaches and tools to help us in this effort and there is plenty of reason for optimism.

After decades of intense investment in the neurosciences, we are closer to get a sense of how the brain machinery helps shape our perceptions, memories, emotions and behaviors, but it is good for us to remain humble about the promises of a purely biological psychiatry. Pharmaceutical companies have produced powerful drugs that have helped millions of individuals with severe mental illness live in communities and outside the confines of institutions. They have also helped define and promote new diagnoses as treatment targets for their products[2], and we are wise to remain aware of how profits and other motives can influence the way we diagnose and treat mental health and addiction problems[3].

For some, the competing explanatory models and paradigms in our field are evidence that we do not know what we are talking about, or that we are practicing a pseudoscience that attempts to "medicalize" normal human emotions and phenomena for profit or other dubious motives. On the contrary, I see this diversity of approaches as a strength, reflecting the complexity of our discipline, and I believe that the vigorous debate between the competing paradigms in our field has created and honed a powerful set of tools that we can put to work today while we wait for even better treatments tomorrow.

Among the most powerful tools we have in psychiatry today are psychotherapeutic approaches such as motivational interviewing, problem solving, cognitive, behavioral and interpersonal therapies. Such skills can be effectively used not only by highly trained psychologists and psychiatrists, but they can be taught to patients, family members, peers, and motivated individuals with limited formal education. Examples include programs in low-income countries in which trained community health workers can provide highly effective treatment to individuals with such problems as depression or post-traumatic stress disorder[4], or the Improving Access to Psychological Therapies (IAPT) program in the UK[5].

As psychiatrists, we strive to understand how our patients' lives are shaped by their unique biology, social circumstances and life experiences. We aim to do more than simply control unwelcome emotions and behaviors, but to help our patients overcome barriers and pursue their dreams. In our work, we draw on several types of evidence: the evidence from state-of-the-art research, our own clinical experience, and most importantly crucial evidence from our patients' own lived experience. Sometimes the most important insights do not emerge until initial efforts at diagnosis and treatment have missed the mark. It helps to stay humble, to keep a close eye on our patients' response to treatment, to measure clinical outcomes and progress towards our patients' personal goals in treatment, and to remain open to changing our approach if patients do not improve as expected, a practice that has become known as "measurement-based care"[6].

Stein et al[1] also mention a second challenge: the lack of access to care even when effective treatments exist. Even in wealthy countries such as the US, fewer than half of those living with mental health and addiction problems have access to effective care. T. Insel, one of the leading figures in American psychiatry, recently pointed out that, during his 13-year tenure as the head of the National Institute of Mental Health, he oversaw an ambitious neuroscience portfolio worth billions of dollars, but remarkably little progress was made in improving access to effective care[7]. We need serious innovation and investments in health services and systems of care to help us close these gaps.

We should also become powerful advocates for our patients' basic needs. We all know that Prozac cannot cure homelessness, loneliness, grief, or the fear of being arrested. We know that the most vulnerable individuals struggling with mental health and addiction problems are sometimes the least likely to get effective care. We need to strongly advocate for better access to care for our patients and for true mental health parity. In what country can one provide truly effective mental health care for $ 52.7, let alone for $ 0.08 per capita?[1] And why do we have to justify spend-

ing on mental health care by promising cost savings in some other area of health or social services? Adequate spending on the mental health of our populations should be a worthy goal in and of itself.

Over the past few decades, psychiatry has come a long way in its efforts to address and overcome the stigma associated with mental illness, but recent critiques show us that our profession is still not immune from biases and systemic racism that can contribute to the stigmatization and oppression of vulnerable groups. It was the year 1974 when a pharmaceutical company marketing to American psychiatrists tapped into racist fears by running an ad featuring a black man with a raised fist and the title "Cooperation often begins with Haldol"[8]. It would probably not happen anymore today, but more subtle expressions of the above biases are still likely to exist in some contexts.

Mental illness and addiction have become recognized as leading causes of health-related disability worldwide, and we have much to learn from our colleagues around the world about different ways to understand mental illness, to address the stigma carried by those living with mental health and addiction problems, and about different approaches to treatment. Recent work on task sharing and collaborative care[9] suggests that we can help more people in need when we partner with colleagues in primary care and with team members who complement our own skills, and when we use technologies that allow us to provide consultation and supervision across distances and ensure that our patients do not fall through the cracks. The experience and joy that come from working together in a well-functioning team can become one of the most rewarding and satisfying aspects of a career in psychiatry.

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DOI:10.1002/wps.21005

Challenges and chances for mental health care in the 21st century

Stein et al[1] provide a comprehensive review of the potentials and pitfalls of mental health care in the 21st century. They discuss current models of diagnosis and classification, novel statistical approaches and digital phenotyping, developments in clinical neuroscience, personalized pharmacotherapy, and evidence-based psychotherapy, as well as perspectives for deinstitutionalization and for community and global mental health. The authors provide a balanced view and suggest that these developments will allow incremental changes rather than paradigm shifts. In light of the wide range of topics addressed by Stein et al, we discuss key challenges and chances for mental health care in a global perspective.

Challenges for global mental health include climate change, displacement of large populations due to war and poverty, income inequality, and inadequate health care services[1-3]. These challenges interact, as climate change can reduce food production and increase violent conflicts, which may displace large parts of the local population, who then face income inequalities and inadequate health care services in the host countries. Income inequality and local poverty are major risk factors for distress, which escalate the mental health burden[3,4]. The COVID pandemic is deepening these pre-existing challenges.

Psychiatric care has traditionally used a reductionist approach focusing on medication and confinement in large institutions[1]. Against this outdated practice of social exclusion, human rights and state-of-the-art treatment concepts demand social inclusion in the community and low-threshold availability of counselling, peer support, psychotherapy and specialized treatment[1,4]. As a medical discipline, psychiatry can address social inequalities and contribute to a call for change. However, a complementary view is required that includes the perspectives of users, families and friends, and the competence of other scientific disciplines, including social sciences and city planning[4].

In spite of widespread calls for improving global mental health care, funding remains inadequate from low- and middle- to high-income countries. Health care resources are often only available for a rich elite, who are mainly treated with medication, while low-threshold psychosocial interventions are lacking for the majority of the population. People with severe mental illness are too often incarcerated or left homeless without health care[4,5]. There is a widespread lack of resources for migrants, refugees, and other minorities.

Culture-, language-, class- and gender-sensitive treatment can be promoted using telemedicine and digital interventions[1]. Participatory and interdisciplinary approaches can integrate disciplinary diversity with stakeholder engagement to fight stigmatization, racist stereotyping, and social exclusion. However, systematic attempts to provide low-threshold treatment to all components of the population are not always successful. Stein et al[1] discuss experiences of substantially increased availability of psychotherapy in the UK, which however did not reduce the prevalence of mental disorders. The authors suggest that emotional distress may more often be diagnosed as depression, thus masking any drop in prevalence rates[1]. Even if psychotherapy resources are available to everyone, access barriers can still exist for those with serious mental illness, who can be hard to treat in outpatient practices.

Psychiatry has long been criticized for failing to define mental illness. Unlike somatic medical disciplines that list specific "diseases" in the ICD, psychiatry addresses "disorders" ranging from dementia to socially undesirable behavior. As a consequence, psychiatry has been portrayed as a social institution that aims to control and normalize behavior, and has more in common with the police and prison system than with medicine[6]. This criticism could actually be exacerbated by new statistical approaches to the assessment and mapping of mental health problems, including the Hierarchical Taxonomy of Psychopathology (HiTOP)[1,7].

Indeed, the HiTOP assesses associations between a variety of manifestations of mental disorders, including "antagonizing and externalizing" and "antisocial" personality traits such as "rebelliousness" and "flirtatiousness"[7]. However, there is a risk of confounding merely socially undesirable traits with symptoms of serious mental illness. If this approach is globally applied to persons belonging to a discriminated minority, who rebel against oppression and experience mental health problems due to social discrimination and exclusion, researchers may even find a genetic correlate and misleadingly reify social problems as mental disorders.

Accordingly, there is a need to define those mental health problems that should be globally addressed by psychiatry as a medical discipline. In medicine, clinically relevant diseases are usually defined by a) impairments of vital functions, i.e., functions relevant for human life and survival, which b) cause harm to the afflicted individual, i.e., individual suffering or impairments in activities of daily living that reduce social participation[8]. Mere deviations from statistical norms do not define whether a condition is a disease – caries can manifest in the majority of a population but is still a dental disease[9].

The impairment of a generally relevant vital function may not be sufficient to constitute a clinically relevant disease if the afflicted person experiences no individual harm. People hearing voices that offer spiritual guidance may not suffer from these experiences and may not be impaired in their activities of daily living. Thus, they can still be regarded as presenting with a dysfunction of the generally vital ability to distinguish between one's own thoughts and external sensory experiences. However, in the absence of personal harm, there is no need to diagnose a clinically relevant disease[8]. We suggest that psychiatry as a medical discipline should focus on clinically relevant diseases and abstain from promoting (historically changing) behavioral norms.

Impairments of vitally relevant mental functions traditionally addressed by psychopathology include clouding of consciousness (as in delirium), impairments of memory and executive functions (as in dementia) or failures to self-ascribe thoughts (as in psychosis)[9]. The first two examples show that there is not really a general lack of biomarkers for psychiatric diagnoses. Also, overlap of biological correlates does not invalidate clinical classifications: cardiovascular disorders and stroke share biological determinants, including high blood pressure, but are treated as separate diseases by distinct medical disciplines (cardiology and neurology).

Neurobiological correlates of mental functions transcend nosological boundaries and may best be conceptualized by a dimensional approach. Computational modeling of behavior can provide objective quantifications that are more easily correlated with neurobiological dimensions than subjective reports[9]. However, Stein et al[1] rightly emphasize that dimensional approaches can be transformed into a categorical classification system simply by providing cutoffs. Dimensional approaches thus neither invalidate clinical knowledge nor a traditional focus on vital mental functions.

But, how do we define which functions are indeed of vital importance for human beings and should be addressed within the health care system? Psychiatry can provide clinical knowledge and a philosophical tradition[9], but has no monopoly on defining what mental functions are universally relevant for human life. To improve global mental health care, representatives of patients and families have to be included when revising classifications, participatory research has to be promoted, and the civil society has to be engaged in all aspects of health care planning.

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DOI:10.1002/wps.21006

From diversity to individualized care: Africa's contribution to psychiatry

The extent of diversity on the African continent is one of the greatest potential contributions of this continent to the world, with a multiplicity of cultures and traditions, religions and other belief systems that dwarf anything found anywhere else on earth. Naturally, therefore, one would be hard-pressed to identify a uniquely "African" viewpoint on mental health and the detection and treatment of mental illnesses.

Africans have lived with psychological distress and mental disorders for as long as humans have lived on the continent, with different cultures and traditions, including religious ones, having different explana-

tory models. Many African communities still utilize relatively culture-specific models to understand the causes of mental illnesses, including demon or spirit possession, or witchcraft[1]. *Jinns* (invisible spirits) in Islamic traditions, and other "evil" spirits in other communities, are considered responsible for conditions presenting with mood disturbances, anxiety, hallucinations, delusions and back pain, among other health problems[2]. These diverse local conceptualizations determine and affect access to and outcomes of care for those with mental illnesses[1].

In our opinion, current and emerging diagnostic and treatment systems must take into consideration these existing models, and endeavour to create a bridge between them and newer ways of understanding mental conditions and health. The extension of the biopsychosocial model to include sociocultural-spiritual components of illness and treatment[3] would encourage holistic and culturally sensitive approaches to addressing Africa's mental health care gap.

As Stein et al[4] point out, classification systems, at their very core, assume a universality of experience and the potential universality of response to investigations and treatments. Novel attempts at understanding mental illness – including the Research Domain Criteria (RDoC), the advances in neurosciences, and even personalized medicine – build upon certain "universalized" assumptions, including those on the nature of mind and the interaction between a person's inner world and his/her environment. From a purely practical perspective, we agree with the implicit notion that a global model of understanding mental health and illness is desirable in the context of a rapidly globalizing world, given the ease of mobility and the resulting complex cosmopolitan cultures that sprout whenever new human communities form. We must, however, remain cognizant of the fact that, even within the most homogeneous communities, every person's experience of the world is unique, and it may be difficult to generalize these experiences even to individuals steeped in the same culture and environment.

Diagnostic and treatment models are therefore required to use a "global" framework of understanding mental health, but ultimately apply this to an individual's unique experiences and background, in order to fully understand personal suffering and generate an explanatory model that makes sense to the individual and to the society from which he/she comes. To implement this approach, however, may be difficult[5,6], because many clinicians are ill equipped with the relevant social and anthropological tools, and because of the problems in creating appropriate research platforms, due to the variety of explanatory ideas.

There are inherent conceptual weaknesses in attempting to identify components of explanatory narratives, in much the same manner as it would be difficult to develop a global glossary of symptom contents for something like auditory hallucinations. Treating individual explanatory narratives as part of the diagnostic process as well as an integral component of treatment planning might yield better results than attempting an in-depth understanding of the subject through quantitative research methods.

Even with culturally sensitive approaches to diagnosis and treatment, there is no level of cultural understanding that can replace the information on an individual's own lived experience and perspectives, which vary widely even within a particular cultural context. Not everyone within a cultural or ethnic group subscribes to what is considered "traditional" to that group, and unquestioning acceptance of cultural or traditional practices in the context of individual patients runs the risk of alienating significant minorities and therefore compromising their access and response to care.

This individualized care model is already present in the management of psychological distress and behavioural problems in African communities that have different attributions for these conditions. In many cases, the practitioner collects information about the individual's context and beliefs, and uses this information to develop an explanatory narrative for the condition and to fashion a remedy that is unique for that person even while utilizing available generic components. For instance, personalized remedies have been described in Ghana, and categorized to include banishing evil spirits, protection from relapse/further attacks, and "awakening the mind"[7].

In these settings where current innovations in care are inaccessible, mainly due to the cost and investments required, attempts have been made to develop separate systems of care in the context of global mental health, including concepts of "task-shifting" or "task-sharing". Unfortunately, these "contextualized" approaches have sometimes resulted in low-income populations getting sub-standard care, while those that can afford it – even within the same settings – are able to access high-quality evidence-based care. We have previously criticized these approaches, as they endorse alternative systems of care based on the assumption that poor people or societies will always remain poor and incapable of accessing care that is of high quality and evidence-based[8].

We argue that global mental health must be truly global, through the application of a global knowledge framework to understand distress and suffering, while developing solutions that take into consideration individual histories, contexts and explanatory models. While an advanced knowledge of brain processes will help us in developing this global framework, an understanding of society and culture, and how individuals interact with and perceive their environment, will be more critical in the encounter with a given patient. The "global" in global mental health should not only be seen as addressing differences *between* societies, but also working with diversity *within* all societies.

In conclusion, we believe that a personalized diagnostic and treatment framework that is based on a core of globally applicable principles is the first step towards addressing inequities in access to care, and ensuring that even the most disadvantaged populations access the best available standard of care. African diversity provides the best example of how this can be approached, and the best substrate for the examination of this concept.

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DOI:10.1002/wps.21007

Adverse childhood experiences and mental health problems in a nationally representative study of heterosexual, homosexual and bisexual Danes

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Non-heterosexual persons more often report adverse childhood experiences (ACEs) than heterosexuals, and they generally bear a greater burden of mental health challenges. However, population-based data on this topic are scarce. In a nationally representative study within the Project SEXUS, one of the world's largest cohort studies on sexual health, we used data from 57,479 individuals in Denmark to explore the interplay between ACEs and mental health problems among self-identified heterosexual, homosexual and bisexual persons, and among self-identified heterosexuals with or without same-sex sexual experience. Compared to heterosexuals, non-heterosexual persons were more likely to report most of the studied ACEs, with odds ratios (ORs) for the ACE category "abuse" ranging from 1.38 to 1.75 for homosexual women, from 1.76 to 2.65 for homosexual men, from 2.52 to 3.64 for bisexual women, and from 1.58 to 6.07 for bisexual men. Furthermore, non-heterosexual persons had consistently and statistically significantly higher odds for mental health problems (ORs: 1.50 to 4.63). Combinations of ACEs with a non-heterosexual identity resulted in markedly elevated odds for mental health problems, particularly among bisexual individuals. This included high odds for suicidal thoughts/attempts among bisexual persons with a history of "neglect" (women: OR=12.82; men: OR=35.24) and "abuse" (women: OR=11.81; men: OR=11.65). Among self-identified heterosexuals, combinations of ACEs with same-sex sexual experience were associated with consistently elevated odds for mental health problems (ORs: 2.22 to 12.04). The greater burden of ACEs among self-identified homosexuals and, most notably, bisexuals may account for part of their excess risk of mental health problems. These findings emphasize the public health importance of preventive measures to minimize the burden of ACEs and avert their harmful long-term effects. Moreover, they highlight the need to safeguard the welfare of children and adolescents with non-conforming expressions of sexuality.

Key words: Homosexuality, bisexuality, heterosexuality, adverse childhood experiences, mental health, self-harm, suicidality

(World Psychiatry 2022;21:427–435)

Adverse childhood experiences (ACEs) are increasingly being recognized as risk factors for a multitude of social and health-related problems, including low educational attainment, substance abuse, self-harm, suicidal behaviour and premature death[1-7]. ACEs include physical, psychological or sexual abuse, neglect, and household challenges such as parental death, divorce or separation, or someone in the family having drug addiction or mental illness.

Compared to self-identified heterosexuals, non-heterosexual individuals more often report ACEs[8-11], and a higher prevalence of mental health problems among non-heterosexuals has been observed in several studies[12-14]. However, despite scientific evidence indicating that non-heterosexuals are more likely to have experienced childhood adversities and to be burdened by mental health challenges, little research has explored the detailed associations of ACEs with mental health problems across sexual identity categories.

Additionally, investigations in this area using nationally representative samples with sufficiently large subgroups of sexual minorities are scarce and, for numerical reasons, studies often analyze homosexual and bisexual individuals together, although the social circumstances and mental health situations may differ considerably between these groups[13,15].

Within the Project SEXUS, one of the world's largest cohort studies on sexual health, we utilized a large and nationally representative sample of self-identified heterosexuals, homosexuals and bisexuals in Denmark to investigate associations of ACEs with measures of poor mental health across sexual identity subgroups. Further, to explore a different dimension of sexual orientation than sexual identity, we also investigated associations of ACEs with mental health problems among self-identified heterosexuals with or without same-sex sexual experience.

METHODS

Project SEXUS cohort

We utilized baseline data collected between 2017 and 2018 in Project SEXUS, a prospective national cohort study with a strict focus on sexual health and well-being and on the interplay between sexual and general health (www.projectsexus.dk)[16].

Overall, 62,675 individuals from a probability-based sample of 15 to 89 year-old Danes provided complete and logically consistent answers to a self-administered online questionnaire, resulting in a response rate of 34.6% according to criteria established by the American Association for Public Opinion Research (AAPOR response rate 1)[17]. An individual weighting procedure was applied in order to ensure national representativeness with respect to sex, year of birth, region of residence, marital status, cultural background and twin status[16,18].

The full Project SEXUS questionnaire covered more than 600 items detailing participants' socio-demographic background, health, lifestyle, relationship issues and sexuality. To include such a large number of items, while ensuring that each participant was presented with a manageable number of questions, some questions were only posed to half of the participants, while others were posed to the other half. Furthermore, logical filter questions

ensured that participants were asked a median of 180 questions, which took a median of 32 min to answer[18].

Sexual identity and same-sex sexual experience

All Project SEXUS respondents were asked to report their sexual identity. In this study, we excluded respondents who considered themselves asexual, those who could not place themselves in any of the presented sexual identity categories, and those who were undecided or did not know what to answer. To focus strictly on sexual identity rather than gender identity, the current study included data from 57,479 cis-gendered Project SEXUS participants, who self-identified as heterosexual, homosexual or bisexual and were 18 years or older when answering the online questionnaire.

Regardless of reported sexual identity, all respondents were asked about their sexual experiences with women and men since age 15 years. We defined individuals with same-sex sexual experience as those who reported at least one same-sex sexual encounter.

ACEs

To capture ACEs, half of the Project SEXUS respondents were asked a series of nine questions about their childhood, to determine if they had experienced one or more of the following before age 18 years: 1. a safe childhood with closeness and care, 2. physical abuse, 3. psychological abuse, 4. sexual abuse, 5. alcohol problems or drug addiction in the household, 6. mental illness or suicide attempts in the household, 7. parental divorce or separation, 8. maternal death or 9. paternal death.

Childhood experiences 1, 2, 3, 5 and 6 were measured using a five-point Likert-scale ranging from "to a very high extent" to "not at all". Experiences 4, 7, 8 and 9 were assessed using the response categories "yes" and "no". For respondents to meet our criteria for having had a particular ACE, we required that experience 1 be reported "to a low extent" or "not at all", that experience 2, 3, 5 or 6 be reported "to some extent", "to a high extent" or "to a very high extent", or that the answer concerning experience 4, 7, 8 or 9 be "yes".

A total of 29,244 respondents provided relevant answers to address associations between ACEs and mental health outcomes. To reduce analytic complexity and gain statistical robustness, the nine individual ACEs were grouped into three categories, respectively labelled "neglect" (ACE 1), "abuse" (ACEs 2 to 4) and "household challenges" (ACEs 5 to 9). Respondents were included in ACE categories "abuse" or "household challenges" if they had experienced at least one of the individual ACEs in that particular category. In addition, we created an ACE score based on the sum of ACEs for each respondent (ACE score range 0-9). In the statistical analyses, ACE scores were categorized as 0, 1-2 or 3+.

Mental health problems

All respondents were asked if they had ever received treatment by a doctor, a psychologist or a similar professional for a mental health problem, if they had ever harmed themselves on purpose without suicidal intent (e.g., by cutting, hitting or burning themselves), and if they had ever had suicidal thoughts with or without an actual suicide attempt.

Response categories were "yes", "no" and "I do not know". Respondents answering "yes" were considered to have the mental health outcome in question.

Statistical analyses

Initially, we estimated sexual identity-specific prevalence data of ACEs and mental health outcomes, and performed logistic regression to calculate associated prevalence odds ratios (ORs) with 95% confidence intervals (CIs), using heterosexuals as reference.

Next, we explored in more detail the interplay between ACEs and mental health problems across sexual identity categories in a series of logistic regression analyses. Specifically, we calculated ORs for associations of each of the three ACE categories ("neglect", "abuse", "household challenges") and each of the three ACE score categories (0, 1-2, 3+) with the studied mental health outcomes across sexual identity categories, using heterosexuals not reporting the ACE category in question and heterosexuals with an ACE score = 0, respectively, as reference.

Finally, in a supplementary analysis restricted to 27,697 self-identified heterosexuals from that half of study participants who had been asked questions about ACEs, we repeated the analysis for the association between ACE scores and mental health outcomes, this time stratifying on same-sex sexual experience ("any" vs. "none"). Specifically, we calculated ORs for the association between ACE score (0, 1-2, 3+) and mental health outcomes, using self-identified heterosexuals without same-sex sexual experience and an ACE score = 0 as reference.

We used demographically weighted data for all analyses. All logistic regression analyses were adjusted for age in 10-year categories and carried out using the nnet package in R (version 4.0.2).

RESULTS

ACEs across sexual identity categories

Non-heterosexual individuals were significantly more likely than heterosexuals to report a childhood that was not safe with closeness and care: OR=2.04 (95% CI: 1.12-3.72) for homosexual women; OR=1.89 (95% CI: 1.24-2.87) for homosexual men; OR=2.54 (95% CI: 1.87-3.44) for bisexual women; and OR=1.89 (95% CI: 1.25-2.84) for bisexual men (see Table 1).

A significantly higher proportion of non-heterosexual than heterosexual individuals, especially those with a bisexual identity, had experienced a childhood burdened by physical, psychological or sexual abuse. For homosexual women, the ORs for physical violence, psychological abuse and sexual abuse were, respectively, 1.38 (95% CI: 0.68-2.83), 1.75 (95% CI: 1.11-2.77), and 1.53 (95% CI: 0.77-3.05). For homosexual men, the corresponding ORs were 1.77 (95% CI: 1.18-2.66), 1.76 (95% CI: 1.30-2.40),

Table 1 Adverse childhood experiences (ACEs) among self-identified heterosexual, homosexual and bisexual individuals

	Women			Men		
	ACEs not reported N (%)	ACEs reported N (%)	OR (95% CI)	ACEs not reported N (%)	ACEs reported N (%)	OR (95% CI)
ACE category: Neglect						
Childhood was not safe with closeness and care						
Heterosexual	13,516 (92.4)	1,124 (7.6)	1 (ref.)	12,338 (94.0)	770 (6.0)	1 (ref.)
Homosexual	256 (85.5)	40 (14.5)	2.04 (1.12-3.72)	440 (89.6)	49 (10.4)	1.89 (1.24-2.87)
Bisexual	374 (84.4)	69 (15.6)	2.54 (1.87-3.44)	199 (89.6)	23 (10.4)	1.89 (1.25-2.84)
ACE category: Abuse						
Childhood was burdened by physical violence						
Heterosexual	13,591 (93.1)	1,021 (6.9)	1 (ref.)	12,165 (92.9)	926 (7.1)	1 (ref.)
Homosexual	270 (90.5)	25 (9.5)	1.38 (0.68-2.83)	432 (88.7)	54 (11.3)	1.77 (1.18-2.66)
Bisexual	377 (85.0)	64 (15.0)	2.52 (1.85-3.42)	196 (89.9)	22 (10.1)	1.58 (1.04-2.40)
Childhood was burdened by psychological abuse						
Heterosexual	11,992 (82.8)	2,605 (17.2)	1 (ref.)	11,438 (86.8)	1,640 (13.2)	1 (ref.)
Homosexual	214 (70.1)	81 (29.9)	1.75 (1.11-2.77)	389 (77.5)	100 (22.5)	1.76 (1.30-2.40)
Bisexual	276 (61.4)	167 (38.6)	2.65 (2.12-3.31)	171 (76.3)	50 (23.7)	1.89 (1.41-2.53)
Experienced sexual abuse in childhood						
Heterosexual	13,605 (94.0)	910 (6.0)	1 (ref.)	13,012 (99.2)	105 (0.8)	1 (ref.)
Homosexual	259 (89.7)	35 (10.3)	1.53 (0.77-3.05)	475 (97.8)	10 (2.2)	2.65 (1.10-6.39)
Bisexual	346 (78.8)	92 (21.2)	3.64 (2.77-4.78)	211 (95.0)	10 (5.0)	6.07 (3.33-11.05)
ACE category: Household challenges						
Someone in household had alcohol problems or drug addiction						
Heterosexual	12,237 (84.8)	2,332 (15.2)	1 (ref.)	11,413 (87.2)	1,636 (12.8)	1 (ref.)
Homosexual	216 (76.1)	78 (23.9)	1.48 (0.90-2.43)	402 (85.7)	84 (14.3)	1.07 (0.74-1.55)
Bisexual	319 (74.0)	120 (26.0)	1.80 (1.41-2.32)	180 (83.3)	35 (16.7)	1.28 (0.91-1.80)
Someone in household was mentally ill or tried to commit suicide						
Heterosexual	12,918 (90.2)	1,491 (9.8)	1 (ref.)	11,997 (92.6)	914 (7.4)	1 (ref.)
Homosexual	237 (83.3)	49 (16.7)	1.63 (0.92-2.89)	430 (86.0)	55 (14.0)	1.95 (1.34-2.82)
Bisexual	329 (76.2)	104 (23.8)	2.52 (1.95-3.27)	188 (88.5)	22 (11.5)	1.55 (1.04-2.32)
Parents got divorced/split up						
Heterosexual	11,281 (78.8)	3,322 (21.2)	1 (ref.)	10,607 (79.5)	2,471 (20.5)	1 (ref.)
Homosexual	203 (69.8)	93 (30.2)	1.14 (0.72-1.81)	370 (70.2)	117 (29.8)	1.37 (1.03-1.83)
Bisexual	257 (58.2)	186 (41.8)	1.80 (1.44-2.25)	162 (70.5)	60 (29.5)	1.32 (1.00-1.74)
Mother died						
Heterosexual	14,330 (97.8)	299 (2.2)	1 (ref.)	12,718 (97.2)	385 (2.8)	1 (ref.)
Homosexual	291 (98.1)	5 (1.9)	1.15 (0.24-5.38)	482 (99.0)	8 (1.0)	0.46 (0.13-1.63)
Bisexual	432 (97.7)	11 (2.3)	1.47 (0.72-3.02)	206 (94.2)	12 (5.8)	2.96 (1.71-5.12)
Father died						
Heterosexual	13,978 (95.4)	629 (4.6)	1 (ref.)	12,317 (94.5)	751 (5.5)	1 (ref.)
Homosexual	277 (94.2)	17 (5.8)	1.62 (0.66-3.96)	468 (96.8)	20 (3.2)	0.66 (0.32-1.36)
Bisexual	420 (95.1)	21 (4.9)	1.40 (0.85-2.31)	204 (94.0)	15 (6.0)	1.32 (0.78-2.24)

OR – odds ratio adjusted for age in 10-year categories

and 2.65 (95% CI: 1.10-6.39). For bisexual women, the ORs were 2.52 (95% CI: 1.85-3.42), 2.65 (95% CI: 2.12-3.31), and 3.64 (95% CI: 2.77-4.78). For bisexual men, the ORs were 1.58 (95% CI: 1.04-2.40), 1.89 (95% CI: 1.41-2.53), and 6.07 (95% CI: 3.33-11.05) (see Table 1).

Several challenges within the household were reported significantly more often by non-heterosexual than heterosexual individuals. In particular, more bisexual women (OR=2.52, 95% CI: 1.95-3.27), homosexual men (OR=1.95, 95% CI: 1.34-2.82) and bisexual men (OR=1.55, 95% CI: 1.04-2.32) than heterosexual peers were raised in households where someone was mentally ill or had tried to commit suicide; more bisexual women (OR=1.80, 95% CI: 1.44-2.25), homosexual men (OR=1.37, 95% CI: 1.03-1.83) and bisexual men (OR=1.32, 95% CI: 1.00-1.74) than heterosexual peers had parents who got divorced or split up; and more bisexual than heterosexual men experienced maternal death before age 18 years (OR=2.96, 95% CI: 1.71-5.12) (see Table 1).

Mental health problems across sexual identity categories

Mental health problems were markedly more common among non-heterosexual than heterosexual individuals (see Table 2). In particular, homosexual women were significantly more likely than heterosexual women to have received treatment for a mental health problem (OR=1.66, 95% CI: 1.23-2.24), to have ever harmed themselves on purpose without suicidal intent (OR=2.28, 95% CI: 1.57-3.32), and to have ever had suicidal thoughts or attempted suicide (OR=1.79; 95% CI: 1.32-2.42). The corresponding ORs for homosexual men were 2.33 (95% CI: 1.92-2.83), 1.50 (95% CI: 1.07-2.09), and 2.42 (95% CI: 1.99-2.93). Those for bisexual women were 2.66 (95% CI: 2.26-3.14), 4.46 (95% CI: 3.74-5.31), and 3.56 (95% CI: 3.03-4.18). Those for bisexual men were 2.44 (95% CI: 2.04-2.93), 4.63 (95% CI: 3.69-5.82), and 3.26 (95% CI: 2.71-3.91).

Associations between ACEs and mental health problems across sexual identity categories

Across sexual identity categories, individuals reporting ACEs were more likely to have mental health problems than those without ACEs (Table 3), and higher ACE scores were associated with higher odds of mental health problems (Table 4).

Among homosexual women, those with a history of "neglect" had markedly elevated odds of having ever performed self-harm (OR=10.81, 95% CI: 3.20-36.50) and of having had suicidal thoughts or attempted suicide (OR=5.06, 95% CI: 1.59-16.09). High odds of having performed self-harm (OR=7.19, 95% CI: 3.09-16.72) and of having had suicidal thoughts or attempted suicide (OR=7.13, 95% CI: 3.30-15.38) were also observed among homosexual women with a history of "abuse". Among homosexual men, those with a history of "neglect" or "abuse" had ORs of having had suicidal thoughts/attempts, respectively, of 14.73 (95% CI: 5.44-39.93) and 9.87 (95% CI: 5.48-17.78).

Among bisexual women, those with a history of "neglect" had ORs of having performed self-harm and of having had suicidal thoughts/attempts, respectively, of 13.93 (95% CI: 7.52-25.81) and 12.82 (95% CI: 6.20-26.48), and those with a history of "abuse" had corresponding ORs of 14.11 (95% CI: 9.90-20.11) and 11.81 (95% CI: 8.10-17.21). Among bisexual men, those with a history

Table 2 Mental health problems among self-identified heterosexual, homosexual and bisexual individuals

	Women			Men		
	Mental health problem not reported N (%)	Mental health problem reported N (%)	OR (95% CI)	Mental health problem not reported N (%)	Mental health problem reported N (%)	OR (95% CI)
Ever received treatment for a mental health problem						
Heterosexual	17,344 (62.6)	11,168 (37.4)	1 (ref.)	20,570 (78.7)	5,276 (21.3)	1 (ref.)
Homosexual	256 (44.6)	321 (55.4)	1.66 (1.23-2.24)	534 (59.0)	390 (41.0)	2.33 (1.92-2.83)
Bisexual	307 (34.8)	562 (65.2)	2.66 (2.26-3.14)	266 (58.0)	182 (42.0)	2.44 (2.04-2.93)
Ever performed self-harm						
Heterosexual	26,023 (91.9)	2,555 (8.1)	1 (ref.)	24,826 (95.2)	1,051 (4.8)	1 (ref.)
Homosexual	467 (77.2)	111 (22.8)	2.28 (1.57-3.32)	861 (90.8)	65 (9.2)	1.50 (1.07-2.09)
Bisexual	523 (58.8)	338 (41.2)	4.46 (3.74-5.31)	362 (77.6)	84 (22.4)	4.63 (3.69-5.82)
Ever had suicidal thoughts/attempted suicide						
Heterosexual	21,049 (75.8)	7,175 (24.2)	1 (ref.)	20,579 (78.8)	4,965 (21.2)	1 (ref.)
Homosexual	341 (57.6)	234 (42.4)	1.79 (1.32-2.42)	546 (56.9)	368 (43.1)	2.42 (1.99-2.93)
Bisexual	348 (39.0)	514 (61.0)	3.56 (3.03-4.18)	237 (50.0)	202 (50.0)	3.26 (2.71-3.91)

OR – odds ratio adjusted for age in 10-year categories

Table 3 Associations between categorized adverse childhood experiences (ACEs) and mental health problems among self-identified heterosexual, homosexual and bisexual individuals

	Women			Men		
	Heterosexual OR (95% CI)	Homosexual OR (95% CI)	Bisexual OR (95% CI)	Heterosexual OR (95% CI)	Homosexual OR (95% CI)	Bisexual OR (95% CI)
Ever received treatment for a mental health problem						
ACE category: Neglect						
ACE not reported	1 (ref.)	1.73 (1.09-2.74)	2.78 (2.18-3.55)	1 (ref.)	2.45 (1.85-3.25)	2.62 (2.00-3.44)
ACE reported	2.98 (2.60-3.40)	2.46 (0.78-7.78)	8.10 (3.82-17.16)	3.08 (2.66-3.58)	6.30 (2.78-14.28)	7.76 (3.44-17.48)
ACE category: Abuse						
ACE not reported	1 (ref.)	1.60 (0.95-2.72)	2.54 (1.87-3.43)	1 (ref.)	2.65 (1.95-3.59)	2.47 (1.82-3.34)
ACE reported	2.88 (2.64-3.14)	3.90 (1.80-8.45)	6.32 (4.37-9.14)	2.94 (2.66-3.25)	4.87 (2.84-8.36)	8.00 (4.77-13.43)
ACE category: Household challenges						
ACE not reported	1 (ref.)	1.66 (0.92-2.99)	2.29 (1.63-3.21)	1 (ref.)	3.27 (2.30-4.63)	2.48 (1.75-3.54)
ACE reported	1.84 (1.71-1.98)	2.90 (1.56-5.42)	5.77 (4.17-7.99)	1.86 (1.71-2.02)	3.10 (2.07-4.63)	5.21 (3.58-7.59)
Ever performed self-harm						
ACE category: Neglect						
ACE not reported	1 (ref.)	2.42 (1.35-4.36)	4.76 (3.62-6.27)	1 (ref.)	1.41 (0.84-2.34)	3.72 (2.59-5.36)
ACE reported	4.71 (3.86-5.75)	10.81 (3.20-36.50)	13.93 (7.52-25.81)	3.14 (2.46-4.02)	4.35 (1.45-13.05)	56.86 (23.61-136.97)
ACE category: Abuse						
ACE not reported	1 (ref.)	3.01 (1.54-5.92)	3.80 (2.61-5.53)	1 (ref.)	1.34 (0.71-2.50)	4.54 (2.99-6.90)
ACE reported	3.93 (3.42-4.51)	7.19 (3.09-16.72)	14.11 (9.90-20.11)	4.23 (3.58-5.00)	5.82 (2.85-11.85)	16.97 (9.77-29.46)
ACE category: Household challenges						
ACE not reported	1 (ref.)	2.69 (1.24-5.86)	5.14 (3.41-7.74)	1 (ref.)	1.29 (0.60-2.79)	4.99 (3.09-8.06)
ACE reported	2.32 (2.03-2.65)	5.91 (2.88-12.13)	9.19 (6.67-12.64)	2.12 (1.81-2.49)	3.07 (1.70-5.53)	8.85 (5.67-13.81)
Ever had suicidal thoughts/attempted suicide						
ACE category: Neglect						
ACE not reported	1 (ref.)	1.87 (1.17-2.99)	3.90 (3.05-4.98)	1 (ref.)	2.24 (1.68-2.99)	3.22 (2.44-4.24)
ACE reported	4.46 (3.90-5.10)	5.06 (1.59-16.09)	12.82 (6.20-26.48)	3.58 (3.07-4.17)	14.73 (5.44-39.93)	35.24 (10.70-116.02)
ACE category: Abuse						
ACE not reported	1 (ref.)	1.76 (1.01-3.05)	3.50 (2.58-4.76)	1 (ref.)	2.23 (1.62-3.05)	3.40 (2.51-4.62)
ACE reported	4.29 (3.91-4.69)	7.13 (3.30-15.38)	11.81 (8.10-17.21)	3.51 (3.16-3.89)	9.87 (5.48-17.78)	11.65 (6.56-20.69)
ACE category: Household challenges						
ACE not reported	1 (ref.)	1.73 (0.93-3.21)	3.60 (2.56-5.08)	1 (ref.)	2.70 (1.88-3.88)	3.71 (2.62-5.26)
ACE reported	2.20 (2.02-2.38)	4.31 (2.33-7.97)	8.25 (6.01-11.32)	1.82 (1.67-1.98)	3.84 (2.58-5.72)	6.02 (4.03-9.00)

OR – odds ratio adjusted for age in 10-year categories

of "neglect" had ORs of having performed self-harm and of having had suicidal thoughts/attempts as high as, respectively, 56.86 (95% CI: 23.61-136.97) and 35.24 (95% CI: 10.70-116.02) (see Table 3).

Similarly, odds of self-harm (women: OR=22.82, 95% CI: 14.34-36.32; men: OR=28.28, 95% CI: 13.83-57.85) and of suicidal thoughts/attempts (women: OR=16.61, 95% CI: 10.01-27.57; men: OR=24.26, 95% CI: 10.64-55.32) were markedly greater among bisexuals with at least three ACEs compared with heterosexual peers without ACEs (see Table 4).

Associations between ACEs and mental health problems among self-identified heterosexuals with or without same-sex sexual experience

Among self-identified heterosexuals, individuals with any same-sex sexual experience were generally more likely than indi-

Table 4 Associations between number of adverse childhood experiences (ACEs) and mental health problems among self-identified heterosexual, homosexual and bisexual individuals

	Women			Men		
	Heterosexual OR (95% CI)	Homosexual OR (95% CI)	Bisexual OR (95% CI)	Heterosexual OR (95% CI)	Homosexual OR (95% CI)	Bisexual OR (95% CI)
Ever received treatment for a mental health problem						
0 ACEs	1 (ref.)	1.56 (0.81-2.99)	2.23 (1.50-3.32)	1 (ref.)	3.61 (2.48-5.25)	2.07 (1.37-3.14)
1-2 ACEs	1.74 (1.61-1.89)	3.36 (1.59-7.10)	4.63 (3.25-6.61)	1.93 (1.76-2.11)	2.61 (1.64-4.15)	5.87 (3.95-8.73)
3+ ACEs	3.82 (3.41-4.27)	3.74 (1.50-9.31)	9.18 (5.49-15.36)	3.63 (3.19-4.13)	8.19 (4.08-16.43)	8.28 (4.32-15.87)
Ever performed self-harm						
0 ACEs	1 (ref.)	2.30 (0.89-5.94)	4.25 (2.51-7.18)	1 (ref.)	1.82 (0.83-3.99)	4.46 (2.42-8.23)
1-2 ACEs	2.18 (1.86-2.55)	9.96 (4.34-22.85)	7.89 (5.36-11.62)	2.37 (1.97-2.85)	1.75 (0.72-4.22)	8.84 (5.47-14.30)
3+ ACEs	6.06 (5.06-7.25)	6.41 (2.13-19.30)	22.82 (14.34-36.32)	5.34 (4.28-6.65)	9.53 (4.25-21.37)	28.28 (13.83-57.85)
Ever had suicidal thoughts/attempted suicide						
0 ACEs	1 (ref.)	1.58 (0.77-3.25)	3.01 (1.99-4.56)	1 (ref.)	2.61 (1.75-3.88)	3.91 (2.65-5.78)
1-2 ACEs	2.17 (1.98-2.38)	5.07 (2.46-10.47)	8.15 (5.70-11.68)	1.95 (1.78-2.14)	4.02 (2.58-6.27)	4.65 (3.06-7.06)
3+ ACEs	5.95 (5.29-6.70)	7.13 (2.84-17.89)	16.61 (10.01-27.57)	4.15 (3.64-4.74)	9.49 (4.65-19.36)	24.26 (10.64-55.32)

OR – odds ratio adjusted for age in 10-year categories

Table 5 Associations between number of adverse childhood experiences (ACEs) and mental health problems among self-identified heterosexual individuals with or without same-sex sexual experience

	Women				Men			
	No same-sex sexual experience N (%)	OR (95% CI)	Any same-sex sexual experience N (%)	OR (95% CI)	No same-sex sexual experience N (%)	OR (95% CI)	Any same-sex sexual experience N (%)	OR (95% CI)
Ever received treatment for a mental health problem								
0 ACEs	7,574 (26.7)	1 (ref.)	346 (46.1)	1.89 (1.49-2.40)	7,716 (14.9)	1 (ref.)	176 (23.3)	1.58 (1.11-2.24)
1-2 ACEs	4,342 (40.4)	1.71 (1.58-1.86)	374 (60.6)	3.27 (2.60-4.12)	3,832 (25.8)	1.90 (1.73-2.09)	167 (38.1)	3.01 (2.22-4.08)
3+ ACEs	1,620 (60.2)	3.63 (3.22-4.08)	252 (76.9)	7.21 (5.26-9.88)	1,084 (40.2)	3.63 (3.18-4.15)	70 (45.5)	3.99 (2.55-6.24)
Ever performed self-harm								
0 ACEs	7,600 (3.9)	1 (ref.)	348 (8.6)	2.14 (1.37-3.33)	7,730 (2.5)	1 (ref.)	176 (6.4)	3.15 (1.69-5.91)
1-2 ACEs	4,360 (9.5)	2.14 (1.81-2.52)	371 (17.7)	4.39 (3.15-6.12)	3,841 (6.8)	2.49 (2.06-3.00)	168 (5.6)	2.22 (1.16-4.24)
3+ ACEs	1,616 (18.5)	5.74 (4.73-6.97)	250 (29.7)	11.25 (7.97-15.88)	1,079 (12.5)	5.27 (4.18-6.63)	69 (23.5)	12.04 (6.79-21.33)
Ever had suicidal thoughts/attempted suicide								
0 ACEs	7,521 (14.3)	1 (ref.)	343 (29.3)	2.11 (1.62-2.75)	7,637 (14.4)	1 (ref.)	174 (34.5)	3.23 (2.34-4.47)
1-2 ACEs	4,296 (28.4)	2.14 (1.94-2.36)	365 (45.3)	3.96 (3.14-5.00)	3,779 (26.3)	1.98 (1.80-2.18)	162 (39.0)	3.49 (2.56-4.76)
3+ ACEs	1,593 (51.8)	5.84 (5.15-6.62)	249 (63.6)	8.78 (6.62-11.66)	1,067 (41.7)	4.09 (3.57-4.69)	68 (61.8)	9.08 (5.65-14.59)

OR – odds ratio adjusted for age in 10-year categories

viduals without such experience to report ACEs. Further, mental health problems were significantly more common among those with same-sex sexual experience than among those without such experience, even in strata of individuals reporting no ACEs (see Table 5).

Moreover, combinations of ACEs with any same-sex sexual experience were associated with markedly elevated odds of all studied mental health problems (ORs: 2.22 to 12.04). For instance, heterosexuals with same-sex sexual experience and at least three ACEs had more than 10-fold greater odds of self-harm than the reference group of heterosexual individuals with no same-sex sexual experience and no ACEs (women: OR=11.25, 95% CI: 7.97-15.88; men: OR=12.04, 95% CI: 6.79-21.33) (see Table 5).

DISCUSSION

In this nationally representative study of 18 to 89 year-old Danes, non-heterosexual individuals reported ACEs markedly more often than heterosexuals. A similar finding has been previously reported in the literature, although mostly in smaller and less representative samples[8-11], and different interpretations have been offered. Firstly, it has been hypothesized that childhood maltreatment could independently influence adult sexual orientation[10,19], although no studies have thus far been able to reach firm conclusions on the causal dynamics of such a relationship. Secondly, it has been suggested that a nascent non-heterosexual identity might increase the risk of childhood adversities through two different pathways: a) adolescents who disclose their non-heterosexual orientation may be targeted for maltreatment[10,19], and b) children who will later form a non-heterosexual identity may be more likely to display gender non-conforming behaviours, which could increase their risk of maltreatment[10,19,20].

Regarding the latter hypothesis, several studies have found childhood gender non-conformity to be more prevalent among non-heterosexual individuals[21-23]. In a small study including 142 non-heterosexual and 148 heterosexual individuals, the reported excess of childhood harassment among non-heterosexuals diminished after controlling for childhood gender non-conformity[24]. A similar dynamic may have been at play in our study, as we previously reported a considerably higher prevalence of childhood gender non-conformity among homosexual (women: 57.5%; men: 54.6%) and bisexual (women: 43.6%; men: 24.9%) individuals compared with heterosexuals (women: 19.4%; men: 15.2%)[18]. Unfortunately, however, we were unable to include data about gender non-conformity in the present analyses, because questions concerning ACEs and childhood gender non-conformity were posed to non-overlapping segments of study participants.

A markedly higher prevalence of mental health problems among non-heterosexual than heterosexual individuals has also been previously reported in other datasets[12-14,25,26]. This increased mental morbidity may be interpreted within the frame of "minority stress", where adverse phenomena such as stigma, prejudice, discrimination and exclusion produce a hostile and distressing social environment for non-heterosexuals, leading to higher rates of mental health problems[13,26]. In a Danish context, we observed that stigma-related experiences are remarkably common in non-heterosexual persons. Among participants in the Project SEXUS cohort, sexual orientation-associated bullying or harassment was reported by as many as 51% of homosexuals and 13% of bisexuals. Additionally, experiences of sexual orientation-associated physical violence were reported by 18% of homosexuals and 5% of bisexuals[18]. A history of multiple ACEs has been reported to strongly increase vulnerability to interpersonal violence later in life[6].

Our study revealed that combinations of ACEs with a non-heterosexual identity were associated with markedly elevated odds of mental health problems. Only few prior studies have investigated such links between ACEs and mental health problems across different sexual identities. In a US study, researchers reported that the probability of substance use in combination with mental health disorders increased with higher numbers of ACEs, and that non-heterosexuals were at consistently higher risk of comorbid substance use and mental health problems than heterosexuals, irrespective of the number of ACEs[27]. In another US investigation carried out in high-school students, heterosexuals and non-heterosexuals with an ACE score of 2 or more had 4-fold and 13-fold greater odds, respectively, of suicidal ideation compared to heterosexuals reporting no ACEs[28].

In our study, bisexuals reported more ACEs than heterosexual and homosexual individuals, and they were at particularly elevated risk of mental health problems. The former finding is consistent with a US study reporting a higher prevalence of ACEs and a higher mean ACE score among bisexuals compared to both heterosexuals and homosexuals[11]. The observed greater burden of mental health problems in Danish bisexuals also accords well with other findings from the US, Australia and a recent meta-analysis, where bisexuality was more strongly associated with a range of mental health problems than heterosexual and homosexual orientations[13,15,26].

Reasons for the excess risk of both ACEs and mental health problems among bisexual persons are not well-established. However, having neither a heterosexual nor a homosexual identity has been suggested to somehow constitute an additional stressor on top of belonging to a sexual minority[15]. Bisexual individuals may also be more likely than homosexuals to lack social support[15,29] and to experience stress due to small or non-existent peer communities for bisexual people[13].

Associations between childhood circumstances and mental health among heterosexuals with or without same-sex sexual experience have received limited scientific attention. US researchers explored whether maltreatment in childhood increased the likelihood of same-sex sexual identity, behaviour and attraction in a nationally representative sample of more than 34,000 individuals, concluding that childhood sexual abuse and non-sexual maltreatment were positively associated with all three examined measures of non-heterosexual orientation[19]. Another large US study on the relationship between ACEs and substance use in combination with mental health disorders included five different sexual orientation subgroups: homosexual, bisexual, unsure, discordant heterosexual (with same-sex sexual attraction or behaviour) and concordant heterosexual (with no same-sex sexual attraction or behaviour). Higher prevalences of most ACEs and mental health disorders were observed among the discordant heterosexuals than among the concordant heterosexuals[27].

Additionally, in a prospective cohort of 946 New Zealanders, both women and men who reported even minor same-sex sexual attraction were at greater risk of self-harm than peers who were exclusively attracted to members of the other sex[30]. In combination with our findings, it appears that same-sex sexual behaviour and attraction exhibit rather similar associations as non-heterosexual sexual identity with indicators of poor mental health, implying that sexual non-conformity, i.e., any departure from strict

and exclusive heterosexuality, is somehow linked with a greater risk of mental health problems.

Our study has several strengths. Firstly, it is based on a large and detailed dataset comprising nationally representative baseline data in Project SEXUS, one of the world's largest cohort studies on sexual health[16,18]. Due to the large size of our dataset, we were able to investigate associations between ACEs and mental health problems across sexual identity categories for both women and men. Unlike several prior studies[8,24,28], we analyzed homosexual and bisexual respondents separately rather than pooling all non-heterosexuals in one group. Additionally, like only few other studies[19,27,30], we explored associations of ACEs with mental health problems not only across sexual identity categories, but also according to same-sex sexual experience among self-identified heterosexuals.

Our study also has some limitations. Due to the cross-sectional nature of our questionnaire data, we cannot make any firm causal inferences from the observed associations between ACEs and mental health problems among heterosexual, homosexual and bisexual participants or among self-identified heterosexuals with or without same-sex sexual experience. Additionally, potential bias resulting from different reporting probabilities for childhood adversities and mental health problems in the compared groups needs consideration. For instance, if non-heterosexuals are more likely than heterosexuals to recall ACEs or to report experienced childhood events as ACEs[10,19], information bias cannot be ruled out. Overall, however, we consider it unlikely that differential reporting, if present, would explain more than a small part of the observed marked excess of ACEs and mental health problems in non-heterosexuals and self-identified heterosexuals with same-sex sexual experience.

CONCLUSIONS

In this large, nationally representative study covering the age span 18-89 years, we document more ACEs and more mental health problems among non-heterosexuals than heterosexuals, and especially so among bisexuals. We also document a greater burden of mental health problems among self-identified heterosexuals with any same-sex sexual experience, and we show that combinations of ACEs with either a non-heterosexual identity or any same-sex sexual experience are associated with a markedly elevated burden of mental health problems.

Our findings, together with those of prior studies, indicate that ACEs may be partly responsible for the observed marked excess of mental health problems among homosexuals, bisexuals and self-identified heterosexuals with same-sex sexual experience, and they emphasize the public health importance of preventive measures to minimize the burden of ACEs and to avert their harmful long-term effects. Further, our study highlights the need to safeguard the integrity and welfare of children and adolescents with non-conforming expressions of sexuality. Finally, health care providers should keep in mind that there may well be clinically relevant links between patients' sex lives and their mental well-being.

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DOI:10.1002/wps.21008

Potential for prediction of psychosis and bipolar disorder in Child and Adolescent Mental Health Services: a longitudinal register study of all people born in Finland in 1987

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Current strategies to predict psychosis identify only a small proportion of individuals at risk. Additional strategies are needed to increase capacity for prediction and prevention of serious mental illness, ideally during childhood and adolescence. One possible approach would be to investigate systems in which psychosis risk factors are concentrated during childhood. One notable such system is represented by Child and Adolescent Mental Health Services (CAMHS). Although psychotic disorders are uncommon in CAMHS, many risk factors for psychosis are highly prevalent in young people who enter this system. We hypothesized, therefore, that youth attending CAMHS would be a high-risk group for psychosis if followed into adulthood and, furthermore, that CAMHS systems would capture a substantial proportion of future psychosis cases. We constructed a total population cohort study of all Finns born in 1987 (N=55,875), linking together extensive register data on health care contacts from birth through age 28 years. We identified all individuals diagnosed with a psychotic or bipolar disorder by age 28 (N=1,785). The risk of psychosis/bipolar disorder by age 28 years was 1.8% for individuals who had not attended CAMHS during childhood or adolescence, whereas it was 12.8% for those with a history of any outpatient CAMHS contact (odds ratio, OR=7.9, 95% CI: 7.2-8.7). Furthermore, the risk of psychosis/bipolar disorder by age 28 years was 2.3% for individuals without a history of inpatient CAMHS admission, whereas it was 24.0% for those with a history of inpatient CAMHS admission (OR=13.3, 95% CI: 11.9-14.9), and 36.5% for those with a history of inpatient CAMHS admission in adolescence (age 13-17 years) (OR=24.2, 95% CI: 21.2-27.6). Individuals who attended CAMHS but received no mental disorder diagnosis had an equally high risk of subsequently developing a psychosis/bipolar disorder as individuals who did receive a diagnosis (OR=0.9, 99.5% CI: 0.7-1.1). Compared to other CAMHS attendees, individuals who developed psychosis or bipolar disorder were more likely to have had an initial CAMHS diagnosis of depressive or other mood disorder (OR=2.3, 99.5% CI: 1.6-3.0) and disruptive behaviour disorder (OR=1.7, 99.5% CI: 1.2-2.5). Of all psychosis/bipolar diagnoses by age 28 years, 50.2% occurred in individuals who had, at some point in childhood or adolescence, attended CAMHS, indicating that CAMHS represent not only a high-risk but also a high-capacity system for prediction of psychosis/bipolar disorder. These findings suggest an enormous, untapped potential for large-scale psychosis/bipolar disorder prediction and prevention research within existing specialist CAMHS.

Key words: Psychosis, schizophrenia, bipolar disorder, prediction, prevention, Child and Adolescent Mental Health Services, high-risk groups

(World Psychiatry 2022;21:436–443)

The identification of individuals at risk for psychosis has been a major focus of psychiatric research in the past 25 years[1-8]. The dominant paradigm in this area has been the ultra-high risk or clinical high risk (CHR) approach[3,4,7,9], which involves structured assessments of attenuated psychotic symptoms or frank but brief psychotic symptoms, aiming to identify individuals at risk for psychotic disorder[1,3,10-12].

There have been thousands of papers published using the CHR paradigm[13], and such has been the impact of this work that CHR clinics are now considered a standard component of mental health services in many countries[14-18]. Building on this progress, research aimed at identifying individuals at elevated risk of (psychotic and non-psychotic) bipolar disorder has also grown in recent years[19-25].

An important challenge for the field, which has been recently highlighted, is that the CHR approach identifies only a small proportion of individuals who are at risk for psychosis, even at leading centres with well-established, free-access specialist CHR clinics[13,26-28]. In a 2-year review of South London mental health services, researchers found that only 4.4% of all psychosis cases received a CHR diagnosis prior to their first psychosis diagnosis[26], while the corresponding proportion was reported to be 13.7% in Melbourne[29]. These findings emphasize the need for additional, higher-capacity approaches to psychosis prediction. An alternative to the symptom-based approach of the CHR paradigm is to take a system-based approach, i.e. to investigate systems in which psychosis risk factors are concentrated during childhood.

Child and Adolescent Mental Health Services (CAMHS) are specialist psychiatric services for children and adolescents covering a distinct catchment area[30]. Psychotic and bipolar disorders are uncommon diagnoses in CAMHS; a large majority of these diagnoses occur in adult mental health services[31,32], and the reasons for presenting to CAMHS differ significantly from those leading to attendance of adult mental health services[33-36]. However, many of the risk factors associated with psychosis are heavily enriched in youth attending CAMHS, including not only mental disorders but also, for example, problems with motor coordination, cognitive function, language acquisition, social communi-

cation, and interpersonal relationships[37-42]. We hypothesized, therefore, that CAMHS could represent an important high-risk system for psychosis and bipolar disorder when attendees were followed into adulthood.

Using national register data, we carried out a longitudinal study of all individuals born in Finland in 1987. We calculated the absolute risk of psychosis and bipolar disorder in individuals who had one or more contacts with CAMHS in childhood or adolescence (age 0-17 years). We also assessed the proportion of psychosis and bipolar disorder cases that were preceded by a CAMHS contact (i.e., predictive capacity), the prospective risk of psychosis or bipolar disorder in individuals who had attended CAMHS, and the latency between the first CAMHS contact and the first psychosis or bipolar disorder diagnosis. As secondary analyses, we also investigated whether particular categories of index diagnoses were more predictive of psychosis and bipolar disorder than others.

METHODS

Study population

We used data from the nationwide 1987 Finnish Birth Cohort study[43], which includes all Finns born in the year 1987 (N=59,476), with official register data recorded from birth until December 31, 2015. The overall study is governed by the Finnish Institute of Health and Welfare and has been approved by its Research Ethics Committee (§28/2009).

The current study was approved by the Research Ethics Committee of the Royal College of Surgeons in Ireland (REC202006006). The data were pseudo-anonymized after linkage and before analysis, and were handled following Finnish data protection laws. The study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data from national registers

We used data linked from the Medical Birth Register (sex, date of birth), the Care Register for Health Care (dates and diagnoses of visits in public hospitals), Statistics Finland (deaths), and Digital and Population Data Services Agency (emigrations).

Information on exposures (having a CAMHS contact) and outcomes (psychotic and bipolar disorder diagnoses) were derived from the Care Register for Health Care[44,45]. This register covers all inpatient visits during the cohort members' lifetime, and all outpatient visits to secondary level health care from the year 1998 onwards. For each visit, the register records diagnoses assigned, medical specialty of treatment provided, and information on whether the visit was an inpatient or outpatient one. Diagnoses were coded using the ICD-9, Finnish modification (1987-1995) or the ICD-10 (1996 onwards). The Care Register for Health Care has been widely used for epidemiological research, and the diagnostic validity has been found to be good[44-50].

Youth who had one or more contacts with CAMHS in childhood or adolescence (age 0-17 years) were divided into two groups depending on whether or not they had had an inpatient admission. Those with an inpatient CAMHS admission were further divided into two groups based on whether their first admission occurred in childhood (<13 years) or adolescence (13-17 years).

Outcomes

Individuals who had been assigned a diagnosis of a non-organic psychotic disorder or bipolar disorder by age 28 years were identified from the Care Register for Health Care.

Non-organic psychotic disorders were categorized into three nested groups: schizophrenia (F20.x as in ICD-10; 295 as in ICD-9, Finnish modification); non-affective psychotic disorders (F20.x, F23.x, F28, F29, F22.x, F25.x and F24 as in ICD-10; 295, 297, 298 and 2999C as in ICD-9, Finnish modification); and all psychotic disorders (F20.x, F23.x, F28, F29, F22.x, F25.x, F24, F30.2, F31.2, F31.5, F32.3, F33.3 and F1x.5 as in ICD-10; 295, 297, 298, 2999C, 2691E, 2962E, 2963E and 2964E as in ICD-9, Finnish modification). Bipolar disorder included F31.x and F30.x as in ICD-10, and 2962, 2963, 2964 and 2967A as in ICD-9, Finnish modification.

Statistical analyses

Analyses were conducted using Stata version 16.0. We excluded individuals who had died (N=756; 1.3%), emigrated (N=2,788; 4.7%) or were diagnosed with moderate to profound intellectual disability (N=79; 0.1%) by the end of the follow-up (December 31, 2015), resulting in a final study cohort of 55,875 individuals. We assessed the lifetime prevalence of CAMHS contacts and outcome disorders in percentages and Kaplan-Meier failure functions with Greenwood 95% confidence bands.

We calculated the risk of a psychotic or bipolar disorder up to age 28 years in individuals who had attended CAMHS (separately for each CAMHS contact type and each outcome disorder). We used unadjusted odds ratios (ORs) to compare the risk of first outcome disorder diagnosis among individuals with a CAMHS contact as compared to individuals who had not presented to CAMHS. For individuals who were not diagnosed with a psychotic or bipolar disorder within 3 months of their first outpatient CAMHS contact or in their first inpatient admission, we calculated the median time (with interquartile range, IQR) from first CAMHS contact/inpatient admission to ultimate diagnosis of psychotic or bipolar disorder.

We then calculated the total proportion of all psychosis and bipolar disorder cases who, at some point in childhood, had attended a CAMHS, and of those who had had an inpatient CAMHS admission (before or after age 13 years). To study the predictive capacity of focusing on individuals attending CAMHS, we assessed the proportion of first recorded outcome disorder diagnoses that were preceded by different types of CAMHS contacts.

For our secondary analyses, we investigated the relationship between the index CAMHS diagnoses and the risk of outcome disorders. Confidence levels were Bonferroni corrected for multiple testing. Index diagnosis was defined as a mental disorder diagnosis given within 3 months of the first CAMHS contact or, where the first CAMHS contact was an inpatient admission, a mental disorder diagnosis given during that admission.

RESULTS

The sample included 55,875 individuals (48.5% females). Of these, 7,011 (12.5%) had one or more contacts with CAMHS in childhood or adolescence (age 0-17 years), and 2,261 (4.0%) had at least one inpatient CAMHS admission (first admission when aged <13 years: 1,131, 2.0%; first admission when aged 13-17 years: 1,130, 2.0%).

Within the overall sample, 1,785 individuals (3.2%) had a lifetime diagnosis of any psychosis or bipolar disorder; 1,369 (2.5%) had a lifetime diagnosis of any psychosis; 1,032 (1.8%) had a lifetime diagnosis of non-affective psychoses, whereas the lifetime prevalence of schizophrenia was 0.5% (N=307) and that of bipolar disorder was 1.2% (N=673) (see Table 1). The percentage of individuals receiving their first diagnosis after age 18 years was 80.6% for any psychosis or bipolar disorder; 77.8% for any psychosis; 79.4% for non-affective psychoses; 85.3% for schizophrenia; and 90.6% for bipolar disorder.

Among the individuals who had not attended CAMHS during childhood or adolescence (N=48,864; 87.5%), those who were diagnosed with any psychosis or bipolar disorder by age 28 years were 889 (1.8%). Among the individuals who had one or more contacts with CAMHS in childhood or adolescence (N=7,011; 12.5%), the percentage of those who received a diagnosis of any psychosis or bipolar disorder by age 28 years was 12.8% (N=896) (OR=7.9, 95% CI: 7.2-8.7) (see Table 1).

Of all diagnoses of any psychosis or bipolar disorder by age 28 years, 50.2% (N=896) occurred among individuals who had attended CAMHS during childhood or adolescence (Table 1). Of these individuals, 83.4% received their diagnosis of any psychosis or bipolar disorder later than 3 months after the first CAMHS contact, with a median latency from first CAMHS contact to diagnosis of psychosis or bipolar disorder of 6.5 years (IQR=2.7-10.1) (see Table 2).

Of individuals with at least one inpatient CAMHS admission, 24.0% were diagnosed with psychosis or bipolar disorder by age 28 years, versus 2.3% of those without an inpatient CAMHS admission (OR=13.3, 95% CI: 11.9-14.9) (see Table 3). The percentage of individuals diagnosed with a psychotic or bipolar disorder by age 28 years was 11.5% among those with a first inpatient CAMHS admission before age 13 years (OR=5.5, 95% CI: 4.5-6.6), and 36.5% among those with a first inpatient CAMHS admission when aged 13-17 years (OR=24.2, 95% CI: 21.2-27.6) (see supplementary information).

Of all diagnoses of psychosis or bipolar disorder by age 28 years, 7.3% (N=130) occurred among individuals with first inpatient CAMHS admission before age 13 years. Of these 130 individuals, 0.8% had been diagnosed with psychosis or bipolar disorder as an outpatient prior to first inpatient admission, 5.4% had received this diagnosis on their first inpatient admission, and 93.8% after their first inpatient CAMHS admission. The median latency from first CAMHS inpatient admission to diagnosis of psychosis or bipolar disorder in the latter group was 12.0 years (IQR=8.7-16.2 years) (see supplementary information).

Of all diagnoses of psychosis or bipolar disorder by age 28 years, 23.1% (N=412) occurred among individuals with first inpatient CAMHS admission between ages 13 and 17 years. Of these 412 individuals, 5.3% had been diagnosed with psychosis or bipolar disorder as an outpatient prior to their first inpatient admission, 37.1% had received this diagnosis on their first inpatient admission, and 57.5% after their first inpatient CAMHS admission. The median latency from first CAMHS inpatient admission to diagnosis of psychosis/bipolar disorder in the latter

Table 1 CAMHS contacts and diagnoses of psychosis and bipolar disorder by age 28 years

		Total	No CAMHS contact			CAMHS contact				
Outcome diagnosis		**N**	**N**	**% column**	**% row**	**N**	**% column**	**% row**	**OR**	**95% CI**
Psychosis and/or bipolar disorder	Yes	1,785	889	1.8	49.8	896	12.8	50.2	7.9	7.2-8.7
	No	54,090	47,975	98.2	88.7	6,115	87.2	11.3		
All psychoses	Yes	1,369	684	1.4	50.0	685	9.8	50.0	7.6	6.8-8.5
	No	54,506	48,180	98.6	88.4	6,326	90.2	11.6		
Non-affective psychoses	Yes	1,032	512	1.0	49.6	520	7.4	50.4	7.6	6.7-8.6
	No	54,843	48,352	99.0	88.2	6,491	92.6	11.8		
Schizophrenia	Yes	307	140	0.3	45.6	167	2.4	54.4	8.5	6.8-10.6
	No	55,568	48,724	99.7	87.7	6,844	97.6	12.3		
Bipolar disorder	Yes	673	323	0.7	48.0	350	5.0	52.0	7.9	6.8-9.2
	No	55,202	48,541	99.3	87.9	6,661	95.0	12.1		

CAMHS – Child and Adolescent Mental Health Services, OR – odds ratio

Table 2 CAMHS attendance among individuals diagnosed with psychosis or bipolar disorder by age 28 years

	Schizophrenia (N=307)		Non-affective psychoses (N=1,032)		All psychoses (N=1,369)		Bipolar disorder (N=673)		Psychosis/bipolar disorder (N=1,785)	
	N (%)	Time (yrs.) to diagnosis, median (IQR)	N (%)	Time (yrs.) to diagnosis, median (IQR)	N (%)	Time (yrs.) to diagnosis, median (IQR)	N (%)	Time (yrs.) to diagnosis, median (IQR)	N (%)	Time (yrs.) to diagnosis, median (IQR)
CAMHS attendance	167 (54.4)		520 (50.4)		685 (50.0)		350 (52.0)		896 (50.2)	
Diagnosed in the 3 months after first CAMHS contact	11 (6.6)		95 (18.3)		135 (19.7)		19 (5.4)		149 (16.6)	
Diagnosed >3 months after first CAMHS contact	156 (93.4)	6.8 (3.2-10.7)	425 (81.7)	7.0 (3.0-10.9)	550 (80.3)	6.5 (2.4-10.1)	331 (94.6)	7.3 (3.7-10.7)	747 (83.4)	6.5 (2.7-10.1)
Inpatient CAMHS admission	115 (37.5)		339 (32.8)		449 (32.8)		178 (26.4)		542 (30.4)	
Diagnosed before first admission	1 (0.9)		17 (5.0)		19 (4.2)		4 (2.2)		23 (4.2)	
Diagnosed on first admission	11 (9.6)		98 (28.9)		148 (33.0)		17 (9.6)		160 (29.5)	
Diagnosed after first admission	103 (89.6)	5.8 (1.5-10.6)	224 (66.1)	7.4 (2.3-11.6)	282 (62.8)	6.9 (1.5-11.1)	157 (88.2)	5.6 (2.0-10.3)	359 (66.2)	6.3 (1.5-11)

CAMHS – Child and Adolescent Mental Health Services, IQR – interquartile range

Table 3 Inpatient CAMHS admissions and diagnoses of psychosis and bipolar disorder by age 28 years

		Total	No inpatient CAMHS admission			Inpatient CAMHS admission				
Outcome diagnosis		**N**	**N**	**% column**	**% row**	**N**	**% column**	**% row**	**OR**	**95% CI**
Psychosis and/or bipolar disorder	Yes	1,785	1,243	2.3	69.6	542	24.0	30.4	13.3	11.9-14.9
	No	54,090	52,371	97.7	96.8	1,719	76.0	3.2		
All psychoses	Yes	1369	920	1.7	67.2	449	19.9	32.8	14.2	12.6-16.0
	No	54,506	52,694	98.3	96.7	1,812	80.1	3.3		
Non-affective psychoses	Yes	1,032	693	1.3	67.2	339	15.0	32.9	13.5	11.8-15.5
	No	54,843	52,921	98.7	96.5	1,922	85.0	3.5		
Schizophrenia	Yes	307	192	0.4	62.5	115	5.1	37.5	14.9	11.8-18.9
	No	55,568	53,422	99.6	96.1	2,146	94.9	3.9		
Bipolar disorder	Yes	673	495	0.9	73.6	178	7.9	26.5	9.2	7.7-10.9
	No	55,202	53,119	99.1	96.2	2,083	92.1	3.8		

CAMHS – Child and Adolescent Mental Health Services, OR – odds ratio

group was 3.0 years (IQR=0.9-7.3 years) (see supplementary information).

In order to assess whether certain mental disorder diagnoses were more predictive of psychosis or bipolar disorder than others, we looked at index diagnoses made on initial CAMHS contact (see Table 4). Overall, there was a broad spread of index diagnoses among individuals attending CAMHS who went on to be diagnosed with psychosis or bipolar disorder. Individuals who attended CAMHS but received no mental disorder diagnosis had an equally high risk of psychosis and bipolar disorder as individuals who did receive a diagnosis (OR=0.9, 99.5% CI: 0.7-1.1). The most common diagnoses among individuals subsequently diagnosed with psychosis or bipolar disorder were depressive or other mood disorders (non-psychotic) (24.4%); anxiety, stress-related or somatoform disorders (12.4%); and neurodevelopmental disorders (12.3%).

Compared to other CAMHS attendees, individuals who developed psychosis or bipolar disorder were more likely to have had an initial CAMHS diagnosis of depressive or other mood disorder (24.4% vs. 12.4%; OR=2.3, 99.5% CI: 1.6-3.0) and disruptive behaviour disorder (9.2% vs. 5.6%; OR=1.7, 99.5% CI: 1.2-2.5), and less likely to have been diagnosed with neurodevelopmental disorders (12.3% vs. 19.9%; OR=0.6, 99.5% CI: 0.4-0.8).

Table 4 Diagnoses assigned during the first 3 months after first CAMHS contact and subsequent diagnosis of psychosis or bipolar disorder

		All	No subsequent diagnosis of psychosis/bipolar disorder (N=6,115)			Subsequent diagnosis of psychosis/bipolar disorder (N=747)				
Index CAMHS diagnoses		**N (%)**	**N**	**% row**	**% column**	**N**	**% row**	**% column**	**OR**	**99.5% CI**
Substance use disorders	Yes	236 (3.4)	213	90.3	3.5	23	9.7	3.1	0.9	0.5-1.6
	No	6,626 (96.6)	5,902	89.1	96.5	724	10.9	96.9		
Depressive or other mood disorders (non-psychotic)	Yes	878 (13.7)	758	80.6	12.4	182	19.4	24.4	**2.3**	**1.6-3.0**
	No	5,922 (86.3)	5,357	90.5	87.6	565	9.5	75.6		
Anxiety, stress-related or somatoform disorders	Yes	810 (11.8)	717	88.5	11.7	93	11.5	12.4	1.1	0.8-1.5
	No	6,052 (88.2)	5,398	89.2	88.3	654	10.8	87.6		
Eating disorders	Yes	279 (4.1)	246	88.2	4.0	33	11.8	4.4	1.1	0.6-1.9
	No	6,583 (95.9)	5,869	89.2	96.0	714	10.8	95.6		
Personality disorders	Yes	21 (0.3)	17	81.0	0.3	4	19.0	0.5	1.9	0.4-9.2
	No	6,841 (99.7)	6,098	89.1	99.7	743	10.9	99.5		
Neurodevelopmental disorders	Yes	1,310 (19.1)	1,218	93.0	19.9	92	7.0	12.3	**0.6**	**0.4-0.8**
	No	5,552 (80.9)	4,897	88.2	80.1	655	11.8	87.7		
Disruptive behaviour disorders	Yes	410 (6.0)	341	83.2	5.6	69	16.8	9.2	**1.7**	**1.2-2.5**
	No	6,452 (94.0)	5,774	89.5	94.4	678	10.5	90.8		
Other and unspecified emotional or social interaction disorders	Yes	483 (7.0)	430	89.0	7.0	53	11.0	7.1	1.0	0.7-1.5
	No	6,379 (93.0)	5,685	89.1	93.0	694	10.9	92.9		
Other disorders	Yes	163 (2.4)	150	92.0	2.5	13	8.0	1.7	0.7	0.3-1.6
	No	6,699 (97.6)	5,965	89.0	97.5	734	11.0	98.3		
No mental disorder diagnosis	Yes	2,623 (38.2)	2,351	89.6	38.4	272	10.4	36.4	0.9	0.7-1.1
	No	4,239 (61.8)	3,764	88.8	61.6	475	11.2	63.6		

CAMHS – Child and Adolescent Mental Health Services, OR – odds ratio. Significant values are highlighted in bold prints

DISCUSSION

In a total population study of all individuals born in Finland in 1987 and followed to age 28 years, we assessed the risk of psychotic and bipolar disorders among those who had, at some point in childhood or adolescence, attended specialist CAMHS. In terms of absolute risk, 12.8% of individuals who attended CAMHS received a diagnosis of a psychotic or bipolar disorder, compared to 1.8% of the rest of the population (OR=7.9, 95% CI: 7.2-8.7). This elevated risk is similar to the level of psychosis risk associated with a formal CHR diagnosis in childhood or adolescence: in a recent systematic review of all CHR studies, we found a transition rate to psychosis of 9.5% at 1 year, 12.1% at 2 years, and 16.1% at 5 or more years[51].

An inpatient CAMHS admission during adolescence was associated with a particularly high risk of psychosis and bipolar disorder. More than one third of young people with a first CAMHS inpatient admission when aged 13 to 17 years were diagnosed with psychosis or bipolar disorder by age 28 years. In 37.1% of these cases, the psychosis or bipolar disorder diagnosis occurred during their initial adolescent admission. In nearly 60% of cases, however, the diagnosis was first made later in life, and the median time to psychosis/bipolar disorder in this group was 3.0 years. These findings highlight the importance of a new sharp focus on psychosis and bipolar disorder risk in adolescents who are admitted to inpatient CAMHS, regardless of their reason for admission at that time.

A key finding of our study was that, in contrast to the small proportion of psychosis cases identified by current high risk strategies[26,29], at least half of all individuals diagnosed with psychosis or bipolar disorder by age 28 years had, at some point in their childhood or adolescence, attended specialist CAMHS. Just 16.6% of these psychosis or bipolar disorder cases were diagnosed within 3 months of first attending outpatient CAMHS or on first inpatient CAMHS admission. For the remaining 83.4%, the median time from first CAMHS contact to psychosis or bipolar diagnosis was >6 years. Overall, these findings highlight an enormous untapped potential for prediction of psychosis and bipolar disorder within already existing specialist paediatric mental health services.

Our secondary analyses involved identifying index CAMHS diagnoses of individuals who went on to be diagnosed with psychosis or bipolar disorder, in order to explore whether certain clinical diagnoses were more predictive of later psychosis and bipolar disorder. Previous research has shown that mental disorders in childhood and adolescence are risk factors for later psychosis[37-42,52-55], although it is important to note that only a small proportion of all young people with a mental disorder present to specialist CAMHS. We found that there was a broad spread of index diagnoses among individuals who went on to be diagnosed with psychosis or bipolar disorder. However, importantly, we found that psychosis and bipolar disorder risk was similarly elevated in young people who attended CAMHS but who were not diagnosed with any mental disorder. This finding, together with the fact that only a small proportion of young people with mental disorders attend specialist CAMHS[30], highlights that the psychosis/bipolar disorder risk indexed by CAMHS contact is best considered a system-related rather than a diagnosis-related risk.

Our findings can help guide and advance psychosis research in several important ways. First, and fundamentally, our findings show that specialist CAMHS represent a high-capacity system for future psychosis and bipolar disorder prediction research. Our findings also suggest that ongoing research aimed at refining risk prediction within high-risk groups, such as neuroimaging, cognitive and proteomic work aimed at predicting psychosis in CHR samples[56-59], should also be applied to and tested in (higher-capacity) CAMHS patient samples.

Beyond that, our findings provide guidance on optimal strategies for different types of psychosis and bipolar disorder prediction and prevention research. In studies, for example, where the overall goal is to improve psychosis outcomes, our findings suggest that a total outpatient CAMHS sample would represent the optimal sampling approach, since it has the potential to reach a large proportion of all psychosis and bipolar disorder cases. In studies, on the other hand, where the research approach seeks a very high-risk group – for instance, for a proof of principle study or for targeted intervention studies where adverse treatment effects might be more significant – our findings suggest that recruitment of an adolescent inpatient sample might be optimal.

Our findings also point to the value of preventive intervention research in CAMHS. There is intense interest in pharmacological and psychosocial treatments that might help to prevent psychosis and bipolar disorder[60]. CAMHS patients represent an ideal group for this research, since this population already receives a wide variety of interventions. As exposure to treatment in CAMHS is not random, future preventive research could include the conduction of randomized controlled trials within CAMHS but also the application of causal inference research methods to existing clinical data.

Furthermore, our findings can help advance important aetiology research aimed at understanding the potentially multiple pathways to psychosis. It has long been posited that psychosis may be a shared outcome for a heterogeneous group of diseases[61,62]. Given the relatively low incidence of psychosis in the population, however, this theory has been difficult to test empirically. Imaging studies have shown that core structural brain abnormalities of psychosis are present at the time of diagnosis[61,63], as are many core cognitive deficits[64], meaning that research on developmental aetiology needs to begin earlier in the disease process. However, identifying a suitable (risk-enriched) sample earlier in the disease course in which to carry out this research has been a major challenge. Our findings suggest that children and adolescents attending specialist CAMHS can be an important target in developmental research on psychosis and bipolar disorder aetiology, given the high incidence of these illness outcomes in this population and considering that the median time to diagnosis from first CAMHS contact is >6 years. Identifying pathways to psychosis-related brain abnormalities will, in turn, lead to further opportunities for treatment research.

Our findings also highlight the importance of transition between adolescent and adult mental health services. The reasons for presenting to CAMHS differ from those for presenting to adult mental health services, and only a small minority of CAMHS patients are subsequently referred to the latter services[33-36]. Even in cases where onward referral occurs, transition is often associated with poor planning, disrupted care and very high non-attendance or once-off attendance only[30,65,66]. Our findings highlight the importance of a careful coordination of the above transition.

A key strength of this study was the use of total population, official service-use data, which means that our findings are not just generalizable to, but directly reflect the total population. Replication of our analyses in other countries will be valuable, but it is important to note that the structure, function and attendance at Finnish CAMHS is similar to other Western countries. In a review of CAMHS across 19 European countries, the median proportion of all children and adolescents attending CAMHS per year was 2.0%, while for Finland it was 1.8%[30]. It will also be important to routinely re-assess our findings over time to monitor for changes in the relationship between CAMHS attendance and risk of psychosis and bipolar disorder: this type of routine re-assessment should be considered good practice for any high-risk approach and will be facilitated by the routine collection of necessary data in Finnish health care registers.

A CAMHS focus for psychosis and bipolar disorder prediction is, of course, only possible in countries where these services exist. These include most World Bank category 1 countries, but CAMHS are less common in other countries[30]. The possibility of prediction and prevention of serious mental health disorders adds to the reasons to support the development and/or expansion of CAMHS where they are lacking.

Because our study used clinical data, it only included individuals presenting to specialist mental health services and did not identify all psychopathology in the general population. This, however, was precisely the point of this approach: our aim was not to investigate childhood mental disorders as a risk factor for psychosis or bipolar disorder, but to assess psychosis and bipolar disorder risk associated with contact with a specific system, CAMHS, where these data are available with high validity[30]. It is also important to highlight that our findings are system-specific: they apply to specialist CAMHS and should not be extrapolated to

other (e.g., primary care) mental health services for children and adolescents.

The dataset included information on outpatient visits only from the year 1998 onwards (when the cohort was 11 years old). This could, in theory, lower the prevalence estimate of outcome disorders. However, psychosis or bipolar disorder before age 11 years is extremely rare. Although the follow-up covers a substantial portion of the high-risk age for onset of psychoses and bipolar disorders, their prevalence among the cohort members will continue to rise over time. For this reason, our risk figures should be considered as lower estimates and the true level of risk may be even higher.

CONCLUSIONS

In a total population study of all individuals born in Finland in 1987 and followed up to 28 years, half of all psychosis and bipolar diagnoses occurred in individuals who had attended CAMHS during childhood or adolescence. There was a large window of opportunity for intervention in terms of the time from initial CAMHS attendance to a diagnosis of psychosis or bipolar disorder: >6 years median latency.

These findings highlight an enormous, untapped potential for the prediction of psychosis and bipolar disorder within already existing structures providing specialist paediatric mental health care. They support a new focus for psychosis and bipolar disorder prediction efforts on specialist community and inpatient CAMHS and present exciting new opportunities for psychosis and bipolar disorder prevention research.

ACKNOWLEDGEMENTS

The Finnish 1987 Birth Cohort Study was supported by grants 288960 and 308552 from the Academy of Finland. U. Lång and K. Yates were supported by a Strategic Academic Recruitment award from the Royal College of Surgeons in Ireland. U. Lång was also supported by the European Union Erasmus+ Programme. D. Gyllenberg received an INVEST-flagship grant from the Academy of Finland (no. 320162). M.C. Clarke was supported by an Irish Research Council Award (COALESCE/2019/61). I. Kelleher was supported by the Health Research Board, Ireland (ECSA-2020-005) and St. John of God Research Foundation (project grant 2021). Supplementary information on the study is available at https://osf.io/gku9a/?view_only=dd52319fdb924fd8aa02ac1b0aca1698.

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DOI:10.1002/wps.21009

Use of low-dose quetiapine increases the risk of major adverse cardiovascular events: results from a nationwide active comparator-controlled cohort study

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At standard doses used for schizophrenia or bipolar disorder, quetiapine has been associated with weight gain and increased levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol, which are risk factors for cardiovascular morbidity and mortality. However, this drug is also commonly used off-label at low doses for anxiolytic or hypnotic purposes, and its cardiovascular safety at these doses is unknown. We aimed to assess the risk of major adverse cardiovascular events with use of low-dose quetiapine compared to use of Z-drug hypnotics in a nationwide, active comparator-controlled cohort study. The cohort included new users of either drugs in Denmark from 2003 to 2017, aged 18-85 years, without history of ischemic stroke, myocardial infarction, cancer, and severe mental illness. The main outcome was the occurrence of major adverse cardiovascular events, defined as non-fatal myocardial infarction or ischemic stroke, or death from cardiovascular causes. Selective serotonin reuptake inhibitors (SSRIs) were used as an alternative comparator in sensitivity analyses. Altogether, we compared 60,566 low-dose quetiapine users with 454,567 Z-drug users, followed for 890,198 person-years in intent-to-treat analysis, and 330,334 person-years in as-treated analysis. In intention-to-treat analysis, low-dose quetiapine was associated with an increased risk of major adverse cardiovascular events (adjusted hazard ratio, aHR=1.13, 95% CI: 1.02-1.24, p=0.014) and cardiovascular death (aHR=1.26, 95% CI: 1.11-1.43, p<0.001). In as-treated analysis, continuous low-dose quetiapine use was associated with increased risk of major adverse cardiovascular events (aHR=1.52, 95% CI: 1.35-1.70, p<0.001), non-fatal ischemic stroke (aHR=1.37, 95% CI: 1.13-1.68, p=0.002) and cardiovascular death (aHR=1.90, 95% CI: 1.64-2.19, p<0.001). The risk of major adverse cardiovascular events was greater in women (aHR=1.28, p=0.02) and those aged ≥65 years at initiation (aHR=1.24, p<0.001). Compared to SSRIs, low-dose quetiapine use was associated with an increased risk of major adverse cardiovascular events (aHR=1.42, p<0.001), non-fatal ischemic stroke (aHR=1.27, p=0.0028) and cardiovascular death (aHR=1.72, p<0.001). So, we conclude that the use of low-dose quetiapine is associated with an increased risk of major adverse cardiovascular events, especially in women and the elderly. On the basis of these findings, we suggest that use of off-label low-dose quetiapine for sedative or hypnotic purposes should be discouraged.

Key words: Low-dose quetiapine, major adverse cardiovascular events, death from cardiovascular causes, off-label use, anxiolytic or hypnotic use, cardiovascular safety

(World Psychiatry 2022;21:444–451)

Quetiapine is a second-generation antipsychotic labelled for use in schizophrenia, bipolar disorder, and as adjunctive treatment in major depression[1]. In addition to its antipsychotic effects, quetiapine has anxiolytic, sedative and hypnotic properties, due to its high affinity to serotonergic, histaminergic and muscarinic receptors[2]. These additional properties have led to considerable off-label use of the drug, which has been documented across several countries[3-6]. Quetiapine is now among the most frequently prescribed antipsychotics worldwide, with approximately 2 million users in the US alone[7,8]. Evidence suggests that prescription by non-psychiatrists contributes significantly to the increased off-label, low-dose use of the drug[5,9].

Antipsychotics, in general, have been associated with increased risk of cardiovascular morbidity and sudden cardiac death[10-12]. The increased risk of cardiovascular morbidity is driven by metabolic abnormalities, whereas the increased risk of sudden cardiac death is likely to stem from QT prolongation (increasing the risk of ventricular arrhythmias)[13,14].

While quetiapine has not been associated with clinically significant QT prolongation compared to other antipsychotics[15], it has been found to induce weight gain and considerable increases in the levels of triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol[16], all of which are important risk factors for the development of cardiovascular disease morbidity[17]. In a study of 284,234 non-elderly adults in the US, including 12,094 patients treated with quetiapine and 253,027 receiving antidepressants[18], the use of quetiapine was found to be associated with an increased risk of stroke, hypertensive heart disease, and coronary artery disease.

Whether the increased risk of cardiovascular events observed with standard doses of quetiapine in schizophrenia is also present with the low doses mainly used for anxiety and insomnia is an important question, given the widespread off-label use of the drug. Practical limitations with randomized controlled trials (e.g., small sample size and limited follow-up duration) makes them less suitable to study long-term adverse effects, such as cardiovascular morbidity or mortality. Furthermore, the exclusion of individuals with significant physical comorbidities from those trials limits the generalizability of their findings to the real-world population[19]. For these reasons, observational studies are important to assess the long-term cardiovascular safety of off-label/low-dose antipsychotic treatment in a representative population.

In this study, our aim was to assess the association between prescription of low-dose quetiapine and major adverse cardio-

vascular events with an active comparator-controlled design, using routinely collected health data from nationwide registers. We hypothesized that low-dose quetiapine would be associated with an increased risk of major adverse cardiovascular events compared to Z-drugs and to selective serotonin reuptake inhibitors (SSRIs).

METHODS

Study design

We conducted a new-user, active-comparator cohort study based on data from Danish nationwide health care registers. We included initiators of benzodiazepine-related drugs (Z-drugs) as an active comparator, because this drug class is widely used for the treatment of insomnia[20]. In sensitivity analyses, we also used SSRIs as an active comparator, which are used to treat anxiety, the second off-label indication for low-dose quetiapine. Since SSRIs have been associated with a potential increase in cardiometabolic risk[10], these sensitivity analyses were used to test the generalizability and robustness of the results of the primary analysis. Additionally, we used propensity score weighting methods to control for other potential confounders while utilizing the full cohort size.

Access to pseudonymized health care data was approved by the Danish Health Data Authority. No ethical committee approval is needed for purely register-based studies according to Danish legislation. The study protocol was registered in the European Union Electronic Register of Post-Authorization Studies (EUPAS-38508), and data presentation followed the REporting of studies Conducted using Observational Routinely collected health Data statement for PharmacoEpidemiology (RECORD-PE)[21].

Data sources

Prescriptions of quetiapine, comparators and other medications were identified in the Danish National Prescription Register[22], in which all prescriptions redeemed at community pharmacies are captured. In- and outpatient diagnoses were obtained from the Danish National Patient Register[23] for outcome and comorbidity assessment. Information on vital status and migration was collected from the Danish Civil Registration System[24], and information on cause of death (for outcome assessment) was obtained from the Danish Cause of Death Register[25]. Further description of the registers is provided in the supplementary information.

Exposure

We identified all individuals who had filled prescriptions for quetiapine between January 1, 2003 and December 31, 2017 in the Danish National Prescription Register. The date of their first quetiapine dispensing was taken as the index date. From this population, we excluded individuals who: a) had filled prescriptions for the comparator or other antipsychotics within 365 days before the index date; b) had filled prescriptions for the comparator on the index date; c) had filled prescriptions for quetiapine in tablet strengths >50 mg on the index date; d) had a history of myocardial infarction, stroke, cancer, or severe mental illness (for definitions, see supplementary information); e) had not been continuously residing in Denmark for 365 days before the index date; and f) were <18 or >85 years old on the index date. Individuals in the comparator group were required to fulfill the same conditions.

Outcome measures

The main outcome was the occurrence of major adverse cardiovascular events, defined by first record of either non-fatal myocardial infarction or non-fatal ischemic stroke, or by death from cardiovascular causes. Secondary outcomes were each of the above cardiovascular events. The ICD codes used for outcome-defining events are provided in the supplementary information.

Propensity score

We estimated each individual's propensity to fill prescriptions for low-dose quetiapine using logistic regression, including age, sex, year of cohort entry, and the 100 most influential covariates, selected using a high-dimensional propensity score algorithm[26] assessing all prescription fills and hospital diagnoses within 365 days before the index date (see supplementary information). Covariate balance was assessed using standardized mean differences (SMD), with SMD ≤0.1 indicating sufficient balance.

Intention-to-treat analysis

In intention-to-treat analysis, the study population was restricted to individuals with ≥1 additional prescription within 180 days of the index date, to minimize exposure misclassification. Follow-up began at day 181 and lasted until individuals either experienced the outcome of interest, or died for non-cardiovascular reasons, or were censored. Reasons for censoring were: filling of prescriptions for the other study drug, filling of >1 prescription for other antipsychotics, filling of prescriptions for quetiapine in tablet strengths >50 mg, receiving a diagnosis of a severe mental disorder, emigration, ≥10 years of follow-up, or end of data availability, whichever came first.

To adjust for baseline confounding, we used fine stratification weights by trimming non-overlapping regions of the propensity score distribution and then constructing ten propensity score strata where we weighted Z-drug users (and SSRI users in the sensitivity analyses) according to the distribution of low-dose

quetiapine users. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox regression models adjusted by the fine stratification weights. The proportion of cases attributable to low-dose quetiapine use was calculated as (HR–1)/HR.

These analyses, as well as all the following ones, were conducted using Stata MP, release 16.1 (StataCorp, College Station, TX, USA).

As-treated analysis

To assess the relationship between continuous treatment and outcomes, we conducted an as-treated analysis where individuals were followed from the index date until they either experienced the outcome of interest, or died (from non-cardiovascular reasons), ended their first treatment episode, or were censored. Reasons for censoring were similar to those used in the intent-to-treat analysis, except that the maximum follow-up was confined to five years, as very few individuals remained on treatment beyond that point.

Treatment episodes were constructed by assigning a duration to each prescription corresponding to the number of tablets dispensed (assuming use of one tablet/day). To the duration of each prescription, we added a grace period of 120 days to account for irregular use. Gaps exceeding 120 days were considered as the end of the first treatment episode. These additional 120 days of observation were also added to the last prescription to capture events occurring shortly after (and potentially associated with) the treatment episode, and thus avoid immortal time bias[27].

To adjust for baseline confounding, we used inverse probability of treatment weights and inverse probability of censoring weights estimated from baseline covariates (included in the high-dimensional propensity score algorithm). The inverse probability of censoring weights was updated every 90 days and truncated at the 1st and 99th percentile. Pooled logistic regression was used with the product of inverse probability of treatment weights and inverse probability of censoring weights to estimate HRs, and 95% CIs were computed using robust variance estimators[28].

Subgroup and sensitivity analyses

To assess potential differences in risk between subgroups, we conducted analyses stratified on sex (male/female), age group (</≥65 years), history of ischemic heart disease (yes/no), and history of diabetes (yes/no). Furthermore, we conducted three sensitivity analyses: a) including any tablet strength of quetiapine in the exposure definition, to assess the potential difference in risk with dose; b) using SSRIs as an alternative comparator that targets individuals suffering from anxiety instead of insomnia; and c) excluding individuals with in-/outpatient contacts for major depression, which might increase the risk of cardiovascular events.

Case-control analysis

To investigate whether cumulative dose of quetiapine (as low-dose treatment) was associated with the outcomes, we additionally conducted a case-control analysis nested among quetiapine users.

For each case exposed to quetiapine, we identified the pool of quetiapine users of same sex and birth year who did not have the outcomes and randomly selected 20 such controls among them, or as many as were available if there were <20 controls. The controls were given an index date identical to their matched case. We estimated odds ratios (ORs) with 95% CIs for the association between cumulative quetiapine dose and major adverse cardiovascular events. The cumulative dose of quetiapine was assessed between first prescription and censoring (similar to the intent-to-treat analysis), and analyzed using predefined cumulative total dose strata (2,501-5,000, 5,001-10,000, 10,001-25,000, 25,001-50,000, >50,000 mg). Individuals with a cumulative dose of ≤2,500 mg were used as reference group for the analyses, as this dose corresponds to 100 tablets of 25 mg quetiapine (the smallest marketed package of quetiapine in Denmark). Trends in the association between outcomes and total cumulative quetiapine dose were tested using pooled logistic regression with dose strata as independent variable.

RESULTS

A total of 515,133 patients were included in the cohort (58% females; median age: 49 years, interquartile range, IQR: 36-63). Of these, 60,566 were users of low-dose quetiapine, and 454,567 of Z-drugs. Risk factors for cardiovascular disease and use of preventive medications did not differ significantly between the groups (see Table 1).

The intention-to-treat population (>1 prescription required) included 22,849 low-dose quetiapine users and 131,623 Z-drug users. The total follow-up was 890,198 person-years, with a median of 2.6 years (IQR: 1.2-4.7) for low-dose quetiapine users and 7.0 years (IQR: 3.2-9.5) for Z-drug users. In this population, 59% of low-dose quetiapine users and 55% of Z-drug users had ≥5 prescriptions (see also supplementary information).

In the as-treated population, the total follow-up was 330,334 person-years, with a median follow-up of 7.2 months (IQR: 7.2-11.8) for low-dose quetiapine users and 4.6 months (IQR: 4.3-5.3) for Z-drug users. In this population, 50% of low-dose quetiapine users and 29% of Z-drug users had ≥2 prescriptions (see also supplementary information).

In the intent-to-treat analysis, there were 877 major adverse cardiovascular events among low-dose quetiapine users and 11,464 among Z-drugs users. After adjusting for baseline covariates, the risk for major adverse cardiovascular events was significantly higher with use of low-dose quetiapine (adjusted HR, aHR=1.13, 95% CI: 1.02-1.24, p=0.014; attributable proportion of cases, APC=11%, 95% CI: 2-19%) (see Table 2).

In the as-treated analysis, after adjusting for baseline confound-

Table 1 Baseline characteristics of low-dose quetiapine and Z-drug users

	Intention-to-treat population			SMD		As-treated population			SMD	
	Low-dose quetiapine (N=22,849)	Z-drugs (N=131,623)	Total (N=154,472)	Before FSW	After FSW	Low-dose quetiapine (N=60,566)	Z-drugs (N=454,567)	Total (N=515,133)	Before IPTW	After IPTW
Sex										
Female, N (%)	12,387 (54)	76,244 (58)	88,631 (57)	0.1	<0.1	32,347 (53)	266,113 (59)	298,460 (58)	0.1	<0.1
Age, N (%)										
Median (IQR)	43 (29-59)	54 (42-68)	53 (40-67)	0.5	<0.1	40 (27-54)	50 (38-64)	49 (36-63)	0.4	0.2
18-44 years, N (%)	12,021 (53)	40,256 (31)	52,277 (34)	0.5	<0.1	35,518 (59)	177,099 (39)	212,617 (41)	0.4	0.1
45-64 years, N (%)	6,274 (27)	49,890 (38)	56,164 (36)	0.2	0.1	16,184 (27)	170,825 (38)	187,009 (36)	0.2	0.1
65-85 years, N (%)	4,554 (20)	41,477 (32)	46,031 (30)	0.3	<0.1	8,864 (15)	106,643 (23)	115,507 (22)	0.2	0.2
Year of cohort entry, N (%)										
2003-2005	681 (3)	40,683 (31)	41,364 (27)	0.8	0.1	1,306 (2)	124,303 (27)	125,609 (24)	0.8	0.2
2006-2008	2,193 (10)	32,334 (25)	34,527 (22)	0.4	<0.1	5,047 (8)	110,128 (24)	115,175 (22)	0.4	0.1
2009-2011	4,047 (18)	23,679 (18)	27,726 (18)	<0.1	<0.1	9,881 (16)	85,913 (19)	95,794 (19)	0.1	0.1
2012-2014	7,579 (33)	19,615 (15)	27,194 (18)	0.4	0.1	20,168 (33)	73,492 (16)	93,660 (18)	0.4	0.1
2015-2017	8,349 (37)	15,312 (12)	23,661 (15)	0.6	0.1	24,164 (40)	60,731 (13)	84,895 (16)	0.6	0.1
Comorbidities, N (%)										
Ischemic heart disease	958 (4)	7,629 (6)	8,587 (6)	0.1	<0.1	2,126 (4)	20,508 (5)	22,634 (4)	0.1	0.1
Heart failure	244 (1)	3,196 (2)	3,440 (2)	0.1	<0.1	565 (<1)	7,847 (2)	8,412 (2)	0.1	<0.1
Peripheral vascular disease	435 (2)	4,556 (3)	4,991 (3)	0.1	<0.1	1,025 (2)	11,605 (3)	12,630 (2)	0.1	<0.1
Hypertension	4,135 (18)	34,596 (26)	38,731 (25)	0.2	<0.1	9,297 (15)	94,343 (21)	103,640 (20)	0.1	0.1
COPD	2,859 (13)	18,304 (14)	21,163 (14)	<0.1	<0.1	7,102 (12)	53,355 (12)	60,457 (12)	<0.1	<0.1
Diabetes	1,326 (6)	8,808 (7)	10,134 (7)	<0.1	<0.1	3,213 (5)	24,475 (5)	27,688 (5)	<0.1	0.1
Alcohol-related disorders	6,621 (29)	14,293 (11)	20,914 (14)	0.5	0.1	17,956 (30)	54,648 (12)	72,604 (14)	0.4	0.1
Obesity	1,828 (8)	5,605 (4)	7,433 (5)	0.2	<0.1	4,901 (8)	18,711 (4)	23,612 (5)	0.2	<0.1
Major depression	4,155 (18)	3,764 (3)	7,919 (5)	0.5	0.1	10,278 (17)	10,795 (2)	21,073 (4)	0.5	<0.1
Recent use of medications, N (%)										
Acetylsalicylic acid	1,797 (8)	15,834 (12)	17,631 (11)	0.1	<0.1	3,660 (6)	40,661 (9)	44,321 (9)	0.1	0.1
Statins	2,464 (11)	18,517 (14)	20,981 (14)	0.1	<0.1	5,556 (9)	52,116 (11)	57,672 (11)	0.1	<0.1

SMD – standardized mean difference, FSW – fine stratification weighting, IPTW – inverse probability of treatment weighting, IQR – interquartile range, COPD – chronic obstructive pulmonary disease

ing, the risk of major adverse cardiovascular events was significantly higher with use of low-dose quetiapine (aHR=1.11, 95% CI: 1.00-1.24, p=0.046). With additional adjustment for informative censoring (using inverse probability of censoring weights), continuous use of low-dose quetiapine was significantly associated with major adverse cardiovascular events compared to continuous use of Z-drugs (aHR=1.52, 95% CI: 1.35-1.70, p<0.001; APC=34%, 95% CI: 26-41%) (see Table 2).

Analysis of individual major adverse cardiovascular events showed that the association was mainly driven by an increased risk of cardiovascular death (intent-to-treat analysis: aHR=1.26, 95% CI: 1.11-1.43, p<0.001; as-treated analysis: aHR=1.90, 95% CI: 1.64-2.19, p<0.001). Use of low-dose quetiapine was not associated with increased risk of non-fatal myocardial infarction in either intent-to-treat analysis (aHR=0.91, 95% CI: 0.73-1.14, p=0.42) or as-treated analysis (aHR=0.91, 95% CI: 0.69-1.21, p=0.53). An association between use of low-dose quetiapine and non-fatal ischemic stroke was only present in the as-treated analysis (aHR=1.37, 95% CI: 1.13-1.68, p=0.002) (see Table 2).

The cumulative incidence of major adverse cardiovascular events and secondary outcomes is shown in Figure 1. For major adverse cardiovascular events and cardiovascular death, the difference between groups became evident beyond 3-4 years of follow-up.

In subgroup analyses of the intent-to-treat population, use of low-dose quetiapine had a stronger association with major adverse cardiovascular events among females than males (aHR=1.28, 95% CI: 1.11-1.48 vs. 1.02, 95% CI: 0.90-1.16, p=0.02). Age ≥65 years at

Table 2 Risk of major adverse cardiovascular events and secondary outcomes with use of low-dose quetiapine (QUE) compared to use of Z-drugs (ZDR)

	N. patients QUE/ZDR	N. events QUE/ZDR	Follow-up QUE/ZDR	Hazard ratio (95% CI)	p
Major adverse cardiovascular events					
Intention-to-treat analysis (adjusted)	22,827/131,582	877/11,464	73/817	1.13 (1.02-1.24)	0.014
As-treated analysis (adjusted)	60,564/454,552	850/5,513	59/272	1.11 (1.00-1.24)	0.046
As-treated analysis (fully adjusted)	60,564/454,552	850/5,513	59/272	1.52 (1.35-1.70)	<0.001
Non-fatal myocardial infarction					
Intention-to-treat analysis (adjusted)	22,828/131,588	138/2,895	74/829	0.91 (0.73-1.14)	0.42
As-treated analysis (adjusted)	60,564/454,552	109/1,307	59/273	0.69 (0.52-0.90)	0.007
As-treated analysis (fully adjusted)	60,564/454,552	109/1,307	59/273	0.91 (0.69-1.21)	0.53
Non-fatal ischemic stroke					
Intention-to-treat analysis (adjusted)	22,827/131,586	267/4,378	74/825	0.98 (0.83-1.15)	0.81
As-treated analysis (adjusted)	60,564/454,552	256/1,920	59/273	1.01 (0.83-1.21)	0.95
As-treated analysis (fully adjusted)	60,564/454,552	256/1,920	59/273	1.37 (1.13-1.68)	0.002
Death from cardiovascular causes					
Intention-to-treat analysis (adjusted)	22,828/131,593	565/6,262	74/837	1.26 (1.11-1.43)	<0.001
As-treated analysis (adjusted)	60,564/454,552	558/2,903	59/274	1.37 (1.20-1.56)	<0.001
As-treated analysis (fully adjusted)	60,564/454,552	558/2,903	59/274	1.90 (1.64-2.19)	<0.001

Follow-up in 1,000 person-years. The intention-to-treat analysis is adjusted for baseline confounding by fine stratification weights. The as-treated analysis is adjusted for baseline confounding by inverse probability of treatment weights, or fully adjusted by inverse probability of treatment weights and informative censoring by inverse probability of censoring weights.

initiation of low-dose quetiapine treatment was also more strongly associated with major adverse cardiovascular events (aHR=1.24, 95% CI: 1.10-1.40) vs. initiation at age <65 years (aHR=0.88, 95% CI: 0.75-1.03, p<0.001). A history of ischemic heart disease or diabetes was not significantly associated with an increased risk of major adverse cardiovascular events (p=0.67 and p=0.42, respectively) (see Table 3). None of these subgroups was significantly related to an increased risk of non-fatal myocardial infarction or ischemic stroke, when comparing low-dose quetiapine with Z-drug use. Female sex and age ≥65 years at treatment initiation were associated with increased risk of cardiovascular death, when comparing low-dose quetiapine with Z-drug use (p=0.0086 and p<0.001, respectively) (see supplementary information).

In sensitivity analyses of the intent-to-treat population, low-dose quetiapine use compared with use of SSRIs was associated with an increased risk of major adverse cardiovascular events (aHR=1.42, p<0.001), non-fatal ischemic stroke (aHR=1.27, p= 0.0028) and cardiovascular death (aHR=1.72, p<0.001), but not of non-fatal myocardial infarction (aHR=0.86, p=0.23) (see also supplementary information).

Including all tablet strengths of quetiapine in the exposure definition did not result in increased risk of either major adverse cardiovascular events (aHR: 1.00 vs. 1.13) or cardiovascular death (aHR: 1.07 vs. 1.26). The same was observed when excluding individuals with in-/outpatient contacts for major depression (aHR: 1.27 vs. 1.13 for major cardiovascular events; 1.52 vs. 1.26 for cardiovascular death) (see also supplementary information).

In the case-control analysis, increasing cumulative doses of quetiapine (as low-dose treatment) was not significantly associated with increased risk of major adverse cardiovascular events (p=0.21), while it was associated with a significantly increased risk of cardiovascular death with cumulative doses ≥50,000 mg (OR=1.32, 95% CI: 1.09-1.60, p=0.014) (see supplementary information).

DISCUSSION

In this large cohort study, we found an increased risk of major adverse cardiovascular events with low-dose quetiapine, one of the most frequent uses of any individual antipsychotic medication, compared to use of Z-drugs. This increased risk was mainly driven by an increased risk of cardiovascular death, while we only found an increased risk of non-fatal ischemic stroke with continuous treatment, and no increase in the risk of non-fatal myocardial infarction. The association between use of low-dose quetiapine and major adverse cardiovascular events or cardiovascular death was robust, as it was confirmed when analyzing continuous low-dose quetiapine treatment and when using SSRIs as an alternative comparator.

The increased risk (in intent-to-treat analysis) of major adverse cardiovascular events and cardiovascular death, but not of non-

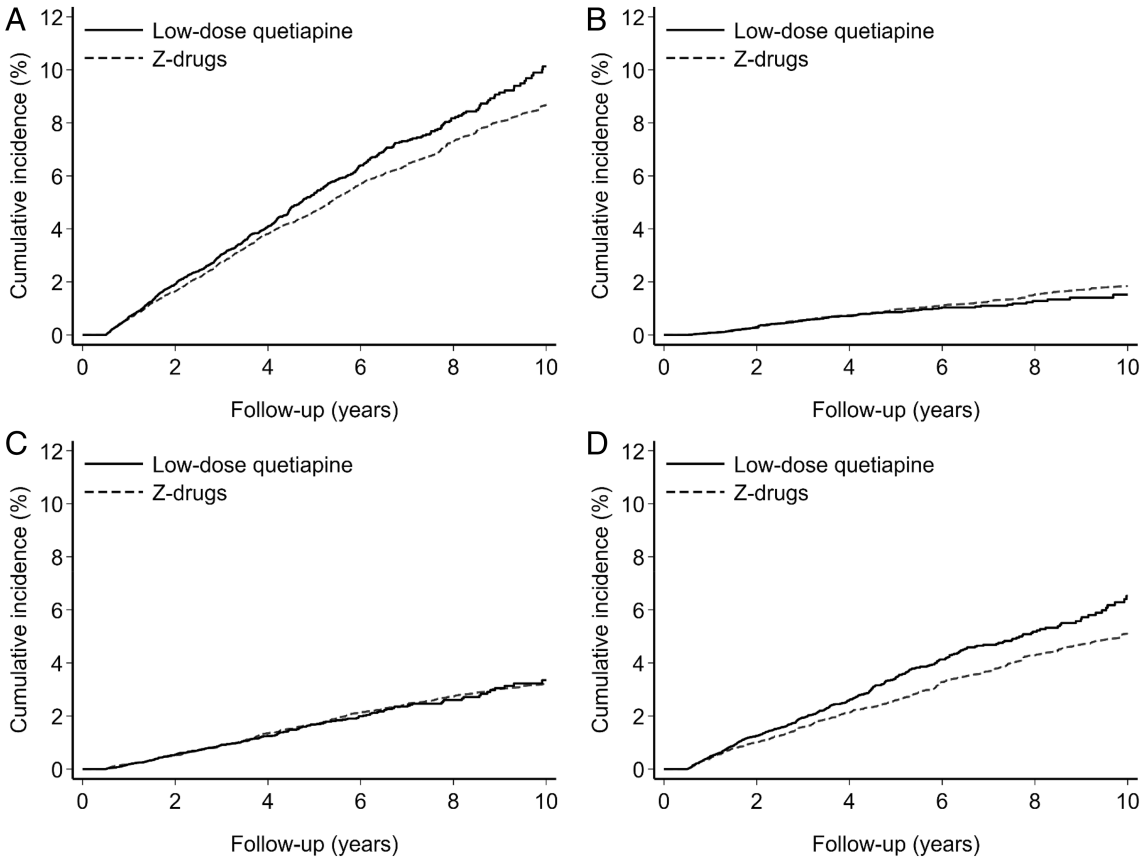

Figure 1 Cumulative incidence of major adverse cardiovascular events with use of low-dose quetiapine compared to use of Z-drugs (intention-to-treat analysis using fine stratification weights). A: major adverse cardiovascular events, B: non-fatal myocardial infarction, C: non-fatal ischemic stroke, D: death from cardiovascular causes

fatal myocardial infarction or ischemic stroke, might seem surprising, given quetiapine's association with dyslipidemia[16]. Actually, the number of non-fatal myocardial infarction or ischemic stroke events during the follow-up period was low in each group. To ensure internal validity, we used strict censoring criteria in both intent-to-treat and as-treated analyses (e.g., filling >1 prescription for other antipsychotics), which might have limited the follow-up duration to capture a potential difference between groups in the number of cardiovascular events. On the other hand, cardiovascular death was assessed based on information from death certificates, which includes both the primary cause of death and any underlying causes of death. Additionally, the outcome definition incorporated a wide selection of cardiovascular diagnoses. Therefore, the increased risk of cardiovascular death might reflect a higher degree of cardiovascular morbidity (e.g., from ischemic heart disease or heart failure) among low-dose quetiapine initiators, potentially caused by dyslipidemia, than is captured by the relatively well-defined conditions of myocardial infarction and ischemic stroke.

The absence of a clear relationship between the risk of cardiovascular outcomes and cumulative quetiapine dose can have different interpretations. First, the observed risk of cardiovascular outcomes might be due to residual confounding by risk factors associated with off-label quetiapine use (e.g., mental illness, smoking, unhealthy lifestyle). However, we adjusted analyses for 100 potentially relevant confounders, making this less likely. Second, even the use of low cumulative doses adopted as reference category in the case-control analysis (≤2,500 mg) might be sufficient to increase the risk of major adverse cardiovascular events, either due to increased lipid levels or other adverse cardiometabolic mechanisms. The latter interpretation is supported by data from randomized controlled trials, where even short-term quetiapine exposure significantly increased lipid levels[16].

Z-drugs users, especially long-term users, might have more physical comorbidities than the average low-dose quetiapine user. Therefore, we conducted a sensitivity analysis with SSRI users as the comparator group. SSRI users were not chosen as the primary comparator, as this drug class can also cause weight gain and possibly increase cardiovascular morbidity/mortality[10], and simultaneously has platelet-inhibiting properties, which might result in a decreased risk of thrombotic events[29], although this has not been demonstrated with certainty[30]. The increased risk of major adverse cardiovascular events, non-fatal ischemic stroke, and cardiovascular death in low-dose quetiapine users vs. SSRI users further supports the results of the main analyses. The small differences between results from the main and sensitivity analy-

Table 3 Subgroup analysis of major adverse cardiovascular events with use of low-dose quetiapine compared to use of Z-drugs in the intention-to-treat population

	Low-dose quetiapine			Z-drugs				
	N. patients (%)	N. events	Rate (per 1,000 person-years)	N. patients (%)	N. events	Rate (per 1,000 person-years)	Adjusted hazard ratio (95% CI)	p
Sex								
Female, N (%)	12,375 (54)	424	10.3	76,226 (58)	5,509	11.3	1.28 (1.11-1.48)	
Male, N (%)	10,452 (46)	453	13.9	55,356 (42)	5,955	18.2	1.02 (0.90-1.16)	0.02
Age group, N (%)								
<65 years	18,276 (80)	268	4.3	90,130 (68)	3,629	6.1	0.88 (0.75-1.03)	
≥65 years	4,551 (20)	609	51.6	41,452 (329)	7,835	34.6	1.24 (1.10-1.40)	<0.001
History of ischemic heart disease, N (%)								
No	21,870 (96)	743	10.5	123,959 (94)	9,745	12.6	1.13 (1.02-1.25)	
Yes	957 (4)	134	51.5	7,623 (6)	1,719	42.4	1.19 (0.93-1.53)	0.67
History of diabetes, N (%)								
No	21,504 (94)	760	10.9	122,781 (93)	9,773	12.7	1.16 (1.05-1.29)	
Yes	1,323 (6)	117	31.5	8,801 (7)	1,691	37.6	1.04 (0.81-1.34)	0.42
Overall estimate	22,827 (100)	877	11.9	131,582 (100)	11,464	14.0	1.13 (1.02-1.24)	

The hazard ratio is adjusted for baseline confounding by fine stratification weights

ses incorporating all tablet strengths of quetiapine (25-400 mg) might suggest that the association between quetiapine dose and cardiovascular outcomes is largely independent of daily dose.

Despite the common and increasing use of low-dose quetiapine as an anxiolytic or hypnotic[3-6,31], no study has investigated its long-term cardiovascular safety in a nationwide setting with long follow-up as the present analysis. Cardiometabolic risk factors with use of low-dose quetiapine have been investigated in smaller cohort studies[32,33] and in one nationwide database study[34], but the evidence of cardiovascular risk/safety has been insufficient[35,36]. The only nationwide database study[34] found increased risk of cardiovascular death with 6-12 months of cumulative exposure, but pooled low-dose quetiapine with low-dose olanzapine, providing no specific evidence for the risks associated with quetiapine.

The present analysis has several strengths. Besides the large number of individuals and the possibility of long-term follow-up in nationwide registers, we applied several design features to further strengthen our confidence in the findings. First, we adopted a new-user, active-comparator design to limit the impact of prior exposure and confounding from mental illness/distress. Second, we attempted to minimize the impact of additional confounding by using a high-dimensional propensity score drawing on all prescriptions and hospital contacts for the population. Third, we used strict censoring criteria to investigate the risk with low-dose quetiapine specifically, and adjusted for informative censoring in as-treated analysis. Lastly, the positive predictive value in the registers is considered high and well-defined in time[23].

Limitations with the present study must also be acknowledged. First, no ideal comparator to off-label, low-dose quetiapine exists, as other antipsychotics have at least some risk of cardiometabolic adverse events and are not used for the same indication as quetiapine, especially outside psychiatry. Z-drugs were chosen as the primary comparator, as they are a common alternative to low-dose quetiapine use as hypnotics[20]. However, Z-drug users are not an ideal comparator, likely having more comorbidities (especially in long-term users) than the average low-dose quetiapine user. As this difference would bias analyses towards less difference between groups, SSRIs, an alternative to low-dose quetiapine use as an anxiolytic, were included as comparator in sensitivity analyses.

Second, long-term follow-up is needed to sufficiently assess cardiovascular safety, but longer follow-up increases the potential influence of other factors on outcomes. Confining the intent-to-treat analysis to individuals with ≥1 additional prescription within 180 days of the first quetiapine prescription, and limiting the maximum follow-up to 10 years were done to minimize the impact of other factors on the observed risk. However, this analytic choice may have led to underestimation of the real number of cardiovascular events in this cohort attributable to low-dose quetiapine use. Third, despite adjusting the analyses for 100 potentially relevant confounders, residual confounding cannot be excluded. However, results were generally consistent and robust across multiple approaches. Finally, since this is a non-randomized database study, associations cannot prove causation.

In conclusion, our findings indicate that low-dose quetiapine use is associated with increased risk of major adverse cardiovascular events, especially cardiovascular death. The risk increases with continuous treatment and in vulnerable populations, including females and the elderly. On the basis of these findings, we suggest that off-label low-dose quetiapine use for sedative or hypnotic purposes should be discouraged.

ACKNOWLEDGEMENTS

This study was supported by the Research Fund of the Mental Health Services in the Region of Southern Denmark (grant no. A2957). The funding source had no role in the design or conduct of the study, data analysis, interpretation, writing of the paper, or the decision to submit the manuscript. The authors want to thank L.C. Lund (University of Southern Denmark) for valuable comments on study design. C.U. Correll and J. Hallas are joint senior authors of the paper. Supplementary information on this study can be found at https://osf.io/658vq/.

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DOI:10.1002/wps.21010

Attention-deficit/hyperactivity disorder as a risk factor for cardiovascular diseases: a nationwide population-based cohort study

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Accumulating evidence suggests a higher risk for cardiovascular diseases among individuals with mental disorders, but very little is known about the risk for overall and specific groups of cardiovascular diseases in people with attention-deficit/hyperactivity disorder (ADHD). To fill this knowledge gap, we investigated the prospective associations between ADHD and a wide range of cardiovascular diseases in adults. In a nationwide population-based cohort study, we identified 5,389,519 adults born between 1941 and 1983, without pre-existing cardiovascular diseases, from Swedish registers. The study period was from January 1, 2001 to December 31, 2013. Incident cardiovascular disease events were identified according to ICD codes. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression model, with ADHD as a time-varying exposure. After an average 11.80 years of follow-up, 38.05% of individuals with ADHD versus 23.57% of those without ADHD had at least one diagnosis of cardiovascular disease (p<0.0001). ADHD was significantly associated with increased risk of any cardiovascular disease (HR=2.05, 95% CI: 1.98-2.13) after adjusting for sex and year of birth. Further adjustments for education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking attenuated the association, which however remained significant (HR=1.84, 95% CI: 1.77-1.91). Further adjustment for psychiatric comorbidities attenuated but could not fully explain the association (HR=1.65, 95% CI: 1.59-1.71). The strongest associations were found for cardiac arrest (HR=2.28, 95% CI: 1.81-2.87), hemorrhagic stroke (HR=2.16, 95% CI: 1.68-2.77), and peripheral vascular disease/arteriosclerosis (HR=2.05, 95% CI: 1.76-2.38). Stronger associations were observed in males and younger adults, while comparable associations were found among individuals with or without psychotropic medications and family history of cardiovascular diseases. These data suggest that ADHD is an independent risk factor for a wide range of cardiovascular diseases. They highlight the importance of carefully monitoring cardiovascular health and developing age-appropriate and individualized strategies to reduce the cardiovascular risk in individuals with ADHD.

Key words: Attention-deficit/hyperactivity disorder, cardiovascular diseases, cardiac arrest, hemorrhagic stroke, peripheral vascular disease, arteriosclerosis, psychotropic medications, psychiatric comorbidities

(World Psychiatry 2022;21:452–459)

Attention-deficit/hyperactivity disorder (ADHD), characterized by pervasive and impairing inattention and/or hyperactivity-impulsivity, is one of the most common neurodevelopmental disorders, with a global prevalence of 2-7% in children and 2.5% in adults[1-3]. The disorder is often comorbid with a number of psychiatric (e.g., anxiety disorders and depression[4]) and physical (e.g., obesity[5] and asthma[6]) conditions.

Prospective studies have previously demonstrated that several psychiatric conditions (e.g., depression[7,8], schizophrenia[9], bipolar disorder[10], and anxiety disorders[11]) as well as neurodevelopmental disorders (e.g., autism[12,13], intellectual disabilities[12], and conduct disorder[12]) are associated with a higher risk for cardiovascular diseases, the leading cause of mortality worldwide[14]. The mechanisms linking psychiatric illness to cardiovascular diseases are complex, but risky health behaviours (e.g., smoking, drinking alcohol, substance abuse, and sedentary lifestyles)[15] and prolonged use of psychotropic medications[16] have been proposed as potential contributors to the risk.

Little is known about the risk for overall and specific groups of cardiovascular diseases in individuals with ADHD. In these individuals, such diseases have mainly been studied as potential adverse effects of pharmacological treatment[17,18], as ADHD medications have been reported to be associated with elevated blood pressure and heart rate, which may increase the risk for severe cardiovascular events (e.g., stroke, myocardial infarction)[19].

Only a few studies have explored the association between ADHD and cardiovascular diseases. A small Dutch study[20] with 231 older adults found no overall association, although elevated levels of ADHD symptoms were associated with increased risk for cardiovascular diseases. A recent Swedish register-based cohort study[21] with 4,288,451 sibling pairs and 1,841,303 family clusters (age: 18-81 years) showed that adults with ADHD were at increased risk for a wide range of physical health conditions, including cardiovascular diseases.

However, in these few previous studies, only broad measures of cardiovascular diseases were used[20,21]. Thus, there are no data about the risk for specific groups of such diseases in ADHD. This is important to inform prevention and treatment strategies, which may vary substantially depending on which specific cardiovascular diseases are most strongly associated with this mental disorder. Furthermore, no previous study has explored the role of psychiatric comorbidities and the use of psychotropic medications in the development of cardiovascular diseases in ADHD. This is an important limitation, as adults with ADHD are frequently treated pharmacologically not only for that condition but also for other concomitant psychiatric disorders (e.g., mood disorders

and substance use disorders), which in turn may influence the risk for cardiovascular diseases[16].

In addition, the role of well-established risk factors for cardiovascular diseases, such as low educational attainment[22], smoking[23], sleep problems[24], metabolic conditions (e.g., obesity[25], type 2 diabetes mellitus[26], and dyslipidemia[27]), as well as cardiovascular family history[24], has never been considered in exploring the association between ADHD and cardiovascular diseases. These modifiable or non-modifiable risk factors have the potential to be included in screening tools to identify people who are at increased risk for cardivascular diseases[28].

Finally, although it is well-established that the prevalence rates of ADHD and cardiovascular diseases are higher in males than in females[29,30], and that the core symptoms of ADHD often decline with increasing age[31], while the incidence of cardiovascular diseases increases substantially with advancing age[32], it is currently unknown if these patterns translate into sex and age differences in the associations of ADHD with cardiovascular diseases. A better understanding of such sex- and age-specific associations is needed for risk stratification and individualized treatment recommendations in individuals with ADHD.

In this register-based cohort study, we aimed to fill these knowledge gaps by investigating the prospective associations between ADHD and the risk of developing a broad range of cardiovascular diseases in adults. We also aimed to examine the extent to which any observed associations could be explained by common psychiatric comorbidities, well-established risk factors for cardiovascular diseases (e.g., low education level, smoking, sleep disorders, and metabolic conditions), use of psychotropic medications, and cardiovascular family history. An additional exploratory aim was to assess the potential impact of sex and age.

METHODS

This study was approved by the regional ethical review board in Stockholm, Sweden (reference number: 2013/862-31/5). The informed consent of the participants is not required for pseudoanonymized register-based research according to Swedish law.

Study cohort and data sources

The study cohort included all individuals born in Sweden between 1941 and 1983, who were alive and residing in Sweden in 2001 (N=5,448,328), the year since which outpatient data became available. We excluded individuals who had a history of any cardiovascular disease before or at baseline, and those who died or emigrated before being diagnosed with ADHD, leaving 5,389,519 individuals aged 18-60 years at baseline.

We followed these individuals from January 1, 2001 until their first diagnosis of any cardiovascular disease, death, emigration, or December 31, 2013 (whichever occurred first), with the oldest cohort member censored at 73 years of age.

Data were obtained by linking multiple Swedish registries with the unique personal identification number assigned to every individual registered in Sweden. The Total Population Register (TPR)[33] includes all individuals in Sweden born since 1932, who were alive in 1963 and later. TPR also contains information on all migrations in or out of Sweden since 1969. The Medical Birth Register (MBR)[34] covers more than 99% of births in Sweden since 1973. The National Patient Register (NPR)[35] contains data on inpatient care since 1973 and outpatient care since 2001. The Prescribed Drug Register (PDR)[36] includes detailed information on all dispensed drugs in Sweden, coded according to the Anatomical Therapeutic Chemical (ATC) classification, since July 1, 2005. The Longitudinal Integration Database for Health Insurance and Labor Studies (LISA)[37] covers the entire Swedish population aged 16 or older since 1990. The Multi-Generation Register (MGR)[38] provides information on biological relationships for all residents in Sweden since 1932. The Cause of Death Register[39] contains information on all registered deaths since 1961.

Measures

ADHD

Individuals with ADHD were identified as those who had received their first ADHD diagnosis (ICD-9 or ICD-10: 314/F90) from the NPR at the age of 3 years or older, or their first prescription of an ADHD medication (ATC codes: N06BA01, N06BA02, N06BA04, N06BA12, N06BA09) from the PDR, or both, before or during the follow-up period.

This approach to identify individuals with ADHD has been validated and is widely used in Swedish register-based studies[21,40,41]. In a sensitivity analysis, we only used diagnoses of ADHD from NPR for case identification, to reflect clinically diagnosed cases.

Cardiovascular diseases

Consistent with previous studies[42,43], incident cardiovascular disease events were defined as the first diagnosis of cardiovascular disease from NPR (including any cardiovascular disease and specific diseases: ischemic heart disease, cerebrovascular disease, venous thrombo-embolism, hypertensive diseases, heart failure, arrhythmias, cardiac arrest, and peripheral vascular disease/arteriosclerosis), or death from cardiovascular disease obtained from the Cause of Death Register (see also supplementary information).

Covariates

We collected information on year of birth, sex, and country of birth (Sweden, other Nordic country, other) from TPR, and on highest educational level – primary or lower secondary, upper secondary, post-secondary, post-graduate, unknown – from LISA as a proxy of socioeconomic status.

Type 2 diabetes mellitus, obesity, dyslipidemia, sleep disorders, heavy smoking (including tobacco abuse and nicotine dependence) and psychiatric comorbidities (including anxiety disorders, autism spectrum disorder, bipolar disorder, conduct disorder, depressive disorder, eating disorders, intellectual disability, personality disorders, schizophrenia, and substance use disorders) diagnosed before the diagnosis of cardiovascular diseases were identified from NPR (see also supplementary information).

Statistical analysis

Main analyses

Cox proportional hazard regression model was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) expressing the rate/risk of cardiovascular diseases in individuals with ADHD, compared with individuals without ADHD, taking attained age as the underlying time scale. ADHD was modelled as a time-varying exposure, that is, individuals were assigned to the unexposed group before the diagnosis of ADHD, and were assigned to the exposed group from the first diagnosis of ADHD or medication prescription for this disorder to the end of follow-up.

The analysis was first conducted for "any cardiovascular disease" as an outcome, and then separately for six major categories (ischemic heart disease, cerebrovascular disease, venous thrombo-embolism, hypertensive diseases, heart failure, and arrhythmias) and 17 individual cardiovascular diseases (acute coronary syndrome, ACS; chronic coronary syndrome without ACS; subarachnoidal bleeding, hemorrhagic stroke, ischemic stroke, other cerebrovascular disease, deep vein thrombosis, pulmonary emboli, essential hypertension, other hypertensive disease, heart failure, ischemic cardiomyopathy, other cardiomyopathy, bradyarrhythmias, takyarrhythmias, cardiac arrest, peripheral vascular disease/arteriosclerosis).

In addition to the underlying attained age, we adjusted for year of birth and sex in model 1. Model 2 further adjusted for education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems, and heavy smoking. We further adjusted for psychiatric comorbidities in model 3. Next, we conducted stratified analyses for "any cardiovascular disease" by sex and age bands (18-30, 31-40, 41-50, 51-60 and 61-73 years) for models 1-3.

The proportionality of hazards over underlying time scale was assessed using a Schoenfeld residuals-based test. There was no evidence of violation of the assumption.

Cumulative incidence of any cardiovascular disease among individuals with or without ADHD was estimated using flexible parametric models that adjusted for attained age, year of birth and sex, and were visualized by standardized survival curves[44]. Cumulative incidence of any cardiovascular disease for each sex (adjusted for year of birth) and age band (adjusted for sex and year of birth) was also estimated.

To further explore the specific contribution of each psychiatric comorbidity to the association between ADHD and any cardiovascular disease, given that the magnitude of their associated cardiovascular disease risk is known to vary[12], models 1 and 2 were repeated by comparing individuals without ADHD to individuals with ADHD only (without any psychiatric comorbidities), and those with ADHD plus each specific psychiatric comorbidity.

Sensitivity analyses

First, we only used the diagnosis from NPR, without information on ADHD medications, to identify individuals with ADHD. Second, because treatment with stimulants (ATC codes: N06BA01, N06BA02, N06BA04, N06BA12), antipsychotics (ATC code: N05A), anxiolytics, hypnotics and sedatives (ATC codes: N05B, N05C), and antidepressants (ATC code: N06A) are known to be associated with cardiovascular diseases[16,45], we excluded individuals with ADHD and ever treated with stimulants or other psychotropic medications during the follow-up period, to rule out the potential impact of medication treatment on the studied associations.

Third, to control for the familial susceptibility to cardiovascular diseases, we excluded those with family history of these diseases, which was defined as any cardiovascular event among any first-degree relative (biological parents and full siblings). Finally, we used ADHD as time-invariant exposure (i.e., individuals with the diagnosis of ADHD were considered as exposed from the baseline to the end of the follow-up, regardless of the timing of the ADHD diagnosis) to further test the robustness of the results.

Data management was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). Data analyses were conducted with R, version 4.0.5 (R Foundation for Statistical Computing) and Stata (version 15.0; Stata Corp LP, College Station, TX).

RESULTS

Cohort description

We followed 5,389,519 individuals for a total of 64,084,464 person-years. Among these, 2,750,621 (51.04%) were males and 2,638,898 (48.96%) were females, with a mean age at study entry of 38.44±12.32 years. A total of 37,027 (0.68%) individuals (55.30% male and 44.70% female) had a diagnosis of ADHD or an ADHD medication prescription (see Table 1).

Individuals with ADHD were more likely to have primary or lower secondary as the highest educational attainment (25.87% vs. 14.79%, p<0.0001). Moreover, they were more likely to be diagnosed with obesity (6.15% vs. 2.16%, p<0.0001), sleep problems (11.20% vs. 2.64%, p<0.0001), heavy smoking (2.82% vs. 0.93%, p<0.0001), and all types of psychiatric comorbidities (p<0.0001), compared to people without ADHD.

The overall mean duration of follow-up was 11.80±2.85 years. During this period, 746,572 individuals were newly diagnosed with cardiovascular diseases. The overall incidence rate of these

Table 1 Baseline characteristics of individuals with and without attention-deficit/hyperactivity disorder (ADHD)

	Total (N=5,389,519)	With ADHD (N=37,027)	Without ADHD (N=5,352,492)
Age (years, mean±SD)	38.44±12.32	30.34±9.25	38.49±12.32
Year of birth (%)			
1941-1950	22.40	2.93	22.54
1951-1960	21.63	12.24	21.70
1961-1971	24.50	28.89	24.47
1977-1983	31.46	55.94	31.29
Sex (%)			
Male	51.04	55.30	51.01
Female	48.96	44.70	48.99
Country of birth (%)			
Sweden	78.94	89.64	78.86
Denmark, Finland, Norway or Iceland	3.69	2.34	3.70
Other	17.37	8.01	17.44
Educational attainment (%)			
Primary or lower secondary	14.87	25.87*	14.79
Upper secondary	41.68	47.69	41.64
Post-secondary	33.39	21.82	33.47
Post-graduate	1.21	0.43	1.22
Unknown	8.85	4.19	8.88
Well-established risk factors for CVD (%)			
Type 2 diabetes	2.93	2.62	2.93
Obesity	2.19	6.15*	2.16
Dyslipidemia	2.04	1.15*	2.04
Sleep problems	2.69	11.20*	2.64
Heavy smoking	0.94	2.82*	0.93
Psychiatric comorbidities (%)			
Anxiety disorders	3.81	41.58*	3.54
Autism spectrum disorder	0.25	11.14*	0.17
Bipolar disorder	0.84	14.05*	0.75
Conduct disorder	0.04	1.22*	0.03
Depressive disorder	4.96	43.15*	4.69
Eating disorders	0.22	2.79*	0.20
Intellectual disability	0.38	3.29*	0.36
Personality disorders	1.23	21.56*	1.09
Schizophrenia	0.55	2.39*	0.54
Substance use disorders	4.09	37.80*	3.85

*Significantly higher in individuals with vs. without ADHD, p<0.0001

diseases within the study period was 1.65 per 100 person-years; it was 1.79% among individuals with ADHD and 1.16% among those without ADHD (p<0.0001).

Main analyses

At the end of the follow-up, the cumulative incidence of any cardiovascular disease was 38.05% (95% CI: 34.87%-41.52%) for individuals with ADHD and 23.57% (95% CI: 23.47%-23.67%) for those without ADHD (p<0.0001) (see also supplementary information).

As shown in Figure 1, adults with ADHD had a more than two-fold increased risk of any cardiovascular disease (HR=2.05, 95% CI: 1.98-2.13), compared with those without ADHD, after adjusting for sex and year of birth (model 1). The association attenuated, but remained significant, when adjusted for education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking in model 2 (HR=1.84, 95% CI: 1.77-1.91). Further adjustments for psychiatric comorbidities (model 3) attenuated but did not fully explain the association (HR=1.65, 95% CI: 1.59-1.71).

Significant associations were observed for all specific cardiovascular diseases across all adjusted models in individuals with ADHD compared with those without ADHD. The highest HRs were found for cardiac arrest (HR=2.28, 95% CI: 1.81-2.87), hemorrhagic stroke (HR=2.16, 95% CI: 1.68-2.77) and peripheral vascular disease/arteriosclerosis (HR=2.05, 95% CI: 1.76-2.38) in model 2. When further adjusting for psychiatric comorbidities, most of the relative risks (20 out of 22 specific cardiovascular diseases) were slightly attenuated but remained statistically significant.

Subgroup analyses

The associations between ADHD and cardiovascular diseases were stronger across all levels of adjustments in males compared to females (HR=1.70, 95% CI: 1.62-1.79 and HR=1.58, 95% CI=1.49-1.68, respectively, in model 3, p<0.001) (see Table 2).

When stratified by age bands, the highest adjusted HR was observed in the youngest adults (18-30 years: HR=2.49, 95% CI: 2.17-2.87, in model 3), while the lowest association was found in the oldest adults (61-73 years: HR=1.22, 95% CI: 1.08-1.37, in model 3, p<0.001) (see Table 2). At the end of the follow-up, the prevalence of cardiovascular diseases was 5.89% among the youngest adults (18-30 years) with ADHD, compared to 2.87% in the non-ADHD group (p<0.0001), while it was 94.26% among the oldest adults (61-73 years) with ADHD, compared to 73.55% for the non-ADHD group (p<0.0001) (see also supplementary information).

Using individuals without ADHD as a reference group, we found that the relative risk of cardiovascular diseases was slightly higher among individuals with ADHD plus any psychiatric comorbidity (HR=1.87, 95% CI=1.79-1.95), compared with ADHD only (HR=1.72, 95% CI=1.59-1.86) (model 2). Specifically, an ad-

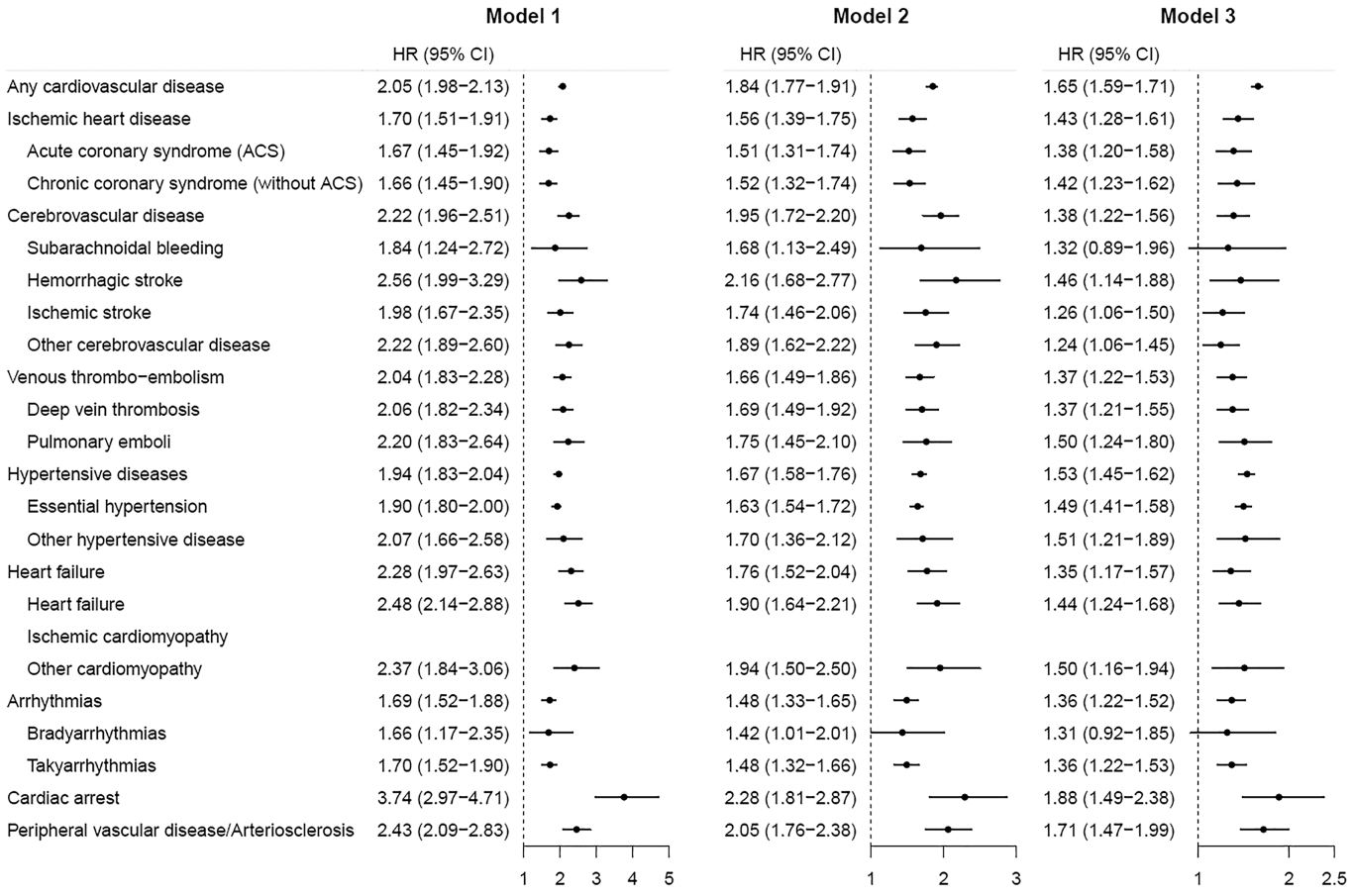

Figure 1 Hazard ratio (HR) with 95% CI of developing different types of cardiovascular diseases among adults with attention-deficit/hyperactivity disorder (ADHD), compared with those without ADHD. Model 1: adjusted for sex and year of birth; model 2: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking; model 3: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems, heavy smoking and psychiatric comorbidities.

Table 2 Association between attention-deficit/hyperactivity disorder (ADHD) and cardiovascular diseases as hazard ratios (HRs) with 95% CI adjusted for covariates

	Model 1	Model 2	Model 3
Overall	2.05 (1.98-2.13)	1.84 (1.77-1.91)	1.65 (1.59-1.71)
Sex			
Male	2.10 (2.00-2.20)	1.89 (1.80-1.98)	1.70 (1.62-1.79)
Female	2.00 (1.88-2.13)	1.76 (1.65-1.87)	1.58 (1.49-1.68)
Age (years)			
18-30	2.78 (2.42-3.19)	2.43 (2.12-2.79)	2.49 (2.17-2.87)
31-40	2.74 (2.53-2.96)	2.36 (2.18-2.55)	2.14 (1.97-2.32)
41-50	2.32 (2.18-2.47)	2.05 (1.93-2.19)	1.82 (1.71-1.94)
51-60	1.67 (1.54-1.80)	1.54 (1.43-1.66)	1.43 (1.32-1.54)
61-73	1.50 (1.33-1.69)	1.33 (1.18-1.50)	1.22 (1.08-1.37)

Model 1: adjusted for sex and year of birth; model 2: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking; model 3: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems, heavy smoking and psychiatric comorbidities

ditional increase in the risk of cardiovascular diseases was found among those with comorbid depressive disorder, personality disorders, anxiety disorders, substance use disorders and eating disorders, compared with ADHD only. The strongest associations were found for eating disorders (HR=2.21, 95% CI: 1.72-2.85) and substance use disorders (HR=2.20, 95% CI: 2.09-2.33) (model 2) (see Table 3).

Sensitivity analyses

Results from sensitivity analyses are presented in Table 4. When ADHD was only defined by diagnosis from the NPR, the cardiovascular risk was similar to that of the main analysis, but with a stronger association (HR=1.76, 95% CI=1.68-1.84 in model 3).

The estimates were similar when excluding individuals with ADHD diagnosis and treated with stimulants (HR=1.77, 95% CI: 1.69-1.85 in model 3) or other psychiatric medications (including antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants) (HR=1.83, 95% CI:1.74-1.91 in model 3).

When restricting our main analyses to individuals without fam-

Table 3 Psychiatric comorbidities and risk of cardiovascular diseases among individuals with attention-deficit/hyperactivity disorder (ADHD) as hazard ratios (HRs) with 95% CI adjusted for covariates

	Model 1	Model 2
No ADHD	1.00 (reference)	1.00 (reference)
ADHD only	1.82 (1.68-1.97)	1.72 (1.59-1.86)
ADHD plus any comorbidity	2.13 (2.04-2.22)	1.87 (1.79-1.95)
ADHD plus anxiety disorders	2.22 (2.09-2.36)	1.92 (1.81-2.04)
ADHD plus autism spectrum disorder	1.55 (1.36-1.77)	1.34 (1.17-1.53)
ADHD plus bipolar disorder	1.87 (1.69-2.07)	1.64 (1.48-1.81)
ADHD plus conduct disorder	2.79 (2.00-3.91)	2.39 (1.71-3.35)
ADHD plus depressive disorder	2.05 (1.93-2.17)	1.77 (1.67-1.88)
ADHD plus eating disorders	2.75 (2.14-3.54)	2.21 (1.72-2.85)
ADHD plus intellectual disability	2.21 (1.79-2.72)	1.67 (1.36-2.06)
ADHD plus personality disorders	2.25 (2.08-2.43)	1.92 (1.77-2.07)
ADHD plus schizophrenia	1.87 (1.49-2.35)	1.59 (1.27-2.00)
ADHD plus substance use disorders	2.53 (2.40-2.67)	2.20 (2.09-2.33)

Model 1: adjusted for sex and year of birth; model 2: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking

ily history of cardiovascular diseases, the risk estimates for cardiovascular diseases remained largely similar (HR=1.65, 95% CI: 1.59-1.71 in model 3).

We generally found the same results across all levels of adjustment when using ADHD as time-invariant exposure (HR=1.64, 95% CI: 1.58-1.70 in model 3).

Table 4 Results from sensitivity analyses on associations between attention-deficit/hyperactivity disorder (ADHD) and cardiovascular diseases as hazard ratios (HRs) with 95% CI adjusted for covariates

	Model 1	Model 2	Model 3
ADHD diagnosis only	2.22 (2.13-2.32)	1.99 (1.90-2.07)	1.76 (1.68-1.84)
Excluding those treated with stimulants	2.25 (2.16-2.36)	2.01 (1.92-2.10)	1.77 (1.69-1.85)
Excluding those treated with other psychiatric medications	2.29 (2.19-2.40)	2.06 (1.97-2.16)	1.83 (1.74-1.91)
Excluding those with family history of cardiovascular diseases	2.06 (1.98-2.14)	1.84 (1.77-1.91)	1.65 (1.59-1.71)
ADHD as time-invariant exposure	2.05 (1.97-2.13)	1.83 (1.77-1.90)	1.64 (1.58-1.70)

Model 1: adjusted for sex and year of birth; model 2: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking; model 3: adjusted for sex, year of birth, education level, birth country, type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems, heavy smoking and psychiatric comorbidities

DISCUSSION

In this large-scale, register-based cohort study, we found that adults with ADHD were more than twice as likely to develop at least one cardiovascular disease, compared with those without ADHD, independently from treatment with psychotropic medications. The increased risk was present across all types of cardiovascular diseases, but the strength of the associations was greatest for cardiac arrest, hemorrhagic stroke and peripheral vascular disease/arteriosclerosis.

Well-established risk factors for cardiovascular diseases (such as type 2 diabetes mellitus, obesity, dyslipidemia, sleep problems and heavy smoking) and psychiatric comorbidities could not fully explain the associations, indicating that ADHD is an independent risk factor for a wide range of cardiovascular diseases. This finding is consistent with a recent two-sample Mendelian randomization study reporting a direct causal effect of ADHD on coronary artery disease[46].

Although the underlying mechanisms remain unclear, plausible biological mechanisms could explain the observed association between ADHD and cardiovascular diseases, including immune system abnormalities[47,48], neuromodulator dysregulation[49,50], and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis[51,52]. The observed associations could also be partly explained by shared etiological components, as suggested in a previous genetically-informed study based on sibling pairs[21].

The observed strength of associations between ADHD and cardiovascular diseases is largely comparable to estimates of associations between these diseases and schizophrenia[9], depression[8], and bipolar disorder[10], and stronger than associations with anxiety disorders[11], obsessive-compulsive disorder[43], and stress-related disorders[42]. In contrast to the available evidence base for other psychiatric disorders[53], the association between ADHD and cardiovascular diseases has been substantially understudied. Our findings call for enhanced clinical awareness of cardiovascular risk among adults with ADHD.

Sex differences in ADHD[29] and cardiovascular diseases[30] are well established, with higher prevalence estimates in males than in females for both conditions, but our study extends this knowledge base by showing that the association between ADHD and cardiovascular diseases is stronger in males than in females. The present study points to the potential value of screening for cardiovascular risk factors in ADHD, particularly targeting young adults and males.

In our study, comorbid eating disorders and substance use disorders significantly increased the risk of cardiovascular diseases among individuals with ADHD. As suggested in previous studies, around 80% of patients with an eating disorder are affected by a cardiac complication[54], and prolonged heavy use of certain substances (e.g., amphetamines, alcohol, tobacco and heroin) substantially increases the risk for several serious cardiovascular problems, including hypertension, stroke and cardiac arrest[55]. Therefore, the appropriate identification and treatment of these psychiatric comorbidities is necessary to successfully impact cardiovascular health among adults with ADHD.

Our findings also suggest that the observed associations between ADHD and cardiovascular diseases are independent from the use of stimulants and other psychotropic medications. A slightly stronger association was even found among individuals with ADHD not treated with antipsychotics, anxiolytics, hypnotics and sedatives, and antidepressants. A seemingly protective effect of psychotropic medications for the risk of cardiometabolic conditions and mortality has been found in other mental disorders[56-59]. However, confounding by indication needs to be carefully considered using other study designs (e.g., within-individuals comparisons). Our results should not be interpreted as indicating that psychotropic medications are free from cardiovascular adverse effects, and they should continue to be used with caution in ADHD patients.

Our study has some limitations. First, the national registers mainly capture the most severe cases, which might have led to an underestimation of the number of patients with milder symptoms of ADHD or less severe cardiovascular diseases. On the other hand, a detection bias (i.e., individuals with ADHD and psychiatric comorbidities may be more likely to be diagnosed with cardiovascular diseases as they have more frequent contacts with the health care system than those without ADHD) cannot be ruled out. Second, the prevalence of ADHD tends to increase over time, reflecting changes in diagnostic practices, and the late inclusion of outpatient specialist care records in the NPR (since 2001) and information on medication in PDR (since 2005) might have led to a loss of early diagnoses of ADHD in our cohort, particularly in older adults. Delayed diagnosis may have resulted in misclassification from exposed to unexposed person-time, which would be most likely to bias estimates towards the null.

Third, as the median age of the study population at the end of the follow-up was 50.49 (range 31-73) years, we might have mostly captured early onset cases of cardiovascular diseases. Therefore, future studies would be necessary to explore the association of ADHD with later onset cardiovascular diseases among older adults. Finally, we had no data on some lifestyle related factors (such as dietary intake and physical activities) that may contribute to the observed association as confounders or mediators. Our results suggest that heavy smoking and sleep problems could explain only a small portion of the associations, but tobacco use and sleep disorders identified from registers might only reflect the most severe cases. Thus, further studies are warranted to clarify the impact of lifestyle related factors on the association between ADHD and cardiovascular diseases.

In conclusion, in this large-scale, register-based cohort study, we found that ADHD is a risk factor for a wide range of cardiovascular diseases, independent from well-established cardiovascular risk factors, psychiatric comorbidities, and psychotropic medication treatment. These findings underscore the importance of carefully monitoring cardiovascular health in adults with ADHD, and highlight a critical need for development of age-appropriate and individualized strategies to reduce the risk of cardiovascular morbidity in ADHD people. Additional studies are needed to confirm our findings and to further explore the mechanisms underlying the association between ADHD and cardiovascular diseases.

ACKNOWLEDGEMENTS

This project has received funding from the European Union's Horizon 2020 research and innovation programme (grant nos. 667302 and 965381). H. Larsson acknowledges financial support from the Swedish Research Council (2018-02599) and the Swedish Brain Foundation (FO2021-0115); Z. Chang from the Swedish Council for Health, Working Life and Welfare (2019-00176); M. Dobrosavljevic from the European Union's Horizon 2020 research and innovation programme (Marie Skłodowska-Curie grant no. 754285); E. Du Rietz from the Swedish Research Council for Health, Working Life, and Welfare, and from the Swedish Society for Medical Research. Supplementary information on this study is available at https://osf.io/8f9xb/.

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DOI:10.1002/wps.21020

A clinically useful conceptualization of emotion regulation grounded in functional contextualism and evolutionary theory

Perhaps nothing is more central to the human experience than emotions. How individuals experience and respond to their emotions has been linked to psychological and physical health and overall well-being[1]. In particular, emotion regulation has been identified as one of the most critical factors contributing to psychopathology and adaptive functioning alike[2].

Despite its clinical importance, conceptualizations of emotion regulation vary greatly. Although some of this variability can be explained by whether the conceptualization focuses on the regulation of emotions at the micro or macro level (with micro level approaches focusing on the specific strategies that people use to influence their emotions, and macro level approaches focusing on the typical ways in which individuals understand and respond to their emotions[3]), some appears to be driven by differences in how emotions and their role in functioning are conceptualized and understood.

Specifically, if emotions (particularly negative emotions) are viewed as potentially disruptive to the pursuit of goals and/or in need of control or modification, then conceptualizations of emotion regulation may emphasize the down-regulation of negative emotions, enhancement or sustainment of positive emotions, and/or modification of the experience or expression of emotions in some way. On the other hand, if the understanding of emotions is grounded in evolutionary theory on the functionality of emotions and their utility in guiding behaviors and valued actions[4-6], then a relevant conceptualization of emotion regulation would emphasize adaptive responses to emotions that facilitate their functional use as information to guide behavior (vs. modification of emotions as the goal). It is this latter approach to the conceptualization of emotion regulation that we recommend as most clinically useful for guiding assessment and intervention.

This approach is best exemplified by the acceptance-based model of emotion regulation[6], which conceptualizes emotion regulation as adaptive ways of responding to emotions, including the understanding, acceptance, and effective use and modulation of emotions[7]. According to this model, adaptive responses to emotions are those that facilitate the functional use of emotions as information and the pursuit of valued actions, whereas maladaptive responses are those that interfere with accessing, using, or learning from the information provided by emotions.

Thus, the acceptance and understanding of emotions are considered the foundational abilities that are necessary for adaptive emotion regulation. Moreover, although the effective modulation of emotions is considered one aspect of adaptive emotion regulation within this model, it is not necessary for adaptive regulation to occur; instead, identifying and labeling emotions and being willing to experience emotions are theorized to be regulating in their own right.

Likewise, although specific modulation strategies are not considered inherently adaptive or maladaptive within this model (as the effectiveness of any strategy can only be evaluated in the context of the individual's goals and situational demands), strategies that facilitate access to the information provided by emotions and application of that information in a functional way are considered more adaptive than strategies that interfere with understanding emotions and the information they provide. Thus, key to determining the adaptiveness of any given strategy in the moment is understanding the function or purpose of that strategy, with strategies that aim to avoid emotions considered less adaptive than acceptance- or approach-based strategies.

Finally, the foundational abilities identified in this model are expected to affect the selection and use of modulation strategies by interacting with the situation to influence the individual's goals. For example, individuals who respond to their emotions with acceptance and a desire to understand and learn from them would generally be expected to choose emotion modulation strategies that do not interfere with accessing or using the information provided by emotions (e.g., talking about their emotions with others, journaling, self-soothing). On the other hand, individuals who negatively evaluate or disregard their emotions may be more likely to choose avoidance strategies that interfere with the functional use of emotions regardless of the context.

Notably, by not suggesting that emotions must be modified, this conceptualization of emotion regulation is consistent with the burgeoning literature on acceptance-based interventions that emphasizes the utility of emotions and the benefits of experiential acceptance[7,8]. Further, by focusing on adaptive responses to emotions rather than the nature or quality of those emotions, this conceptualization separates emotion regulation from the experience of emotions, proposing that intense, reactive or labile emotions are not inherently dysregulated, and even individuals with a temperamental emotional vulnerability can be emotionally regulated (as long as they respond to their emotions in adaptive ways). Indeed, according to this model, how someone responds to an intense or reactive emotion plays a key role in the trajectory, duration and consequences of that emotion (consistent with research suggesting that responses to emotions are more relevant to mental and physical health than an individual's emotional temperament[9]).

Given the substantial impact of emotion regulation on numerous aspects of functioning and health[2], the systematic and reliable assessment of this construct in clinical settings is imperative for effective clinical decision-making. One of the most widely used and extensively supported self-report measures is the 36-item Difficulties in Emotion Regulation Scale (DERS)[6], which is based on the acceptance-based conceptualization of emotion regulation discussed here.

In addition to providing a total score of overall emotion regulation difficulties, this measure provides scores for six subscales assessing difficulties in the key emotion regulation abilities of: emotional acceptance; emotional awareness; emotional clarity; access to effective emotion modulation strategies; controlling im-

pulsive behaviors when distressed; and engaging in goal-directed behaviors when distressed.

Not only are scores on the DERS significantly associated with numerous clinically relevant behaviors (e.g., self-injury, binge eating, substance use) and psychiatric disorders (e.g., borderline personality disorder, anxiety disorders, post-traumatic stress disorder, eating disorders), but extensive research also demonstrates that the DERS is sensitive to change following psychological treatments and can be used to track progress in emotion regulation over the course of treatment[9]. Moreover, although its self-report format increases its feasibility and ease of administration, the DERS is significantly associated with behavioral, neurological and physiological measures of emotion regulation[9].

Beyond established self-report measures such as the DERS, clinicians can use behavioral techniques such as functional analysis to assess individuals' responses to their emotions, including their acceptance and understanding of these emotions, how these emotions inform their behaviors (effectively or ineffectively), and the immediate and long-term emotional, cognitive, behavioral and interpersonal consequences of these responses. Repeated functional analyses with a patient may also increase insight into the functions of and motives for the selection and use of particular modulation strategies across different contexts, as well as highlight instances of emotion regulation inflexibility that can be targeted in treatment.

Although the term "emotion regulation" can imply that emotions require or need modification or modulation, we propose that the modulation of emotions is only one aspect of adaptive emotion regulation, and that effective emotion modulation requires emotional acceptance and understanding. In contrast, a singular emphasis on the modification or modulation of emotions obscures the fact that emotions serve important and necessary functions.

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DOI:10.1002/wps.21021

Detecting and managing non-suicidal self-damaging behaviors

Non-suicidal self-damaging behaviors are actions that carry a high potential for physical harm to result, either as a direct and immediate consequence (e.g., self-cutting), or as a stochastic or accumulated consequence of the behavior (e.g., risky substance use; repetitive fasting or self-induced vomiting), but without associated suicidal intent. These behaviors affect around 10% to 30% of people[1], with substantial associated harms including negative impacts on mental and physical health, poorer educational and occupational outcomes, and excess risk of injury and premature death, including by suicide[2].

Non-suicidal self-damaging behaviors typically begin in adolescence or early adulthood[3], but may not be a focus of clinical attention until they become chronic, entrenched ways of coping. Improving detection and management of these behaviors has the potential to substantially reduce the global morbidity and mortality associated with psychiatric disease. Here, I discuss two problems that limit our ability to realize this goal, as well as suggested actions that could move us closer.

The first problem is that patients' histories of non-suicidal self-damaging behaviors are not routinely assessed in many primary care and behavioral health services. Behavioral health screening tools that are commonly used in primary care settings, for instance, focus on depression, anxiety and risky alcohol and substance use, but do not provide direct information about other forms of non-suicidal self-damaging behaviors.

Indeed, even comprehensive diagnostic interviews and self-reports often lack direct and comprehensive questions about a patient's self-damaging behaviors. This leaves it to the clinician to determine when to probe further, or to the patient to volunteer his/her engagement or history. Impeding the former, high rates of co-occurrence among non-suicidal self-damaging behaviors – estimated between 35% and 50% – may not be obvious. Thus, even when a clinician recognizes that a patient is struggling with one type of non-suicidal self-damaging behavior, he/she may not be cued to assess for other types of non-suicidal self-harm because of a tendency to view these as unrelated clinical problems.

Incorporation of these behaviors into screening measures used in primary care and behavioral health settings could improve their detection, as would development and use of decision-making tools that prompt further assessment of these behaviors whenever patients report substance-, eating- or self-injury related problems.

Impeding the patient to volunteer his/her engagement or history, non-suicidal self-damaging behaviors remain highly stigmatized. Patients who seek help for problems with mood, anxiety or non-behavioral concerns may not disclose non-suicidal self-damaging behavior for fear that it will be misunderstood as being motivated by suicidal intent, or that it will negatively impact the care they receive. Increased screening for non-suicidal self-

damaging behaviors may help reduce both patients' and clinicians' perceptions that these behaviors are something to avoid discussing.

A second problem limiting our progress in detecting and managing non-suicidal self-damaging behaviors arises from unintended consequences of fidelity to superficial features of current diagnostic nosologies. Researchers (and, sometimes, research granting agencies) have often focused inquiries on a particular psychiatric diagnosis or diagnostic category. As a result, many studies do not assess, or exclude, co-occurring behaviors that span multiple principal categories. This has slowed understanding of shared etiologies of non-suicidal self-damaging behaviors and, thus, development and evaluation of potentially efficient treatments.

Likewise, specialist psychiatric services often reflect current diagnostic categorizations, with separation of addiction treatment, eating disorder services, and self-injury treatment (which is commonly referred to personality disorder services). Professional specialties that are commonly integrated in one setting (e.g., dieticians in eating disorder services; physicians who are licensed to provide substance substitution medications in addiction treatment settings) may not be easily accessed in another, leaving potential gaps in care. Available treatment modalities (group vs. individual psychotherapy; psychopharmacology) may also substantively differ, as might the training of affiliated professionals. Thus, there may be non-negligible differences in the treatment that a patient receives depending on conceptualization of the primary diagnosis or problem.

Fortunately, there has been resurgent interest in dimensional, transdiagnostic models of psychopathology in the past decade. The Extended Evolutionary Meta-Model[4], for instance, argues for an idiographic, functional-analytic approach that could more readily identify common behavioral functions, and corresponding treatment strategies, among a diverse set of clinical problems. Development and evaluation of transdiagnostic and modular treatment protocols, as well as attention to so-called "non-specific factors" of therapeutic change, hold promise for identifying essential elements and strategies for managing non-suicidal self-damaging behaviors.

In thinking about ways to improve management of these behaviors, it is worth briefly reflecting on what constitutes "successful" management. It is logical to aim for reductions in the behavior; however, whether abstinence is a desired and appropriate goal for all patients has been questioned. Given that clinical concern often stems from the potential for these behaviors to result in physical harm, incorporation of harm reduction principles may be appropriate. Additionally, evidence-based treatments for substance use and eating disorders suggest the wisdom of incorporating motivational principles, including explicit attention to the patient's readiness for change, when initiating intervention.

While promising treatments for non-suicidal self-damaging behaviors have been developed, the quality of evidence is often limited to preliminary pilot evaluations and uncontrolled trials. Additionally, evidence is often tied to DSM diagnoses (e.g., bulimia nervosa, borderline personality disorder); as a result, the most effective strategies for treating these behaviors in patients who do not meet diagnostic thresholds is unclear, and cross-over effects (e.g., the effectiveness of treatment for bulimia nervosa in reducing non-eating-related self-damaging behaviors) are rarely evaluated.

Overall, cognitive-behavioral, mentalization-based, and emotion regulation-focused group psychotherapies have some level of support for reducing non-suicidal self-damaging behaviors[5]. Cognitive behavioral therapy (CBT) and dialectical behavior therapy (DBT) have been shown to reduce self-damaging eating behaviors, substance use, and non-suicidal self-injury in patients with borderline personality disorder, with stronger effects relative to treatment-as-usual (TAU). Mentalization-based therapy also results in greater reduction in non-suicidal self-injury than TAU[6].

Recent efforts have focused on evaluating interventions that might improve treatment access and reach (e.g., stand-alone group skills training interventions, online or self-guided interventions), but resulting evidence is preliminary. Recommendations regarding patient characteristics that could inform the optimal setting and duration of treatment are not yet clear. Evidence regarding the efficacy of pharmacotherapy in reducing non-suicidal self-damaging behaviors is even more limited, and medication is not currently recommended as a first-line treatment for addressing these behaviors outside of primary diagnoses of eating or substance use disorders[7].

Non-suicidal self-damaging behaviors represent an important clinical concern. Prioritizing these behaviors in screening and assessment may improve their detection. Transdiagnostic models could transform the way we think about and manage these behaviors, helping us appreciate commonalities that may not have previously been apparent. Still, there is room to grow. We should not lose sight of practical benchmarks – changes in practice that are likeliest to stand the test of time are those that ultimately deliver better outcomes for patients, their loved ones, and society.

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DOI:10.1002/wps.21022

New trends in network modeling of psychopathology

The network theory, as outlined in D. Borsboom's seminal paper in this journal[1], postulates that mental disorders may be viewed as emergent phenomena from complex systems, in which symptoms and external factors directly influence each other in a network of interacting components.

From this theoretical frame of mind arose network psychometrics[2,3], the field of study concerned with estimating multivariate statistical models that allow for network representations from data. While these techniques have been predominantly applied to cross-sectional datasets, in which patients are measured only once in efforts to gain insight into nomothetic relationships, they are also promising in forming patient-specific network models designed to uncover idiographic relationships that may facilitate case conceptualization and further guide treatment.

The suite of techniques developed in network psychometrics allows for unique ways to explore relationships in symptom data and beyond, as well as to check the robustness and replicability of these results. Research inspired by the network theory of mental disorders is now vast and taking many directions. Here we introduce some of the most promising new trends in this field.

A meta-analytical framework. As a result of the rapid expansion of the network analytic framework in psychopathology research, and in response to critical arguments on the generalizability of network models obtained from single samples, the novel meta-analytic methodology (i.e., meta-analytic Gaussian network aggregation, MAGNA) represents a central advancement in the field. MAGNA allows researchers to perform meta-analyses of network models, making it possible to aggregate results across multiple studies, and providing a statistical and objective framework to summarize research findings[4]. This methodology has recently been applied to the field of post-traumatic stress disorder, where correlational structures of 52 different samples with a total sample size of N=29,561 have been analyzed under a single pooled network model. The upcoming years are likely to see a rise in meta-analysis of various mental disorders, as well as across a multitude of population subgroups, ultimately leading to stable and generalizable network structures that can further be used in theory formation, as well as in innovative prevention and intervention strategies.

From exploratory to confirmatory network analysis. Network models to date are explorative in nature, allowing researchers to search best-fitting models that could explain links present in empirical data. As a result, most research in the field of network psychometrics is hypothesis-generating and exploratory. As we become more acquainted with the operating principles of such models, moving from exploratory to confirmatory analysis is a natural next step. We see more often that setting up hypotheses about the presence and strength of links in a network structure is intuitive and common, and many new research avenues and developments are currently directed toward confirmatory studies. To this end, it is increasingly more common for network analyses to be at least in part pre-registered, registering not only the dataset to be analyzed and the analytical plan, but also expected findings in the network architecture. In addition, dedicated software now exists to perform confirmatory network analysis[5], which allows for assessing the fit of a pre-defined network architecture in the same manner as a confirmatory factor analysis allows for assessing the fit of a predefined factor model. Finally, recent lines of research investigate the inclusion of prior theoretical knowledge in network estimation.

Longitudinal analysis. The vast majority of network analyses are performed on datasets in which every subject is measured only once, often termed cross-sectional data. While cross-sectional analyses based on large sample sizes can certainly be informative, it has been recognized that the interpretation of such results may be troublesome[6]. Most notably, cross-sectional data cannot distinguish between-person effects (e.g., a person that is on average more anxious also experiences on average more depressed mood) from within-person effects (e.g., whenever a person feels more anxious than his/her average, he/she often also experience higher levels of depressed mood). Longitudinal analysis, in which network models are estimated from either intensive time-series data or large sample panel data, has grown popular in modeling such within-person fluctuations over time. While psychiatric symptoms are often defined over a long period of time, and therefore fluctuate less over time by definition, the problems they represent certainly can fluctuate over time, as can the mood states associated with mental health problems. To this end, longitudinal network analysis presents powerful avenues for future research.

Formal mathematical modeling. While the field of network psychometrics arose from the conceptual thinking in the network theory of mental disorders, it is not necessarily tied to network theory, which conceptualizes mental health as a system of interacting components. Where network psychometrics takes a theory-agnostic bottom-up approach of estimating relationships between symptoms from data, an increasingly popular alternative is to use theory-laden top-down approaches, instead forming networks by using theory to inform mathematical equations that aim to explain how data are generated. While such formal modelling is popular in many fields of science (e.g., such models have been used to inform policy regarding the COVID-19 pandemic), they are yet rarely used in psychopathology. This approach shows great promise, however, both in the formation of nomothetic theories aiming to explain common phenomena[7], as well as in idiographic case conceptualizations of patients in clinical practice[8].

Embracing the complexity of mental health. In attempting to obtain identifiable multivariate models that are estimable from practically obtainable datasets, network psychometrics may make concessions that make the models used deviate from the complex systems thinking that inspired network theory[1]. For example, psychometric network models estimated form cross-sectional data mostly include only pairwise interactions, do not feature phase

transitions between multiple stable states, and include only linear effects, while complex systems thinking often involves the presence of feedback loops, phase transitions between multiple stable states, interactions at different time-scales, and non-linear effects. It may be that the understanding of mental health requires all these concepts and more, being an interplay not only of symptoms but also of numerous other factors, ranging from biological to sociological factors, and from fast effects that span seconds to slow effects that span a lifetime[9]. The development of methods that capture and explain this complexity may be one of the great challenges that mental health research is to face in the coming decades.

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DOI:10.1002/wps.21017

Computer-based virtual reality assessment of functional capacity in primary psychosis

The concept of functional capacity has been studied for almost 20 years[1,2]. This concept includes the abilities and skills that are essential for an individual to function independently in a variety of community settings, including work, school, and social situations such as with friends or family[3].

Most researchers in the field believe that the accurate evaluation of functional capacity serves as a close proximal indicator for real-world functioning. If a clinician's assessment of functional capacity could allow an accurate representation of the specific skills that an individual would need to perform in various daily life situations, that could provide a method of prediction and a target for treatment planning and intervention. This would have broad applicability, as we know that these functional capacity deficits are also present in the early course of psychotic illness, so they are not simply a consequence of an established primary psychosis[4].

One single measure of functional capacity has for years dominated the field: the University of San Diego Performance Based Skills Assessment (UPSA) and UPSA-Brief[5]. The UPSA was designed to assess the capacity of individuals to perform skills in five areas that are critical to independent living, which are covered by five subtests: planning/organization (e.g., planning a trip to the beach/zoo); managing finances (e.g., counting change, writing a check); communication skills (e.g., calling the doctor to reschedule an appointment); using transportation (e.g., reading a bus route map); and household management (e.g., completing a shopping list, reading a recipe). Each subtest yields a score ranging from 0 to 20. Subtest scores are summed to create a total score (range = 0-100).

While research on functional capacity was underway, another important predictor of daily functioning – neurocognition – was garnering a lot of attention[6]. Neurocognitive functioning includes components such as short-term memory, verbal learning and memory, concentration, reasoning and problem-solving, and speed of processing. Many of these cognitive domains have in their own right been shown to be robust predictors of daily functioning. The problem is that, although the UPSA has become the most recognized measurement of functional capacity, it has a great deal of overlap with measures of neurocognitive functioning. On the other hand, neurocognitive functioning alone, although an important predictor of functional outcome in daily life, does not explain all of the ways in which an individual with a primary psychotic disorder can achieve success in life.

The administration of the UPSA requires specific training and involves a cumbersome set of test props, several of which are outdated in today's technologically driven world – for example, a push-button desktop telephone rather than a mobile phone. The outdated nature of the UPSA is even more apparent when assessing samples of young, early course patients. Clearly, more needs to be done to develop innovative ways to assess functional capacity and to understand its relationship to daily functioning in individuals with early or later phase schizophrenia.

The development and validation of computer-generated virtual reality environments is providing the opportunity to assess functional capacity in a new and unique way. The Virtual Reality Functional Capacity Assessment Tool (VRFCAT)[7] creates a realistic, interactive and immersive environment consisting of four scenarios: exploring a kitchen; catching a bus to a grocery store; finding/purchasing food in a grocery store; and returning home on a bus. Dependent variables include time to completion, number of errors on 12 tasks within the virtual environment, and the number of times that an individual failed to complete a task.

The VRFCAT and MATRICS Consensus Cognitive Battery (MCCB) scores are empirically correlated but separable, as evidenced by a robust 2-factor solution in the combined factor analyses of these measures, which improved on the fit of a unifactorial model[8]. In contrast, combined factor analyses confirm that the

MCCB and the UPSA would be best described by a joint unifactorial solution. Having determined that the VRFCAT is separable is a good first step, but next we need to determine whether the VRFCAT can be used clinically to assess functional capacity.

Another computer-based virtual reality test of functional capacity is the Virtual City[9]. In this test, the virtual environment consists of a 6x6 block city scape with a central park and over 80 residential, commercial, institutional and office buildings. Embedded within the city are various "targets", such as a playground and a hospital. The environment includes distal cues to aid in orienting such as a mountain range along one boundary, a hot air balloon, and a radio tower. Participants use a videogame controller with simple forward/reverse and left/right levers to navigate around the virtual city. A 5-min practice session of free navigation before the beginning of trials, restricted to an area of the virtual city not used during subsequent trials, ensures familiarity with controller operations.

More research is needed to determine whether computer-based virtual reality assessment tools such as the VRFCAT and the Virtual City can be used more broadly in clinical settings. Research has shown that the VRFCAT is correlated with neurocognition, but also found it to be separable from neurocognition, which supports the notion that the tool provides a valid assessment of the clinically important features of functional capacity. Furthermore, whether these recently developed and innovative virtual reality approaches might be useful in the differential prediction of various domains of functioning, such as work functioning versus social functioning, needs to be examined.

In addition, the role played by psychological factors such as amotivation, defined as the absence of either intrinsic and/or extrinsic aspects of motivation, needs to be taken into account. Firstly, amotivation might limit the effort one puts forth in performing a virtual reality task, resulting in a false impression of poor functional capacity skills. This sort of evaluation of effort needs to be built into the test procedure or at least accounted for by the examiner. Moreover, even for those individuals who can demonstrate good functional capacity on a test, amotivation could limit engagement in real-world activities of daily living such as school, work, or prosocial behaviors. Unfortunately, demonstrating good functional capacity skills does not ensure that one will have successful functioning when there is a lack of commitment to life's goals.

Further, any assessment tool used with individuals who have a primary psychotic disorder needs to consider the impact that symptoms might have on test performance. Although many researchers believe that test performance is free of symptom influence, that is usually true of positive, but not negative symptoms, which have been shown to adversely influence neurocognitive test performance.

A computer-based virtual reality test taking into account these additional clinically relevant components could be an important step in treatment planning for the individual with a primary psychotic disorder.

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DOI:10.1002/wps.21024

Implementation strategies for the new World Mental Health Report in low-resource settings

Mental health conditions are very burdensome for all societies, and the situation has been made worse by the COVID-19 pandemic. Yet, health and social systems of most countries are poorly geared to take care of mental health needs of people and populations. The "care gap" is directly responsible for enormous suffering and frequent human rights violations.

The World Health Organization (WHO) and the global mental health community have been trying to close the "care gap" for at least three decades, and have achieved some success in relation to interest in and understanding of mental health issues, amplification of voices of people with lived experience of mental health conditions, generation and compilation of relevant research, development of evidence-based implementation tools, and global governance and leadership (e.g., WHO Comprehensive Mental Health Action Plan 2013-2030[1]). But progress has been slow, as mental health systems and services remain ill-equipped to meet people's needs in most countries. Inequities, in fact, have become worse during the COVID-19 pandemic in many settings.

The new *World Mental Health Report: Transforming Mental Health for All* emphasizes the urgency of the action needed to ensure better mental health for the world's population[2]. The report suggests that this can be achieved by deepening the value and commitment given to mental health, reshaping the environments that influence mental health, and developing community-based mental health services capable of achieving universal health coverage (UHC) for mental health.

From the perspective of low- and middle-income countries (LMICs), the report provides useful strategic guidance, evidence on successful delivery and scaling up of effective interventions across poor-resource settings, and a compilation of implementation tools (e.g., the ICD-11; the WHO World Mental Health Surveys; the mhGAP Intervention Guide; the EQUIP: Assessing and Building Competencies for Psychological Interventions; the WHO QualityRights; the Mental Health and Psychosocial Support Minimum Service Package; and the WHO UHC Compendium) to support them in their efforts to achieve this ambitious transformation[2]. It also highlights that, in many settings, digital technologies can be used to strengthen mental health systems[2]. The report also showcases narratives from many LMICs of people with lived experience of mental health conditions that show that people's expectations from and needs for effective health and social support are not so different from those in better resourced settings.

However, a sobering fact is that, despite global efforts to correct the "care gap", the proportion of people with common mental disorders who receive minimally adequate care is between 1% in low-income countries and 10% in better resourced middle-income countries such as India and China[3,4]. The gap could well be increasing – the India State-Level Disease Burden Initiative shows that the proportional contribution of mental disorders to the total disease burden in India almost doubled from 1990 to 2017[5]. Also, key threats to public mental health and development such as economic downturns and social polarization, public health emergencies, humanitarian emergencies and forced displacement, and the climate crisis disproportionately affect the populations living in LMICs[2].

The new report exhorts countries to take transformative action based on local realities. However, this recommendation is faced with a huge "implementation gap". Many LMICs have significant structural barriers that limit the scaling up of services when they attempt it on their own. The governments of many low-income countries have very little to spare for mental health from their low overall government expenditure; similarly, low resource middle-income countries find it difficult to secure the double funding needed to scale up community mental health care while somehow managing their precarious specialized mental health care[6].

There has been a call for a multi-sectoral and multi-organizational partnership for global mental health to address the challenge of financing and stewarding a global scaling up of mental health services[7]. But, in view of the complexity of determinants and heterogeneity of conditions characterizing mental health, a strategy modelled on the United Nations (UN)'s Every Woman Every Child strategy – that coordinates WHO's Partnership for Maternal, Newborn and Child Health and World Bank's Global Financing Facility – may be better suited to support the scaling up of services for mental health.

Such a strategy may also be well placed to utilize the Health-4Life Fund on non-communicable diseases (NCDs) and mental health established in 2021 under the auspices of the UN Interagency NCD Task Force. This Fund is designed to support LMICs with initial grants to stimulate multi-stakeholder and multi-sectoral action at country level, increase domestic funding, and improve policies, legislation and regulation. Regional interagency mechanisms such as the Every Woman Every Child Latin America and the Caribbean initiative could deepen implementation of global strategies at the regional level through data-driven advocacy, capacity building, and policy and program solutions[8].

The big question is: "Will different departments and programs of WHO and of other UN agencies work together to implement the new Mental Health Report vision?".

The report suggests that countries should set up in-depth processes to adapt global recommendations to their local context, e.g., to weigh up needs, resources, evidence of impact and models of intervention to ensure that resources are allocated, and services provided, appropriately and efficiently. But many national health authorities in LMICs do not have the technical capacity for evaluating the increasingly voluminous and complex scientific data. These needs could be handled by the creation of National Mental Health Technical Advisory Groups (on the lines of National Immunization Technical Advisory Groups)[9] with a legislative or administrative status within countries. Such bodies could empower

governments to formulate rational policies through evidence-based decision-making and help adapt global recommendations to local contexts for the entire range of mental health actions.

National Mental Health Technical Advisory Groups should comprise multidisciplinary groups of national experts (e.g., academics and health care professionals, scientific societies and non-governmental organizations, and representatives from civil society). They could collect, review, assess and organize scientific evidence on specific mental health-related topics; offer specialized technical and operational assistance to improve levels of implementation; and provide a monitoring function to maintain momentum towards agreed-upon targets and goals, and suggest course corrections when needed.

The WHO could perhaps recommend that countries establish such bodies through the World Health Assembly resolution towards the attainment of the WHO Comprehensive Mental Health Action Plan 2013-2030 goals (the number of Technical Advisory Groups established or strengthened could itself serve as a target for global mental health response). The WHO and its partners (including funding agencies) could support countries to establish their Technical Advisory Group, network it with local and regional collaborators, and strengthen its capacity to use evidence-based processes for decision-making aligned with international standards. Will WHO come forward to assist countries in developing the technical capacity that is sorely needed in LMIC capitals, from New Delhi to Maseru?

The new World Mental Health Report is a welcome opportunity to harness and catalyze the growing momentum towards applying the large body of scientific evidence to achieve a scaling up of effective interventions for mental health and well-being globally and specifically in low-resource settings.

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DOI:10.1002/wps.21032

Burnout: a case for its formal inclusion in classification systems

Burnout is variably viewed as a social phenomenon, a psychological state, or a clinical condition. It currently lacks formal status as a mental disorder, not being listed in the DSM-5 and being simply positioned as an "occupational phenomenon" in the ICD-11, despite having a general population prevalence in the order of 30%, being debilitating, costing over US$ 300 billion/year to the global economy, and having status as an occupational "disease" in several European countries[1].

A recent review[2] concluded that "it would be inappropriate, if not premature, to introduce burnout as a distinct mental disorder within any existing diagnostic classificatory system". In opposition, we offer a case for its formal listing by responding to the arguments put forward in that review and in other papers which may have prevented burnout from being accorded such recognition.

The first argument has been that burnout is solely a Western cultural phenomenon – in effect, a culture-bound syndrome. On the contrary, there are reports of high burnout rates in Africa, South America and Asia[1]. Furthermore, even if burnout were indeed a culture-bound syndrome, this would not necessarily argue against its listing in classification systems, since psychiatry has long categorized many culture-bound syndromes (e.g., koro).

A second point has been that burnout is a "new" phenomenon. On the contrary, while the term was coined in the mid-1970s, an early forerunner was "acedia" (listed in the 4th century AD as a cardinal sin), whose core symptoms were mental and physical exhaustion, torpor, non-productive activity, cognitive impairment, and a state of non-caring[3], largely corresponding to the current conceptualization of burnout.

A third consideration has been that burnout is commonly perceived as a "normative" condition. This may be true, but the same judgment would also hold for "stress", "anxiety" and other psychological conditions that are not always of clinical status, a reality generally addressed by adding a functional impairment component to their clinical definition.

A fourth argument refers to the variegated conceptualizations present in the literature. Currently dominant is a triadic symptom model of burnout weighting emotional exhaustion, depersonalization/lack of empathy, and decreased personal accomplishment[4]. There are, however, several two-dimensional models and even measures weighting exhaustion as the only symptom[5]. If burnout simply corresponds to exhaustion, the term would be redundant, and its conceptualization could be validly challenged. Defining a syndrome with only one or two symptom criteria would also be problematic.

However, more multi-faceted models and measures of burnout exist. The Burnout Assessment Tool (BAT)[6] comprises four "core" and two "secondary" dimensions. The former are physical and mental exhaustion; mental distance (e.g., avoidance of contact with others, cynicism); emotional impairment; and cognitive impairment. The latter are psychological symptoms (e.g., insomnia, anxiety, worry) and psychosomatic complaints.

We have recently proposed a new definitional model of burnout[7] represented by a measure (the Sydney Burnout Measure, SBM)[1] which captures domains of exhaustion, cognitive impair-

ment, loss of empathy, withdrawal and insularity, and impaired work performance, as well as several anxiety, depression and irritability symptoms which are viewed as common burnout concomitants. The consistency across the BAT model, the SBM construct and descriptions of acedia argues for the validity of such a broader conceptualization of burnout and for a potentially meaningful set of operational criteria.

Another issue is that of context specificity, with burnout long viewed as a work-related phenomenon and with "work" restricted to formal/paid employment. It has been argued[2] that, if burnout's work-specific context were removed, two of the promulgated symptoms (i.e., depersonalization/cynicism at work, and reduced professional efficacy) would become irrelevant and reduce burnout's definition to exhaustion only. Clinically, however, we observe burnout in individuals not formally employed (e.g., parents looking after children with disabilities, or people caring for elderly relatives with high demands), while others have argued that "work" in the context of burnout should be viewed more broadly[6]. Thus, the context specificity concern is a straw man argument.

A further key argument[2] has been that burnout is actually depression (and thus is already classified). Whether burnout is or not synonymous with depression has long been debated[8]. A recent meta-analysis[9] of 69 studies reported an overall correlation of r=0.52 between burnout and depression, concluding that the two conditions, although sharing some features, are "different and robust constructs". Indeed, although anxiety and depression correlate moderately to highly, this does not mean that they are synonymous, and diagnostic manuals have long listed separate categories of depressive and anxiety disorders. We argue for viewing the relationship between burnout and depression similarly.

We now consider how burnout might be diagnosed as a mental disorder, respecting the need for a set of criteria/requirements in accord with DSM and ICD models.

We suggest a criterion A requiring a work-based stressor, but allowing that it may occur in formal (i.e., paid) or informal (i.e., unpaid) "work" environments: "The individual has been exposed to excessive formal or informal work demands, that are generally in the form of excessive workload pressures but can also reflect physical environment, work inequity, role conflict or unfair treatment factors".

A criterion B would list five symptoms (generated in empirical studies noted earlier): a) exhaustion (i.e., lack of energy across the day, lethargy, fatigue, waking up feeling tired); b) cognitive disturbance (i.e., concentration is foggy, attention less focused, material needs to be re-read); c) loss of feeling in work or outside of work (the individual feels disengaged, less empathic, and experiences a loss of *joie de vivre*); d) insularity (e.g., tendency to avoid others and to socialize less, deriving less pleasure from social interaction); e) compromised work performance (e.g., less driven to meet work responsibilities, contributing less at work, finding little things and chores frustrating, quality of work compromised in general and/or by making mistakes). To reduce the risk of over-diagnosis, we suggest that all five symptoms should be present.

A criterion C would require (in line with the DSM and ICD) that the symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

A criterion D ("not caused by a medical condition or by the physiological effects of a drug or medication") is important to impose, as individuals may score high on burnout measures and meet the criterion B as a consequence of a range of other psychological conditions (e.g., depression), medical conditions (e.g., severe anaemia, post-COVID state), treatments (e.g., chemotherapy) or the effects of certain drugs.

In conclusion, we believe that reasons for not listing burnout as a clinical condition can be countered, and offer candidate criteria for consideration, thus making a case for its formal inclusion in classification systems.

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DOI:10.1002/wps.21025

Tolerability and efficacy of paroxetine and naltrexone for treatment of compulsive sexual behaviour disorder

Compulsive sexual behaviour disorder (CSBD) has recently been introduced in the ICD-11. However, despite increasing research on its psychological and neural mechanisms, little is known about the efficacy of pharmacotherapy in people with this condition[1].

To date, only some case reports and one small (28 males) randomized controlled trial (RCT) have provided some evidence for the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the reduction of sexual compulsivity[2]. Several case studies and one small (20 males) open-label study reported the clinical usefulness of the opioid antagonist naltrexone in CSBD[3]. Most studies were conducted before CSBD diagnostic guidelines were

proposed in 2019.

We aimed to assess the safety and efficacy of an SSRI (paroxetine) and of naltrexone in male patients seeking treatment at an outpatient sexology clinic who met the ICD-11 diagnostic guidelines for CSBD. For this purpose, we conducted a 20-week double-blind and placebo-controlled RCT, approved by the local ethics review board in accordance with the Declaration of Helsinki.

Among the 73 recruited heterosexual cisgender men (mean age: 35.7±8.1 years), 24 were randomly assigned to paroxetine (20 mg/day), 24 to naltrexone (50 mg/day), and 25 to the placebo condition. No significant group differences were observed with respect to CSBD symptoms or demographic characteristics prior to treatment.

Results from the trial confirmed that paroxetine and naltrexone represent safe treatment options for CSBD. The total discontinuation rate was 15.1%, with the following causes for stopping medication: adverse effects (five patients, 6.8%: two with paroxetine, three with naltrexone); lack of improvement or worsening of CSBD symptoms (two patients, 2.7%, both with placebo); irregular medication intake (one patient, paroxetine group). Three patients (4.1%) discontinued/failed to show up at follow-up (two in paroxetine and one in naltrexone group). No difference in treatment non-adherence was noted between groups ($F_{2,57}$=0.25, p=0.78).

The most bothersome and persistent side effects included sedation (29.2% with paroxetine, 37.5% with naltrexone, and 0% with placebo), apathy (8.3%, 8.3% and 0%, respectively), orgasmic dysfunction (2.8%, 0% and 0%, respectively), erectile dysfunction (12.5%, 0% and 8%, respectively), and weight gain (16.7%, 4.2% and 12%, respectively). No medication-related serious side effects occurred during the trial.

We observed a significant effect of time on severity of CSBD symptoms using self-report questionnaires: Hypersexual Behavior Inventory ($F_{1,55}$=83.59, p<0.001, η^2=0.60), Brief Pornography Screen ($F_{1,47}$=34.66, p<0.001, η^2=0.42) and Sexual Addiction Screening Test ($F_{1,47}$=17.06, p<0.001, η^2=0.27). However, there was no difference between the conditions at any time point, nor an interaction of time and condition. Self-reported frequency of pornography consumption ($F_{1,57}$=28.69, p<0.001, η^2=0.34) and duration of pornography consumption ($F_{1,52}$=7.863, p<0.01, η^2=0.13) decreased over the time of treatment across all conditions. No condition or interaction (time x condition) effects were noted.

On the other hand, clinical interviews revealed that patients treated with paroxetine or naltrexone, compared to placebo, were more likely to achieve at least 30 days of cessation of any compulsive sexual behaviour at treatment week 8 (X^2=7.097, p=0.029, Cramer's V=0.34); to have a reduced frequency of sexual binges at week 20 (X^2=6.935, p=0.031, Cramer's V=0.34); and to have a decrease in frequency of CSBD symptoms at both time points (week 8: X^2=12.250, p=0.016, Cramer's V=0.31; week 20: x^2=8.208, p=0.017, Cramer's V=0.37). They also reported higher satisfaction with treatment effects at both time points (week 8: X^2=15.801, p=0.003, Cramer's V=0.35; week 20: X^2=1.886, p=0.018, Cramer's V=0.31).

Using smartphone-administered daily ecological momentary assessment (EMA), we observed a significant interaction (time x condition) effect in craving for sexual activity ($F_{6,1011.57}$=3.12, p=0.005). Patients receiving paroxetine reported significantly less craving for sexual encounters in the last week of treatment (estimated marginal means, EMMs=3.71, SE=0.55) compared to baseline (EMMs=4.88, SE=0.48) (c=1.17, lower control limit, LCL=0.07, upper control limit, UCL=2.27, p=0.03). A significant interaction (time x condition) effect was also found in craving for pornography viewing ($F_{6,1020.12}$=2.54, p=0.002). Craving for pornography in the 20th week of treatment with paroxetine (EMMs=2.69, SE=0.48) was significantly lower compared to baseline (EMMs=3.97, SE=0.39) (c=1.28, LCL=0.07, UCL=2.49, p=0.03).

To summarize, our double-blind placebo-controlled RCT demonstrated that paroxetine and naltrexone are safe and well-tolerated by men with CSBD. Patients usually reported mild and transient side effects with either medication, and most complaints were similar to reports on safety and tolerability profiles of paroxetine and naltrexone in their registered indications, except for a high incidence of sedation reported by naltrexone users. A 6.8% discontinuation rate due to adverse effects is relatively low compared to other studies[4,5].

Based on clinical interviews, both medications were found to be more effective than placebo in reducing CSBD symptoms. Such a superiority of both active treatment arms over placebo was visible at the 20th week, but as early as the 8th week. EMA provided support for higher effectiveness in reducing craving for sexual encounters and pornography viewing in the paroxetine condition. However, based on data from self-report questionnaires and self-reported pornography consumption, the superiority of paroxetine and naltrexone over placebo did not reach statistical significance. Therefore, the clinical efficacy of these drugs in CSBD should be confirmed by further studies.

The high effectiveness of placebo in CSBD may be related to such factors as disclosing the problem, motivation for change, and initiation of therapy while receiving external support from the study team. Prior research[6] has also demonstrated high placebo response rates in gambling disorder treatment. Such results warrant further attention to non-specific factors related to therapy as meaningful for clinical improvement in CSBD.

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Supplementary information on the study is available at https://osf.io/zexm4.

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DOI:10.1002/wps.21026

Mortality in persons with recent primary or secondary care contacts for mental disorders in Finland

Excess mortality among persons with mental disorders has been consistently documented[1,2], but the mortality risk over a full spectrum of mental disorders treated both in primary and secondary care remains to be explored at a nationwide level.

Integration of mental health care in primary care services is considered a priority in low-, middle-, and high-income countries[3], and depression and anxiety are among the top ten most common reasons for visits in primary care[4]. The global shortage of mortality data concerning mental disorders in primary care may lead to an overestimation of the population-wide burden of the full spectrum of treated mental disorders[5,6].

Excess mortality is related to a variety of risk factors at the individual, health system and social levels[7]. Mental disorders are associated with socioeconomic factors and an increased vulnerability to several physical conditions, with complex bi-directional pathways[8]. Physical comorbidities contribute to the majority of life-years lost in people with mental disorders, and low socioeconomic position (SEP) associates with mental disorders and physical conditions, as well as with mortality in the general population[9].

This national register-based open cohort study aimed to: a) assess the excess mortality in persons with mental disorders seen in both primary and secondary care, and compare these estimates with secondary care data only; b) determine the extent to which adjusting for physical comorbidities and individual-level socioeconomic factors affects the estimates.

We used individual-level register data concerning all citizens with Finnish background aged at least 20 years and living in Finland at some point between January 1, 2011 and December 31, 2017. We identified all deaths (using the Finnish Causes of Death Register), the dynamic population at risk of death (through Population Registers), and all mental health contacts (using Care Register for Health Care, in which primary care has been included since 2011) during that period. The ethical review board of the Finnish Institute for Health and Welfare approved the study protocol. Data were linked with the permission of Statistics Finland (TK-53-1696-16) and the Finnish Institute of Health and Welfare. Informed consent is not required for register-based studies in Finland.

A history of mental health related contacts was defined as having any contact with secondary care psychiatric inpatient or outpatient services, or with primary care, with a diagnosis of any mental disorder (i.e., ICD-10 chapter V, or International Classification of Primary Care-2 chapter P) within the previous year.

We collected data on the following individual-level variables: sex, urbanicity of residence area, region of residence, living alone status, level of educational attainment, economic activity, and equivalized household net income deciles. Income measurement with a three-year lag was used to account for potential reverse causation. Physical comorbidity was assessed using the Charlson Comorbidity Index (CCI), categorized by previously used cut-points: none, 1-3, and ≥4.

Three sets of data were collected and analyzed separately, concerning: a) individuals seen in primary and secondary care combined, compared with those without such contacts; b) individuals seen in primary and secondary care separately, compared with those without such contacts; c) individuals seen in secondary care only, compared to all individuals without such contacts (including individuals with possible primary care treatments), which is the traditional approach.

Mortality rate ratios (MRRs) were estimated using a Poisson regression model. Men and women were analyzed separately. To investigate the association between physical comorbidities and mortality, a stratified analysis for the CCI categories was performed. In addition, the ICD-10 diagnostic blocks were analyzed separately. We performed sensitivity analyses using three- and five-year histories of mental health related contacts. R and Stata were used for the analyses.

During the period between 2011 and 2017, we observed 4,417,635 individuals (51.3% women), contributing 28,049,912 person-years. Along that period, 860,287 (19.5%) of all observed individuals had mental health related contacts, more commonly in primary care. Mood disorders was the most commonly used ICD-10 diagnostic block. Altogether, 357,119 persons died (50.3% women), of whom 44,364 (12.4%) had had some contact with psychiatric secondary or primary care within the previous year.

Age and calendar year adjusted MRRs of 2.83 (95% CI: 2.79-2.87) and 1.79 (95% CI: 1.76-1.82) were observed for men and women with a one-year history of primary or secondary care mental health contacts, compared to those without. After SEP adjustments, MRRs of 2.17 (95% CI: 2.13-2.20) and 1.71 (95% CI: 1.68-1.74) were observed. After further adjustments for physical comorbidities, the estimates decreased to 1.63 (95% CI: 1.60-1.65) and 1.20 (95% CI: 1.18-1.22), respectively. These SEP and comorbidity adjusted MRR estimates were 27% and 42% lower, respectively, compared to the MRRs of 2.24 (95% CI: 2.19-2.30) and 2.07 (95% CI: 2.01-2.12) obtained with the traditional approach considering secondary care only.

In diagnosis-specific analysis, the highest SEP and comorbidity adjusted MRRs were observed in disorders related to substance use. Excess mortality varied by age and turned to decrease in both men and women starting from the age of 35 years (see supplementary information).

Individuals with recent primary care mental health contacts had more commonly diagnosed physical comorbidities than individuals treated in psychiatric secondary care (24.5% vs. 18.1% of person-time). The presence of physical comorbidities modified the association between mortality and a one-year history of mental health contact: excess mortality related to mental disorders was the highest in people without comorbidities, and the lowest in people with multiple comorbidities. Sensitivity analysis with three- or five-year histories of treated mental disorders, instead of one year, showed only a little difference (see supplementary information).

These findings confirm the previously reported evidence of an excess mortality in people with mental disorders, but also suggest that the previously published MRR estimates would have been considerably lower if primary care had been included in those analyses. As mental disorders are commonly treated in primary care, the current results are likely to have generalizability, especially in high-income countries. They provide a more optimistic view of the burden of mental disorders and highlight the diversity of these disorders in the population.

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This study was supported by grants from the Jalmari and Rauha Ahokas Foundation, the Finnish Psychiatric Association, and the Signe och Ane Gyllenberg Foundation. The authors thank A. Solismaa for helpful comments on this letter. Supplementary information on the study is available at https://kmmsks.github.io/mpsc.

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DOI:10.1002/wps.21027

Severe breakthrough COVID-19 infections in vaccinated patients with schizophrenia in Israel

Patients with schizophrenia show a substantial reduction in risk of COVID-19 severe illness and related mortality when vaccinated, as compared to non-vaccinated samples[1]. However, the emergence of new variants and the increased frequency of breakthrough infections[2], especially among vulnerable groups[3], raise questions regarding the long-term effectiveness of vaccines in reducing overall morbidity and mortality in these patients.

In a study conducted in Scotland, the risk of COVID-19-related hospital admission was doubled in individuals infected with the B.1.617.2 (delta) when compared to the alpha variant, and was particularly increased in those with five or more relevant comorbidities[4]. These findings suggest that individuals with schizophrenia, who are known to suffer from an excess of physical comorbidities[5,6], might present a differential pattern of risk during infection waves even if vaccinated.

To explore whether vaccinated individuals with schizophrenia present a higher risk for breakthrough infections, severe course of illness, and mortality, compared with vaccinated controls from the general population, we utilized the database of Clalit Health Services (CHS), the largest health care organization in Israel. The database was mined at the end of November 2021, almost a year after the launch of the vaccination plan in Israel, and after the fourth infection wave in Israel began to subside[7,8].

A total of 34,797 individuals diagnosed with schizophrenia at the onset of the pandemic were extracted, along with a sample of individuals with no diagnosis of schizophrenia, matched for age and gender[9]. For the current study, individuals who were not vaccinated were removed, and the sample was then re-matched for age, sex, and number of vaccinations (first, second, and booster). After excluding cases with infection prior to the vaccination plan or with inaccurate dates (4.7% of the sample), the overall sample included 24,354 subjects in the schizophrenia group, and 24,196 controls, matched for age, sex and vaccination coverage at a 1:1 ratio (total N=48,550).

The study was approved by the CHS institutional review board. Informed consent was waived due to the anonymous nature of the data. Hazard ratios (HRs) were assessed with Cox proportional hazard regression. Crude and adjusted models were assessed to control for demographic and clinical risk factors. Estimated projections of the cumulative probability of the three outcomes were obtained with Kaplan-Meier analysis. Differences in incidence of outcomes between the study groups were calculated using the incidence rate ratio (RR). Statistical analyses were performed using SPSS software, version 25.

There were 2,233 individuals infected in the total sample (4.59%), with 1,019 in the schizophrenia group (4.18%) and 1,214 in the control group (5.01%). A total of 210 individuals were hospitalized due to COVID-19 (0.43%), including 164 (0.67%) from the schizophrenia group and 47 (0.19%) from the control group. There were 29 deceased cases (0.05%) due to COVID-19, including 23 from the schizophrenia group (0.09%) and 6 from the control group (0.02%).

Survival analyses indicated that individuals with schizophrenia exhibited a significantly lower estimated probability of being infected compared with controls (log-rank test = 4.33, p=0.037); after controlling for risk factors, this difference became non-significant (HR=0.93, 95% CI: 0.84-1.03, p=0.14). On the other hand, individuals with schizophrenia showed a significantly sharper increase in the probability of being hospitalized as time progressed (log-rank test = 62.93, p<0.001), and continued to present a significantly higher risk for hospitalization even after controlling for demographic and clinical risk factors (HR=2.68, 95% CI: 1.75-4.08, p<0.001). Estimated projections of cumulative probability of mortality also differed significantly between the groups: individuals with schizophrenia were more likely to die due to COVID-19 (log-rank = 11.04, p=0.001), although this difference became non-significant after controlling for risk factors (HR=2.18, 95% CI: 0.80-

5.90, p=0.12).

To assess whether overall differences in risk between individuals with schizophrenia and controls changed during the fourth infection wave, we examined the RR of infection, hospitalization and mortality for the two groups between June and August 2022, and compared it with prior (January to May 2021) and subsequent (September to November 2022) periods. The results indicated that the RR for infection was slightly inverted during the fourth wave of infection (RR=1.021, 95% CI: 0.90-1.15) as compared with the prior (RR=0.98, 95% CI: 0.84-1.15) and subsequent (RR=0.62, 95% CI: 0.52-0.74) periods. The RR of COVID-19-related hospitalization was larger during the fourth infection wave (RR=4.19, 95% CI: 2.41-7.27) as compared with the prior (RR=3.65, 95% CI: 2.29-5.82) and subsequent (RR=3.15, 95% CI: 1.42-6.99) periods. Similarly, the RR of mortality was higher during the fourth infection wave (RR=7.61, 95% CI: 0.93-61.89) compared with the prior (RR=3.60, 95% CI: 0.99-13.08) and subsequent (RR=3.01, 95% CI: 0.60-14.95) periods.

Overall, these results suggest that vaccinated patients with schizophrenia are at increased risk for COVID-19-related hospitalization than are controls from the general population, even after controlling for demographic and clinical factors, and even when accounting for the extent of vaccination coverage through matching. Furthermore, although the overall mortality rates in the total sample were low and therefore affected the magnitude of incidence rate differences between the groups, mortality cases were more frequent in the schizophrenia group, and the RR tended to increase during the fourth infection wave. The increased risk of adverse COVID-19 outcomes for vaccinated individuals with schizophrenia during infection waves highlights the importance of conducting longitudinal studies to continuously monitor the extent of risk for patients with severe mental illness.

In this study we were not able to determine the type of COVID-19 variants. Additional studies are needed to explore whether specific variants present a greater risk for individuals with severe mental illness. Future studies should also aim to differentiate between complications that are fully related to COVID-19 and those that are secondary to other medical conditions.

The findings reported in this study indicate that individuals with schizophrenia, although taking advantage from vaccination, continue to be an at-risk group for adverse COVID-19 outcomes, which calls for the need to develop outreach programs aimed at facilitating prevention strategies for individuals with severe mental illness.

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The authors are grateful to A. Nachman and E. Horowitz Leibowitz for their assistance.

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DOI:10.1002/wps.21028

The response pattern to SSRIs as assessed by the Montgomery-Åsberg Depression Rating Scale: a patient-level meta-analysis

The effect size for antidepressants vs. placebo varies considerably among the 17 symptoms rated by the Hamilton Depression Rating Scale (HDRS)[1]. Using patient-level data (N=~13,000) from the development programs of citalopram, duloxetine, paroxetine and sertraline, we reported that there are sizeable effects on HDRS items such as depressed mood and psychic anxiety, which appear already after one week of treatment, but negligible effects, throughout the treatment period, on items that may capture side effects of selective serotonin reuptake inhibitors (SSRIs), such as insomnia, somatic anxiety, gastrointestinal symptoms, genital symptoms, and weight change[1-3]. Other authors have reported similar findings[4,5].

While the Montgomery-Åsberg Depression Rating Scale (MADRS) overlaps with the HDRS[6], there are significant differences between the two scales with respect to how the various symptoms are described. Moreover, the MADRS includes some key depressive symptoms not explicitly rated by the HDRS, such as inability to feel and concentration difficulties. Patient-level analyses of the impact of SSRIs on individual MADRS items may thus allow us to assess to what extent symptom-level findings based on HDRS ratings generalize to other instruments, and may further our understanding of the effects of SSRIs on different depressive symptoms.

We report here symptom-level MADRS ratings from 4,243 subjects participating in twelve acute phase placebo-controlled trials of an SSRI in major depression (see supplementary information). Our aims were: a) to investigate the time-course and magnitude of the effects of SSRIs on individual MADRS items; b) to assess the relation of individual MADRS items to the MADRS total score; and c) to compare drug-placebo differences for the total score of

a six-item unidimensional MADRS subscale (MADRS-6)[7] – consisting of the items reported sadness, apparent sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts – with those for the total score of the full MADRS.

Outcome measures were assessed using linear mixed models. The models included baseline score on the outcome parameter as a covariate, fixed effects for time (week), treatment (SSRI or placebo), trial, and the interaction between treatment and time. Within-subject correlations were modelled using an unstructured covariance matrix, and denominator degrees of freedom were estimated using the Kenward-Roger approximation. The parameters of interest were treatment group means over time, as well as effect sizes and levels of significance for the between-treatment comparisons.

We assessed the following outcome measures: a) the total score of the MADRS scale; b) the total score of the MADRS-6 subscale; and c) the scores on all individual MADRS items. Week 6 was selected as endpoint since that was the last available evaluation in 9 out of 12 trials. All analyses were conducted in SAS version 9.4.

All individual items showed statistically significant separation between drug and placebo at endpoint, with endpoint effect sizes ranging between 0.08 (reduced appetite) and 0.38 (apparent sadness as well as reported sadness). Five MADRS items (i.e., apparent sadness, reported sadness, inner tension, pessimistic thoughts, and suicidal thoughts) showed significant separation in favor of SSRIs after one week of treatment, with increasing separation over time until endpoint. Three items (i.e., concentration difficulties, lassitude, and inability to feel) showed significant separation in favor of SSRIs after two or three weeks of treatment and onwards. One item, reduced appetite, separated in favor of placebo after one and two weeks of treatment, but not thereafter. Reduced sleep displayed a nominally negative effect size (–0.05) at week 1, but a small though significant effect size favoring SSRIs at endpoint (0.09). The effect size was 0.37 at endpoint for the full MADRS and 0.40 for the MADRS-6 subscale (see also supplementary information).

Thus, with respect to items that overlap in content, the response pattern to SSRIs observed with MADRS appears very similar to that seen using HDRS[1]. Taken together, these results suggest that the general response pattern for SSRIs in depression is not conditional on the specific features of any particular rating instrument, but reflect true symptom-level effects of these treatments.

The effects on the three MADRS items that have only partially corresponding items in the HDRS were positive, but took somewhat longer time to develop. While concentration difficulties and anhedonia improved significantly after two weeks of treatment and onwards, lassitude required three weeks of treatment to display significant improvement (which also lasted throughout the trial).

Recent reports suggest a blunting of emotions to be a possible side effect of SSRIs, while also acknowledging a correlation between the presence of this symptom and depression severity[8]. It is hence of interest to note that SSRIs *reduced* the score on the inability to feel item in the MADRS – a symptom not included in the HDRS – with an effect size (0.32) similar to those noted for inner tension and the two sadness items (0.35-0.38). Thus, while the possibility that drug treatment may elicit this symptom in some subjects should not be overlooked, and requires further study, the net impact on emotional blunting of treating depressed subjects with an SSRI for 6 weeks appears favorable rather than harmful.

The effect sizes for individual MADRS items at endpoint generally displayed less dissimilarity than those reported for HDRS items. With the exception of reduced sleep and reduced appetite, which displayed endpoint effect sizes of 0.09 and 0.08, respectively, item-level effect sizes ranged from 0.23 (concentration difficulties) to 0.38 (reported and apparent sadness). In line with this, the difference between the full scale total score on the one hand, and the total score for the 6-item subscale, or the scores on the best performing individual items, on the other, was markedly smaller for the MADRS as compared to the HDRS[1].

In summary, symptom-level analyses on MADRS data show a response pattern highly similar to that seen in HDRS analyses, suggesting that the observed effects are not related to particularities of any chosen scale, but do reflect the true symptom-level profile of SSRIs when used for depression. While the MADRS, like the HDRS, includes some items (i.e., reduced sleep and reduced appetite) that may be contaminated by SSRI side effects[3], hence introducing a negative bias as compared to placebo, the total score of the MADRS is less impacted by the inclusion of such items than is the HDRS total score.

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Supplementary information on this study is available at https://osf.io/9527c/?view_only=2167a99597cd4bdc965ffeadda63bc47.

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DOI:10.1002/wps.21029

The WPA Scientific Sections: a global resource for education, research and care

The WPA currently comprises 66 Scientific Sections, a testament to the clinical and scientific richness of contemporary psychiatry. Like no other medical discipline, psychiatry reaches beyond a mere biological model of health and illness, integrating psychology, philosophy, spirituality, social sciences, and hands-on care into its practice. It is WPA's mission to further this unique character across the globe through its Scientific Sections.

In the last five years, the WPA has upped its efforts to enhance the communication of its Scientific Sections with each other, with other bodies of the Association, and with other global organizations[1,2]. This has led to many new initiatives, among them the Education, Science, Publication, and Research Initiative (ESPRI)[3], the WPA Exchange Program[4], and an active involvement of the Association in competitively funded research grants. Furthermore, the Sections have been instrumental in shaping the development of various online resources to help alleviate the impact of recent disasters on mental health (e.g., COVID-19 pandemic, Russia's war against Ukraine).

The ESPRI was introduced in 2020 as a vehicle to jumpstart research projects in low- and middle-income countries (LMICs), with the WPA providing seed funding to (preferably) early career investigators for carrying out scientific projects of relevance to their respective country or region and for which funding would be difficult to obtain otherwise. At this point, the WPA has funded six projects from around the globe, addressing a variety of issues: major depression in old age (Tanzania); psychological impact of Ebola and COVID-19 (Liberia); genomics of bipolar disorder (Nigeria); poverty alleviation for persons with mental health problems (Pakistan); transdiagnostic and transcultural web-based psychotherapeutic tools (Pakistan); and development of training tools for the examination and documentation of the psychological sequelae of torture and war (UK, Austria and Syria).

While the topics are quite different, the common denominator of these ESPRI projects is that they implement or pilot novel approaches that eventually can lay the foundation for larger third party-funded projects. All projects need to be supported by at least one WPA Scientific Section. The WPA encourages ESPRI projects to be spearheaded by early career psychiatrists and requires that the respective institutions provide matching funds to an ESPRI investigator, either as cash awards or in-kind support. It is WPA's hope that this approach will help increase both the national and international visibility of promising researchers from LMICs.

WPA's commitment to early career colleagues has also been the driving force behind the establishment of the WPA Exchange Program (worldpsychiatryexchangeprogram.wordpress.com), conceptualized and spearheaded by the Early Career Psychiatrists Section. Open to the members of this Section (which welcomes physicians currently in postgraduate psychiatric training or within 7 years after specializing in psychiatry), the program is meant to support cross-continent exchanges to engage in clinical, research or teaching activities. At present, institutions from Belgium, Brazil, Croatia, Iran, New Zealand, Tunisia and the UK have joined the program. After a delay of over one year due to the COVID-19 pandemic, first placements of candidates have been made. The WPA leadership is looking forward to hearing from participants about their experiences and suggestions on how to further develop this program.

To further strengthen its role not only as an umbrella organization of national psychiatric societies but also as a platform and resource to perform state-of-the-art research of global scope, the WPA encourages Scientific Sections to take an active role in applying for competitive funding, given the unique expertise represented across them. This push for scientific visibility recently proved successful: under the leadership of the Secretary for Scientific Sections and the Section on Genetics in Psychiatry, the WPA is now a partner and institutional investigator in the multinational research consortium PSY-PGx (www.PSY-PGx.org), funded by the European Commission within the Horizon 2020 framework.

PSY-PGx is the first non-commercial, large-scale, international psychiatric pharmacogenomics initiative with the overarching aim to produce robust data that will eventually contribute to precision psychiatry, reducing individual and societal burden of psychiatric illness[5]. The WPA will take a leading role in the dissemination and education aspects, directing its efforts both at the clinical community and the general public. With the expert guidance provided by the Section on Genetics in Psychiatry, the WPA will use its recently launched learning management system (LMS)[6], diverse conference formats, as well as bespoke tools to inform psychiatrists around the world about the latest developments in pharmacogenomics of relevance to everyday clinical work.

A key component and major strength of this activity is a close collaboration with representatives of service users and carers. To this end, the WPA will perform this research together with representatives of its Service Users and Family Carers Advisory Group (www.wpanet.org/wpa-service-users-and-family-carers)[7] and of GAMIAN (www.gamian.eu). Like the WPA, GAMIAN receives its own funding within PSY-PGx.

Very recently, another project (PSYCH-STRATA) submitted to the European Commission, focusing on multimodal predictors of treatment resistance in psychiatry, was granted funding for five years. As with PSY-PGx, the WPA will co-lead the global dissemination efforts and help make the patients' voices heard.

It is WPA's first and foremost goal to advance mental health for people all over the world, to encourage the highest possible standards of clinical practice and ethical behavior in psychiatry, and to be a voice for the dignity and human rights of patients and their families. This is never more important than in times of exceptional crises like the ones we are witnessing today, with the COVID-19 pandemic[8] and the Russian war of aggression against Ukraine[9] taking their toll on the most vulnerable. With the help of its Scientific Sections, the WPA has been able to develop valuable online resources to aid in alleviating the suffering

caused by these crises.

Over the past decade, WPA Scientific Sections have substantially contributed to the Association's global leadership in psychiatric practice and care. WPA's strength lies in its global reach and diversity. And these are not just hollow words: with almost each Section having members in every corner of the world, the WPA cannot only raise its voice but also lend its hand whenever and wherever psychiatric expertise is needed.

The WPA will continue to foster collaboration between its Scientific Sections. Only through a well-developed intersectional infrastructure, will the Association be able to achieve its goals as laid out in its triennial Action Plan[10-12]. WPA's intersectional activities (e.g., symposia, courses, workshops) have become a staple of WPA meetings and will be showcased in a WPA Thematic Congress on Intersectional Collaboration, "New Horizons in Psychiatric Practice: Creative Ideas and Innovative Interventions", to be held in Malta on November 10-12, 2022.

Thomas G. Schulze
WPA Secretary for Scientific Sections

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DOI:10.1002/wps.21011

We share more attributes than we think: the crucial input of epidemiology

Psychiatric epidemiology, as is the case for most domains in psychiatry, does not have strict borders in what goes under its umbrella. Still, it can be broadly defined as covering, among other subjects, the various environmental and genetic etiologies, the course and prevalence, and the two-way relation of societal factors in mental disorders, all in large samples of individuals.

An interesting observation is that psychiatric epidemiology consolidates a major axiom, simple at first look, but profound in its implications: broadly speaking, humans share much more common mental attributes than we had thought. In fact, studying very large populations across the globe has taught us very clearly that there are major highways which seem to be predetermined by the simple fact that we belong to a given species.

Be it the effects of prenatal factors, including genetics, of childhood adversities, of major trauma, war, economics, chronic illnesses or temperament; be it schizophrenia, post-traumatic stress disorder or phobias; all studies point increasingly in cross-national samples to similar conclusions. This makes the field of psychiatric epidemiology quite interesting, echoing its origins in the more sociological approach to mental health and now looking at the variety of biological markers and their relation to determinants of onset, course and treatment of mental health disorders. This has been, understandably, a very exciting field, which has defined the lifelong commitment of members of the WPA Section on Psychiatry Epidemiology and Public Health over the years.

This Section was founded in 1967 and re-named "Epidemiology and Community Psychiatry" until 1997, when it acquired its present name. The Section gathered progressively the most prestigious experts in psychiatric epidemiology and public health, such as J. Wing, who was its president for years, and designed the famous Present State Examination (PSE), followed by the Schedule for Clinical Assessment of Neuropsychiatry (SCAN)[1]; H. Hafner, who conducted a unique work on the epidemiology of schizophrenia[2]; and N. Sartorius, who worked on behalf of the World Health Organization all over the world, and led among others the influential International Pilot Study of Schizophrenia[3].

Other prominent Section members pioneered the discipline by launching extensive populations surveys, such as T. Helgason in Iceland, with a birth cohort of more than five thousand probands followed up to their deaths[4], and A. Leighton and J. Murphy in Canada, who set up the Stirling County Study, a large population survey allowing to study population mental health up to the fourth generation[5].

To this list we can add L. Robins, who designed the Diagnostic Interview Survey (DIS)[6], the first diagnostic interview usable by lay interviewers, a huge step in mental health epidemiology, whose DSM-III computerized algorithms allowed to evaluate the prevalence of mental disorders in the US in the Epidemiological Catchment Area Study, a landmark in the field under the leadership of D. Regier[7]. That instrument stimulated the development of the now worldwide used and continuously evolving Composite International Diagnostic Interview (CIDI)[8], which, under the inspiring leadership of R. Kessler, was used in the World Mental Health (WMH) Initiative, that gathered surveys in 40 countries all around the world, and is still growing, with more than 1,000 publications so far (www.hcp.med.harvard.edu/wmh). The output from WMH covers a huge variety of subjects, including prevalence, risk factors, burden, course, treatment, conceptualizations and definitions of most mental disorders. Many of the WMH contributors are active members of our Section.

Looking back, the Section has been able to organize twenty meetings all around the world. The themes of these meetings reflected the large scope of epidemiology and public health in the domain of psychiatry and mental health. Some meetings were more clinically oriented, such as "The Chronically Mentally ill" (Baltimore, US, 1982), "Primary Care and Psychiatric Epidemiology" (Toronto, Canada, 1989), and "From Epide-

miology to Clinical Practice" (Turku, Finland, 1999). Others focused on longitudinal perspectives, such as "The Course and Outcome in Mental Health Disorders" (Groningen, The Netherlands, 1993), "Prediction is Psychiatric Epidemiology: from Childhood and Adolescents to Adulthood" (Lisbon, Portugal, 2010), and "Epidemiology of Mental Disorders Across Lifespan and Development" (New York, US, 2018). Some focused more on research, such as "A Search for Causes: Epidemiological Approaches" (New York, US, 1995), "Psychiatric Epidemiology and Social Sciences" (Oslo, Norway, 1991), "Theory Evidence and Psychiatric Epidemiology" (Paris, France, 2003), and "Psychiatric Epidemiology Meets Genetics: The Public Health Consequences" (Munich, Germany, 2016). Two meetings focused on "The Future of Epidemiology" (Edinburgh, UK, 1985, and Baltimore, US, 2001).

Public health aspects were the focus of several more meetings: "Unmet Needs" (Sydney, Australia, 1997), "Epidemiology and Medical Economics" (Brisbane, Australia, 2006) and "From Epidemiology to Mental Health Planning" (Saskatoon, Canada, 2008). Others focused more on risk factors, such as "Mental Health and Urbanization: Challenges of Societies in Transformation" (Sao Paulo, Brazil, 2012) and "Trauma and Mental Health" (Nara, Japan, 2014). The forthcoming meeting will be held for the first time in Africa, in Morocco: "Learning from Diversities Across the World: Implications for Psychiatric Epidemiology", scheduled for October 2022.

We carry a tradition in our meetings, which is to minimize parallel sessions, in order to foster real exchange between the presenters and the audience. We thus set up a theme and then try, as much as possible, to organize sessions coherent with this theme, with highly recognized speakers and much time devoted to active discussions. The concentration of highly committed specialists during these meetings has been a great source of inspiration for many beginners in the field, and has been decisive for the career of many young researchers. The atmosphere is typically friendly, and sessions deal with a very limited number of topics, which allows beginners and experts to dig deeper.

In conclusion, the broad perspective of epidemiology and public health in all areas of mental health encourages international collaboration, and crucially examines how much, in fact, humans look alike and how lessons learned from one site can be generalized to humans all over.

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DOI:10.1002/wps.21012

WPA communications under reorganization

The problem of communications is one of the highest priorities in all international organizations. This has become especially noticeable after the start of the COVID-19 pandemic and the subsequent restrictions on direct communication between members of any organization[1]. An effort to restructure communication processes in the WPA was long overdue, and the new leadership of the Association has had to significantly expand and change many functions in this process, and to introduce a new WPA communication concept[2-5].

In every organization, communications can be divided into internal and external. Internal, in our case, are communications between all components of the WPA: the Executive Committee, the WPA Secretariat, the Zonal Representatives (the Board), the WPA Council, the Collaborating Centers[6], the Scientific Sections, the various Committees and, of course, Member Societies. External communications include any exchange of each component of the WPA with the outside world.

One of our immediate tasks has been the problem of digitalization of the work of the WPA Secretariat. As a result of the pandemic, the WPA has faced a major crisis, with a variety of financial and organizational problems[2,7]. The whole Association has had to step up to solve these problems and become stronger and more professional. This move has involved changing the roles, responsibilities and tools of the Secretariat, with the active support of all components of the Association[8].

It was decided to actively implement digital tools designed for internal communication, to use an automation and integration system to reduce time-consuming and repetitive tasks, and to more actively apply planning and workload management. It was also necessary to streamline the management of stakeholders and the exchange of documentation, and to determine in advance the workload forecast.

The Secretary General is required to keep ongoing relations with the various components of the WPA, which includes regular work with the Secretariat, developing strong relationships with the members of the Executive Committee, maintaining relations with Member Societies and Scientific Sections, liaising with the WPA communications consultant, overseeing communications with relevant media, and reporting regularly to the President[8].

The Secretariat must carefully track records of all incoming e-mails on the website and respond to individual inquiries within 24 hours of receipt. It oversees the management of all subscriptions associ-

ated with the site, uploads all the relevant documents, and keeps the membership updated about all major events concerning the Association[9]. The WPA Secretariat also keeps track of all standard letters regarding fees and administration, maintains mailing lists/contacts, and ensures that they are up-to-date for all WPA components. Despite the objective difficulties of the past six months and the increased workload, the Secretariat has generally managed to transition successfully to this new communication model.

A necessary part of optimizing communication has been to reorganize the WPA website (www.wpanet.org)[10,11]. In general, the work on the restructuring of the WPA website has been completed, but it has not been easy to meet the limited budget allocated for solving important tasks. These include the Association's presence on the Internet and social media; copywriting, editing and preparation of presentations, publications and communications with stakeholders; and providing advice and support when needed.

In terms of the Internet and social media, a communications consultant has been appointed to manage the WPA website, developing and uploading content as needed. This includes creating, editing and uploading news; creating and/or updating new pages, layouts, forms, menu items as needed; uploading new training webinars and other materials to the educational portal, as well as edited documents or texts such as presidential messages and position statements.

A new initiative of the last few months has been the upgrade of the Association's presence in social networks. At the initiative of the President, special WPA sections have been created in various networks, such as Facebook and YouTube, and a number of new materials have been developed for psychiatrists around the world. With the help of the communications consultant, a whole series of recordings have been uploaded on YouTube, such as memoirs of former WPA presidents and reports of members of the Executive Committee on their duties and responsibilities.

One of the highest priorities and important areas of work, successfully promoted and organized in practice, has been the creation of a quarterly electronic WPA Newsletter[8]. The first issue has been delivered in June 2021, with more than 40 articles from various components of the WPA. Four subsequent issues have been then released, and this process continues successfully.

The electronic WPA Newsletter is published quarterly. The Secretary General is responsible for its publication, but the overall coordination of this ambitious project is ensured directly by the WPA President. The WPA Executive Committee approves the plan and structure of each issue of the Newsletter.

A new very stimulating and promising initiative has been the launch of a WPA electronic journal, a kind of digest of the most interesting recent scientific publications in the field of psychiatry, prepared by young professionals from different countries[12].

In conclusion, it can be said that the process of reorganization of WPA communications is developing in accordance with the initial plan.

Petr V. Morozov
WPA Secretary General

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DOI:10.1002/wps.21013

Update on WPA Scientific Meetings

It has been an uncertain, unpredictable and turbulent time during the past two years, due to the COVID-19 pandemic[1]. This time has brought with it many challenges but has also provided the WPA with many opportunities. We have strived together and advanced in terms of holding high-quality WPA meetings. We are proud of these accomplishments, and the WPA could have not achieved them without the strong commitment of the organizers, including Member Societies and Scientific Sections[2]. Also, the contribution of the Executive Committee in quickly reviewing and approving the proposed meetings, the work of the Standing Committee for Scientific Meetings, and the continuing support of the WPA Secretariat have to be acknowledged.

For this time of limited in-person gathering, the WPA has built a state-of-the-art platform designed to make the virtual experience easy, educational, convenient, interactive and memorable. The virtual format meeting, implemented this way, is an excellent way to allow WPA Member Societies to network, continue to build bonds with each other, and allow all to participate within their own safety. Virtual meetings have allowed us to create new opportunities and make the events even more accessible to a worldwide audience.

The WPA has continued to closely monitor the global risk assessment regarding the pandemic and its impact on international travel to hold face-to-face meetings. It appears that we start seeing some light at the end of the tunnel, since certain travel restrictions have been gradually lifted around the world. The Association is having now again face-to-face meetings, starting from the World Congress of Psychiatry in Bangkok, Thailand, held from August 3 to 6, 2022. We hope that the future WPA meetings will again promote the unique bonds that hold our Member Societies together and get all these Societies re-energized and re-engaged during the coming years. For sure, the WPA will adjust to and embrace whatever the future normalcy/normality we will be facing during the post-pandemic era.

At the same time, the WPA aims to promote an increasing understanding of public mental health among professionals and the public, including collaboration with

patient and family organizations[3,4]. The scientific meetings are geared up to align with the WPA Action Plan 2020-2023 and to address its priorities[5-8].

The programme of WPA meetings has been in full swing. We have continued to do our utmost to promote the mission of the Association and to contribute to its achievements and success, working closely with the Executive Committee and the Secretariat to oversee and co-ordinate all official meetings and manage applications for co-sponsored meetings, and maintaining responsibility for the development of proposals to host the World Congresses of Psychiatry, and assist in all aspects of their organization[9,10].

The following meetings are confirmed or proposed for the near future: the Thematic Congress "Treatment and Management of Mental Disorders in a Post-Pandemic Era", Tbilisi, Georgia, October 14-16, 2022; the Intersectional Thematic Congress "New Horizons in Psychiatric Practice: Creative Ideas and Innovative Interventions", Malta, November 10-12, 2022; the Regional Congress "African Psychiatry in the 21st Century: Achievements and Future Perspectives", Hammamet, Tunisia, December 8-10, 2022; the Thematic Congress "Mental Health in a New Era", Karachi, Pakistan, March 3-5, 2023; the Regional Congress "Building Awareness – Bridging Treatment Gap", organized by the South Asian Association for Regional Cooperation (SAARC) Psychiatric Federation, Kolkata, India, April 14-16, 2023; and the World Congress of Psychiatry, Vienna, Austria, September 28-October 1, 2023.

There are more WPA meetings and co-sponsored meetings in the pipeline and we will update the list regularly.

In light of the past two years, the WPA will not succumb to the "pandemic fatigue" and will not detour its path. Now is time for the Association to press on with its mission and vision. We are confident that, by embracing these opportunities, taking global action and working closely together with international collaborations, we will overcome all the challenges. Together we shall move forward and continue to define the future in psychiatry.

Edmond H. Pi
WPA Secretary for Scientific Meetings

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DOI:10.1002/wps.21014

WPA educational initiatives: reaching different stakeholders in the mental health field

Due to the COVID-19 pandemic, there has been a major restriction in access to face-to-face educational opportunities[1]. Mental health professionals working in underserved regions have suffered greatly, as expertise in mental health field is mostly concentrated in high-income countries. Yet, the WPA has been able to set up an education portal in its website, and to launch a variety of educational activities including live webinars, recorded webinars, and educational courses[2-6].

We have now more than twenty recorded webinars, covering a diverse range of topics, from mental health prevention to early intervention, psychiatric rehabilitation and recovery services. In the education portal, there are mental health resources in eighteen different languages, which are visited by professionals from many countries across the world. Apart from the education portal, the WPA website also provides updated mental health resources in relation to the COVID-19 pandemic and to supporting mental health professionals working for people adversely affected by the war in Ukraine.

Moving ahead, there will be regular live webinars once a month on a range of mental health topics, with the support from experts of WPA Scientific Sections. There will also be live webinars delivered by service users and carers, in collaboration with the WPA Advisory Group of Service Users and Carers[7]. Such webinars will provide fresh insight to the participants about how users and carers can play a significant role in the design, delivery and evaluation of mental health services even in resource-constrained regions around the globe.

While educational resources and live webinars available in the WPA education portal address the knowledge needs of various stakeholders, they cannot meet the requirements of skills transfer and acquisition among mental health professionals. To target this area, the WPA Workgroup on Volunteering has conducted two pilot projects in Mexico and Pakistan[8].

These two projects have provided enormous insight about the way forward with volunteering in terms of skill transfer and acquisition in a culturally sensitive and relevant manner. There were high levels of satisfaction among the expert volunteering trainers and the trainees from both hosting countries. For the second pilot project, the local expert trainers were also involved, and the expert volunteers were able to build up trust and long-lasting relationships with them to collaborate in developing a local training programme for psychiatric trainees in child and adolescent psychiatry. Such training can pave the way forward for the future set-up of national child and adolescent mental health services across Pakistan.

The Workgroup has now opened the application for further projects to all WPA Member Societies and would expect to provide more volunteering experiences from different countries as well. It is the aspiration of the Workgroup that additional Member Societies from other continents such as Africa, South America and Europe will be able to participate in this programme.

While the WPA has developed new strategies to disseminate mental health knowledge and skills to various stakeholders, it is also important for the Association to understand the training needs of the various Member Societies, so that more proactive

and in-reach efforts can be made to support those countries in need of more extensive and systematic educational support.

A WPA global survey on the training landscape of psychiatrists has been conducted in 2019/2020 with the aim to depict a comprehensive profile of training levels and experiences of psychiatrists around the world[9,10]. This is providing valuable guidance to the WPA about focusing its resources and effort to support those countries with most pressing shortage of training for their psychiatrists.

Upon the conclusion of the first phase of this survey, the WPA has received responses from most of the Member Societies with a large number of psychiatrists, so that the results have been representative of the current training profiles of countries with good mental health resources. Yet, the limited responses from regions with underserved populations have led the Association to planning for a second phase of the survey. In order to encourage responses from Member Societies of these latter regions, we will send them e-mail requests along with the report of the first phase of the survey. It is hoped that this will arouse their interests in contributing their local training data, so that the final survey report can come up with a more representative training landscape of psychiatrists around the globe.

Last but not least, the WPA is acutely aware that some educational resources available in the education portal or used in volunteering projects might not be culturally appropriate and relevant, given that most of them were developed in the Western world with relatively more mental health resources. We now endeavour to work with a range of WPA Scientific Sections to develop new guidelines on various mental health disorders with particular attention to the needs of low- and middle-income countries.

Indeed, in the WPA survey of training needs of psychiatrists around the globe, there have been comments from respondents that more culturally relevant and appropriate training resources in the form of books, videos, workshops and webinars would need to be developed to cater for professionals working in low- and middle-income countries[11]. For example, most national guidelines on treatment of psychoses were developed in Western countries and have been used as educational resources for mental health professionals across the globe. Many medications available in Western countries might not be available in countries with limited mental health resources. A truly international guideline should take into account cultural differences in resources, clinical presentations, relevant and acceptable treatments, and prognoses[12].

The period covered by the current WPA Action Plan[3-5] will end in 2023. It is our aspiration that the above educational initiatives bring about some positive changes in global psychiatric education before this term ends. All interested readers are welcome to send us their comments and feedback.

Roger M.K. Ng
WPA Secretary for Education

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DOI:10.1002/wps.21015

Update on the activities of the WPA Secretary for Publications

Like many other national and international associations and organizations, particularly among those working in the field of mental health, the WPA has had to face, since the beginning of 2020, an unprecedented accumulation of obstacles to the development of exchanges and projects that are at the heart of its most specific mission, i.e., its capacity to foster exchanges that make the mental health world a global village and to build bridges across political, economic and cultural divides.

Thus, with the notable exception of the persistent success of *World Psychiatry*, which is, by far, WPA's main publication, the WPA editorial policy has had to reduce what is one of its essential leverages: those face-to-face scientific interactions which, beyond the sharing of new trends and developments, are as much an opportunity to meet our colleagues from around the world, to build innovative projects with them and support their effective implementation[1-3].

Doing against all odds, my activity as Secretary for Publications has been therefore mainly concerned with contributing to the efforts made by the WPA Executive Committee (under the President's committed leadership) to keep the flame of the association alive by using as much as possible the means to do so at a distance[4-8].

We have been able to keep on organizing remote sessions on WPA-related books and publications at our virtual World Congresses in 2020 (Bangkok) and 2021 (Cartagena), with the active participation of several WPA Scientific Sections and the partnership of several international associations. After this, we have resumed a face-to-face organization during the Bangkok 2022 World Congress, with the same high number of presentations as in previous virtual and face-to-face versions.

In this same perspective, we have also been able to resume, with a relatively limited delay, the project of publishing another WPA co-sponsored thematic issue in an English-speaking regional mental health journal. On the initiative of J. Mari, who is a member of our Committee on Publications, it is, this time, an issue of the Brazilian journal *Trends in Psychiatry and Psychotherapy*, dealing with cannabis and the questions raised by its decriminalization and the forms that its regulation takes in the different regions of the world.

We have to mention as well the progress made on projects to publish state-of-the-art books on various topics, particularly those resulting from the Working Groups set up

by the President[6]. The first one is scheduled to be on child and adolescent psychiatry.

Finally, a word must be said about the continuing efforts to diversify the language used by the WPA at various levels: first, in its online resources, through its new website set up during H. Herrman's presidency[9]; second, through the development of virtual symposia in French and Spanish at WPA meetings (one of the few positive consequences of the development of this communication modality); and finally, in this same field, through the efforts made to avoid that the legitimate international reactions provoked by the invasion of Ukraine by Russia penalize our Russian colleagues by depriving them of the translations in Russian of several WPA works, thanks to the efforts of the translation team led by our Secretary General P. Morozov[10].

Michel Botbol
WPA Secretary for Publications

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DOI:10.1002/wps.21019

Acknowledgement
This publication has been partially supported by
an unrestricted educational grant from Janssen-Cilag SpA,
which is hereby gratefully acknowledged.