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Saving the UN Convention on the Rights of Persons with Disabilities – from itself

The United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD) is a problem child of international human rights law. Like the girl with a little curl right in the middle of her forehead, immortalized in rhyme by H.W. Longfellow, when it's good, it's very, very good, and when it's bad it's horrid[1]. In embodying the rights of people with disabilities to accessibility, education, health, privacy, and other conditions likely to encourage their flourishing, the CRPD offers hope to people around the world whose disabilities have been the basis for their exclusion from the usual aspirations of life. However, in promoting restrictions in Article 12 on governments' abilities to intervene to protect the interests and rights of disabled persons, the CRPD – at least as interpreted by the UN Committee on the Rights of Persons with Disabilities (the Committee), set up to oversee its implementation[2] – may end up hurting the very people it purports to help.

As Szmukler notes in his thoughtful essay in this issue of the journal[3], the CRPD is being interpreted by the Committee as precluding any involuntary intervention targeted at people with disabilities. Thus, under this view of the CRPD, elderly persons with dementia, no longer able to care for their own needs but unwilling to accept management of their finances, health, or living situations by a guardian, could not be compelled to do so. People intending to end their lives as a result of major depression could not be hospitalized against their will, nor could persons suffering from psychosis who are refusing to eat because they believe their food is poisoned. Someone in the manic stage of bipolar disorder would be free to dissipate his family's savings or wreck her business. In the name of protecting all these people from discrimination, they would be free to destroy their own lives and ruin the lives of their loved ones.

I have considered elsewhere how we arrived at this state[4]. In short, blame is due to a drafting process that was captured by some of the most radical elements of the patients' rights movement, which are willing to sacrifice the well-being of persons with disabilities to achieve what they see as their long-term political goals. It falls as well on the many governments around the world that thoughtlessly ratified the CRPD without considering its implications. Here, though, I want to focus on strategies for addressing the problems raised by the CRPD going forward. As best I can tell, there are three alternatives: ignore the CRPD, reinterpret it, or amend it.

Ignoring the CRPD, or at least those portions of it that are particularly problematic, might not seem like a viable alternative, given that the overwhelming majority of countries in the world – 177 at last count[5], with the US a major exception – have ratified the document. In practice, however, that may not be the case. Szmukler cites a recent decision of the European Court of Human Rights which he characterizes as reinterpreting the CRPD, but which could equally well be considered simply to have ignored Article 12 and its limitations. The court held that "The [appointment of a substitute decision maker for a person with intellectual disabilities] was proportional and tailored to the applicant's circumstances, and was subject to review by competent, independent and impartial domestic courts. The measure taken was also consonant with the legitimate aim of protecting the applicant's health, in a broader sense of his well-being"[6]. Along similar lines, as Dawson[7] notes, several countries ratified the Convention with reservations that would negate the more restrictive aspects of Article 12, or in their biennial reports have simply asserted that they were in compliance when they clearly were not.

Reinterpreting the CRPD in ways that differ from the approach taken by the Committee is another way of dealing with the problems. Those efforts have included arguments that protecting vulnerable people does not constitute discrimination – indeed, ignoring their vulnerability may be discriminatory[4,7]; that when rights protected by the CRPD are in conflict, e.g., preservation of life vs. exercise of legal capacity, the more important right should take precedence[8]; and that even the language of Article 12 itself appears to recognize that limitations on a person's decision-making power may be necessary[7]. Szmukler's analysis of the ways in which "will" and "preferences" – key terms in the CRPD – may be in conflict, and the logic in privileging sustained will over short-term preferences, falls into this category as well. In my view, all of these critiques of Article 12, which is a deeply flawed and internally inconsistent provision, are cogent. However, given the low probability that the Committee will be led by these critiques to change its interpretation, the arguments' efficacy will likely depend either on persuading states to ignore the counterproductive aspects of the CRPD or to pursue a more radical remedy, namely amendment of the CRPD.

Amending the CRPD may be the most effective long-term solution to the problems that so many governments and commentators have identified. It will not be an easy process. Drafting the CRPD required a roughly five-year effort, involving scores of non-governmental organizations and hundreds of individuals[9]. However, the CRPD itself (Article 47) envisions a less arduous process by which amendments can be made, allowing any state that is a party to the CRPD to propose an amendment, which can be considered with the support of one-third of states and adopted by a vote of two-thirds. Resistance can be anticipated from the Committee and the more radical parts of the disability rights movement that succeeded initially in capturing the drafting process; hence, success will depend on mobilization of governmental agencies, professional organizations, academics, family organizations, and disabled persons themselves to lobby their governments regarding the need for change. Only amending Article 12 can definitively reverse the extreme interpretation of the Committee and remove the

specter of international condemnation of any country that fails to comply with its approach.

Until that occurs, we can anticipate that governments and others responsible for the welfare of people rendered vulnerable by their disabilities will – and I would suggest should – ignore the Convention when it would interfere with a commonsense approach to protecting citizens who in one way or another are incapable of protecting themselves. For the future, the lesson to be learned is the critical importance of involvement of state representatives, professional organizations, and individual experts representing mainstream positions in the process of drafting crucial international documents.

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Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders

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Following approval of the ICD-11 by the World Health Assembly in May 2019, World Health Organization (WHO) member states will transition from the ICD-10 to the ICD-11, with reporting of health statistics based on the new system to begin on January 1, 2022. The WHO Department of Mental Health and Substance Abuse will publish Clinical Descriptions and Diagnostic Guidelines (CDDG) for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders following ICD-11's approval. The development of the ICD-11 CDDG over the past decade, based on the principles of clinical utility and global applicability, has been the most broadly international, multilingual, multidisciplinary and participative revision process ever implemented for a classification of mental disorders. Innovations in the ICD-11 include the provision of consistent and systematically characterized information, the adoption of a lifespan approach, and culture-related guidance for each disorder. Dimensional approaches have been incorporated into the classification, particularly for personality disorders and primary psychotic disorders, in ways that are consistent with current evidence, are more compatible with recovery-based approaches, eliminate artificial comorbidity, and more effectively capture changes over time. Here we describe major changes to the structure of the ICD-11 classification of mental disorders as compared to the ICD-10, and the development of two new ICD-11 chapters relevant to mental health practice. We illustrate a set of new categories that have been added to the ICD-11 and present the rationale for their inclusion. Finally, we provide a description of the important changes that have been made in each ICD-11 disorder grouping. This information is intended to be useful for both clinicians and researchers in orienting themselves to the ICD-11 and in preparing for implementation in their own professional contexts.

Key words: International Classification of Diseases, ICD-11, diagnosis, mental disorders, clinical utility, dimensional approaches, culture-related guidance

In June 2018, the World Health Organization (WHO) released a pre-final version of the 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11) for mortality and morbidity statistics to its 194 member states, for review and preparation for implementation[1]. The World Health Assembly, comprising the ministers of health of all member states, is expected to approve the ICD-11 at its next meeting, in May 2019. Following approval, member states will begin a process of transitioning from the ICD-10 to the ICD-11, with reporting of health statistics to the WHO using the ICD-11 to begin on January 1, 2022[2].

The WHO Department of Mental Health and Substance Abuse has been responsible for coordinating the development of four ICD-11 chapters: mental, behavioural and neurodevelopmental disorders; sleep-wake disorders; diseases of the nervous system; and conditions related to sexual health (jointly with the WHO Department of Reproductive Health and Research).

The mental disorders chapter of the ICD-10, the current version of the ICD, is by far the most widely used classification of mental disorders around the world[3]. During the development of the ICD-10, the WHO Department of Mental Health and Substance Abuse considered that different versions of the

classification had to be produced in order to meet the needs of its various users. The version of the ICD-10 for statistical reporting contains short glossary-like definitions for each disorder category, but this was considered to be insufficient for use by mental health professionals in clinical settings[4].

For mental health professionals, the Department developed the Clinical Descriptions and Diagnostic Guidelines (CDDG) for ICD-10 Mental and Behavioural Disorders[4], informally known as the "blue book", intended for general clinical, educational and service use. For each disorder, a description of the main clinical and associated features was provided, followed by more operationalized diagnostic guidelines that were designed to assist mental health clinicians in making a confident diagnosis. Information from a recent survey[5] suggests that clinicians regularly use the material in the CDDG and often review it systematically when making an initial diagnosis, which is counter to the widespread belief that clinicians only use the classification for the purpose of obtaining diagnostic codes for administrative and billing purposes. The Department will publish an equivalent CDDG version of ICD-11 as soon as possible following approval of the overall system by the World Health Assembly.

More than a decade of intensive work has gone into the development of the ICD-11 CDDG. It has involved hundreds of content experts as members of Advisory and Working Groups and as consultants, as well as an extensive collaboration with WHO member states, funding agencies, and professional and scientific societies. The development of the ICD-11 CDDG has been the most global, multilingual, multidisciplinary and participative revision process ever implemented for a classification of mental disorders.

GENERATING THE ICD-11 CDDG: PROCESS AND PRIORITIES

We have previously described the importance of clinical utility as an organizing principle in developing the ICD-11 CDDG[6,7]. Health classifications represent the interface between health encounters and health information. A system that does not provide clinically useful information at the level of the health encounter will not be faithfully implemented by clinicians and therefore cannot provide a valid basis for summary health encounter data used for decision making at the health system, national and global level.

Clinical utility was, therefore, strongly emphasized in the instructions provided to a series of Working Groups, generally organized by disorder grouping, appointed by the WHO Department of Mental Health and Substance Abuse to make recommendations regarding the structure and content of the ICD-11 CDDG.

Of course, in addition to being clinically useful and globally applicable, the ICD-11 must be scientifically valid. Accordingly, Working Groups were also asked to review the available scientific evidence relevant to their areas of work as a basis for developing their proposals for ICD-11.

The importance of global applicability[6] was also strongly emphasized to Working Groups. All groups included representatives from all WHO global regions – Africa, the Americas, Europe, Eastern Mediterranean, Southeast Asia, and Western Pacific – and a substantial proportion of individuals from low- and middle-income countries, which account for more than 80% of the world's population[8].

A shortcoming of the ICD-10 CDDG was the lack of consistency in the material provided across disorder groupings[9]. For the ICD-11 CDDG, Working Groups were asked to deliver their recommendations as "content forms", including consistent and systematic information for each disorder that provided the basis for the diagnostic guidelines.

We have previously published a detailed description of the work process and the structure of the ICD-11 diagnostic guidelines[9]. The development of the ICD-11 CDDG occurred during a period that overlapped substantially with the production of the DSM-5 by the American Psychiatric Association, and many ICD-11 Working Groups included overlapping membership with corresponding groups working on the DSM-5. ICD-11 Working Groups were asked to consider the clinical utility and global applicability of material being developed for the DSM-5. A goal was to minimize random or arbitrary differences between the ICD-11 and the DSM-5, although justified conceptual differences were permitted.

INNOVATIONS IN THE ICD-11 CDDG

A particularly important feature of the ICD-11 CDDG is their approach to describing the essential features of each disorder, which represent those symptoms or characteristics that a clinician could reasonably expect to find in all cases of the disorder. While the lists of essential features in the guidelines superficially resemble diagnostic criteria, arbitrary cutoffs and precise requirements related to symptom counts and duration are generally avoided, unless these have been empirically established across countries and cultures or there is another compelling reason to include them.

This approach is intended to conform to the way clinicians actually make diagnoses, with the flexible exercise of clinical judgment, and to increase clinical utility by allowing for cultural variations in presentation as well as contextual and health-system factors that may affect diagnostic practice. This flexible approach is consistent with results of surveys of psychiatrists and psychologists undertaken early in the ICD-11 development process regarding the desirable characteristics of a mental disorders classification system[3,10]. Field studies in clinical settings in 13 countries have confirmed that clinicians consider the clinical utility of this approach to be high[11]. Importantly, the diagnostic reliability of the ICD-11 guidelines appears to be at least as high as that obtained using a strict criteria-based approach[12].

A number of other innovations in the ICD-11 CDDG were also introduced by means of the template provided to Working Groups for making their recommendations (that is, the "con-

tent form"). As a part of the standardization of information provided in the guidelines, attention was devoted for each disorder to the systematic characterization of the boundary with normal variation and to the expansion of the information provided on boundaries with other disorders (differential diagnosis).

The lifespan approach adopted for the ICD-11 meant that the separate grouping of behavioural and emotional disorders with onset usually occurring in childhood and adolescence was eliminated, and these disorders distributed to other groupings with which they share symptoms. For example, separation anxiety disorder was moved to the anxiety and fear-related disorders grouping. Moreover, the ICD-11 CDDG provide information for each disorder and/or grouping where data were available describing variations in the presentation of the disorder among children and adolescents as well as among older adults.

Culture-related information was systematically incorporated based on a review of the literature on cultural influences on psychopathology and its expression for each ICD-11 diagnostic grouping as well as a detailed review of culture-related material in the ICD-10 CDDG and the DSM-5. The cultural guidance for panic disorder is provided in Table 1 as an example.

Another major innovation in the ICD-11 classification has been the incorporation of dimensional approaches within the context of an explicitly categorical system with specific taxonomic constraints. This effort was stimulated by the evidence that most mental disorders can be best described along a number of interacting symptom dimensions rather than as discrete categories[13-15], and has been facilitated by innovations in the coding structure for the ICD-11. The dimensional potential of the ICD-11 is most clearly realized in the classification of personality disorders[16,17].

For non-specialist settings, the dimensional rating of severity for ICD-11 personality disorders offers greater simplicity and clinical utility than the ICD-10 classification of specific personality disorders, improved differentiation of patients who need complex as compared to simpler treatments, and a better mechanism for tracking changes over time. In more specialized settings, the constellation of individual personality traits can inform specific intervention strategies. The dimensional system eliminates both the artificial comorbidity of personality disorders and the unspecified personality disorder diagnoses, as well as providing a basis for research into underlying dimensions and interventions across various personality disorder manifestations.

A set of dimensional qualifiers has also been introduced to describe the symptomatic manifestations of schizophrenia and other primary psychotic disorders[18]. Rather than focusing on diagnostic subtypes, the dimensional classification focuses on relevant aspects of the current clinical presentation in ways that are much more consistent with recovery-based psychiatric rehabilitation approaches.

The dimensional approaches to personality disorders and symptomatic manifestations of primary psychotic disorders are described in more detail in the respective sections later in this paper.

Table 1 Cultural considerations for panic disorder

- The symptom presentation of panic attacks may vary across cultures, influenced by cultural attributions about their origin or pathophysiology. For example, individuals of Cambodian origin may emphasize panic symptoms attributed to dysregulation of *khyâl*, a wind-like substance in traditional Cambodian ethnophysiology (e.g., dizziness, tinnitus, neck soreness).

- There are several notable cultural concepts of distress related to panic disorder, which link panic, fear, or anxiety to etiological attributions regarding specific social and environmental influences. Examples include attributions related to interpersonal conflict (e.g., *ataque de nervios* among Latin American people), exertion or orthostasis (*khyâl cap* among Cambodians), and atmospheric wind (*trúng gió* among Vietnamese individuals). These cultural labels may be applied to symptom presentations other than panic (e.g., anger paroxysms, in the case of *ataque de nervios*) but they often constitute panic episodes or presentations with partial phenomenological overlap with panic attacks.

- Clarifying cultural attributions and the context of the experience of symptoms can inform whether panic attacks should be considered expected or unexpected, as would be the case in panic disorder. For example, panic attacks may involve specific foci of apprehension that are better explained by another disorder (e.g., social situations in social anxiety disorder). Moreover, the cultural linkage of the apprehension focus with specific exposures (e.g., wind or cold and *trúng gió* panic attacks) may suggest that acute anxiety is expected when considered within the individual's cultural framework.

ICD-11 FIELD STUDIES

The ICD-11 field studies program also represents an area of major innovation. This program of work has included the use of novel methodologies for studying the clinical utility of the draft diagnostic guidelines, including their accuracy and consistency of application by clinicians as compared to ICD-10 as well as the specific elements responsible for any observed confusion[19]. A key strength of the research program has been that most studies have been conducted in a time frame allowing their results to provide a basis for revision of the guidelines to address any observed weaknesses[20].

Global participation has also been a defining characteristic of the ICD-11 CDDG field studies program. The Global Clinical Practice Network (GCPN) was established to allow mental health and primary care professionals from all over the world to participate directly in the development of the ICD-11 CDDG through Internet-based field studies.

Over time, the GCPN has expanded to include nearly 15,000 clinicians from 155 countries. All WHO global regions are represented in proportions that largely track the availability of mental health professionals by region, with the largest proportions coming from Asia, Europe and the Americas (approximately equally divided between the US and Canada on the one hand and Latin America on the other). More than half of GCPN

members are physicians, predominantly psychiatrists, and 30% are psychologists.

Approximately a dozen GCPN studies have been completed to date, most focusing on comparisons of the proposed ICD-11 diagnostic guidelines with ICD-10 guidelines in terms of accuracy and consistency of clinicians' diagnostic formulations, using standardized case material manipulated to test key differences[19,21]. Other studies have examined scaling for diagnostic qualifiers[22] and how clinicians actually use classifications[5]. GCPN studies have been conducted in Chinese, French, Japanese, Russian and Spanish, in addition to English, and have included an examination of results by region and language to identify potential difficulties in global or cultural applicability as well as problems in translation.

Clinic-based studies have also been conducted through a network of international field study centers to evaluate the clinical utility and usability of the proposed ICD-11 diagnostic guidelines in natural conditions, in the settings in which they are intended to be used[11]. These studies also evaluated the reliability of diagnoses that account for the greatest proportion of disease burden and mental health services utilization[12]. International field studies were located in 14 countries across all WHO global regions, and patient interviews for the studies were conducted in the local language of each country.

OVERALL STRUCTURE OF THE ICD-11 CHAPTER ON MENTAL, BEHAVIOURAL AND NEURODEVELOPMENTAL DISORDERS

In the ICD-10, the number of groupings of disorders was artificially constrained by the decimal coding system used in the classification, such that it was only possible to have a maximum of ten major groupings of disorders within the chapter on mental and behavioural disorders. As a result, diagnostic groupings were created that were not based on clinical utility or scientific evidence (e.g., anxiety disorders being included as part of the heterogeneous grouping of neurotic, stress-related, and somatoform disorders). ICD-11's use of a flexible alphanumeric coding structure allowed for a much larger number of groupings, making it possible to develop diagnostic groupings based more closely on scientific evidence and the needs of clinical practice.

In order to provide data to assist in developing an organizational structure that would be more clinically useful, two formative field studies were conducted[23,24] to examine the conceptualizations held by mental health professionals around the world regarding the relationships among mental disorders. These data informed decisions about the optimal structure of the classification. The ICD-11 organizational structure was also influenced by efforts by the WHO and the American Psychiatric Association to harmonize the overall structure of the ICD-11 chapter on mental and behavioural disorders with the structure of the DSM-5.

The organization of the ICD-10 chapter on mental and behavioural disorders largely reflected the chapter organization originally used in Kraepelin's Textbook of Psychiatry, which began with organic disorders, followed by psychoses, neurotic disorders, and personality disorders[25]. Principles guiding the ICD-11 organization included trying to order the diagnostic groupings following a developmental perspective (hence, neurodevelopmental disorders appear first and neurocognitive disorders last in the classification) and grouping disorders together based on putative shared etiological and pathophysiological factors (e.g., disorders specifically associated with stress) as well as shared phenomenology (e.g., dissociative disorders). Table 2 provides a listing of the diagnostic groupings in the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders.

The classification of sleep disorders in the ICD-10 relied on the now obsolete separation between organic and non-organic disorders, resulting in the "non-organic" sleep disorders being included in the chapter on mental and behavioural disorders of the ICD-10, and the "organic" sleep disorders being included in other chapters (i.e., diseases of the nervous system, diseases of the respiratory system, and endocrine, nutritional and metabolic disorders). In ICD-11, a separate chapter has been created for sleep-wake disorders that encompasses all relevant sleep-related diagnoses.

Table 2 Disorder groupings in the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders

Neurodevelopmental disorders
Schizophrenia and other primary psychotic disorders
Catatonia
Mood disorders
Anxiety and fear-related disorders
Obsessive-compulsive and related disorders
Disorders specifically associated with stress
Dissociative disorders
Feeding and eating disorders
Elimination disorders
Disorders of bodily distress and bodily experience
Disorders due to substance use and addictive behaviours
Impulse control disorders
Disruptive behaviour and dissocial disorders
Personality disorders
Paraphilic disorders
Factitious disorders
Neurocognitive disorders
Mental and behavioural disorders associated with pregnancy, childbirth and the puerperium
Psychological and behavioural factors affecting disorders or diseases classified elsewhere
Secondary mental or behavioural syndromes associated with disorders or diseases classified elsewhere

The ICD-10 also embodied a dichotomy between organic and non-organic in the realm of sexual dysfunctions, with "non-organic" sexual dysfunctions included in the chapter on mental and behavioural disorders, and "organic" sexual dysfunctions for the most part listed in the chapter on diseases of the genitourinary system. A new integrated chapter for conditions related to sexual health has been added to the ICD-11 to house a unified classification of sexual dysfunctions and sexual pain disorders[26] as well as changes in male and female anatomy. Moreover, ICD-10 gender identity disorders have been renamed as "gender incongruence" in the ICD-11 and moved from the mental disorders chapter to the new sexual health chapter[26], meaning that a transgender identity is no longer to be considered a mental disorder. Gender incongruence is not proposed for elimination in the ICD-11 because in many countries access to relevant health services is contingent on a qualifying diagnosis. The ICD-11 guidelines explicitly state that gender variant behaviour and preferences alone are not sufficient for making a diagnosis.

NEW MENTAL, BEHAVIOURAL AND NEURODEVELOPMENTAL DISORDERS IN THE ICD-11

Based on a review of the available evidence on scientific validity, and a consideration of clinical utility and global applicability, a number of new disorders have been added to the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders. A description of these disorders as defined in the ICD-11 diagnostic guidelines and the rationale for their inclusion are provided below.

Catatonia

In the ICD-10, catatonia was included as one of the subtypes of schizophrenia (i.e., catatonic schizophrenia) and as one of the organic disorders (i.e., organic catatonic disorder). In recognition of the fact that the syndrome of catatonia can occur in association with a variety of mental disorders[27], a new diagnostic grouping for catatonia (at the same hierarchical level as mood disorders, anxiety and fear-related disorders, etc.) has been added in the ICD-11.

Catatonia is characterized by the occurrence of several symptoms such as stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypies, psychomotor agitation, grimacing, echolalia and echopraxia. Three conditions are included in the new diagnostic grouping: a) catatonia associated with another mental disorder (such as a mood disorder, schizophrenia or other primary psychotic disorder, or autism spectrum disorder); b) catatonia induced by psychoactive substances, including medications (e.g., antipsychotic medications, amphetamines, phencyclidine); and c) secondary catatonia (i.e., caused by a medical condition, such as diabetic ketoacidosis, hypercalcemia, hepatic encephalopathy, homo-

cystinuria, neoplasm, head trauma, cerebrovascular disease, or encephalitis).

Bipolar type II disorder

The DSM-IV introduced two types of bipolar disorder. Bipolar type I disorder applies to presentations characterized by at least one manic episode, whereas bipolar type II disorder requires at least one hypomanic episode plus at least one major depressive episode, in the absence of a history of manic episodes. Evidence supporting the validity of the distinction between these two types includes differences in antidepressant monotherapy response[28], neurocognitive measures[28,29], genetic effects[28,30], and neuroimaging findings[28,31,32].

Given this evidence, and the clinical utility of differentiating between these two types[33], bipolar disorder in ICD-11 has also been subdivided into type I and type II bipolar disorder.

Body dysmorphic disorder

Individuals with body dysmorphic disorder are persistently preoccupied with one or more defects or flaws in their bodily appearance that are either unnoticeable or only slightly noticeable to others[34]. The preoccupation is accompanied by repetitive and excessive behaviours, including repeated examination of the appearance or severity of the perceived defect or flaw, excessive attempts to camouflage or alter the perceived defect, or marked avoidance of social situations or triggers that increase distress about the perceived defect or flaw.

Originally called "dysmorphophobia", this condition was first included in the DSM-III-R. It appeared in the ICD-10 as an embedded but incongruous inclusion term under hypochondriasis, but clinicians were instructed to diagnose it as delusional disorder in cases in which associated beliefs were considered delusional. This created a potential for the same disorder to be assigned different diagnoses without recognizing the full spectrum of severity of the disorder, which can include beliefs that appear delusional due to the degree of conviction or fixity with which they are held.

In recognition of its distinct symptomatology, prevalence in the general population and similarities to obsessive-compulsive and related disorders (OCRD), body dysmorphic disorder has been included in this latter grouping in the ICD-11[35].

Olfactory reference disorder

This condition is characterized by a persistent preoccupation with the belief that one is emitting a perceived foul or offensive body odour or breath, that is either unnoticeable or only slightly noticeable to others[34].

In response to their preoccupation, individuals engage in repetitive and excessive behaviours such as repeatedly checking

for body odour or checking the perceived source of the smell; repeatedly seeking reassurance; excessive attempts to camouflage, alter or prevent the perceived odour; or marked avoidance of social situations or triggers that increase distress about the perceived foul or offensive odour. Affected individuals typically fear or are convinced that others noticing the smell will reject or humiliate them[36].

Olfactory reference disorder is included in the ICD-11 OCRD grouping, as it shares phenomenological similarities with other disorders in this grouping with respect to the presence of persistent intrusive preoccupations and associated repetitive behaviours[35].

Hoarding disorder

Hoarding disorder is characterized by the accumulation of possessions, due to their excessive acquisition or to difficulty discarding them, regardless of their actual value[35,37]. Excessive acquisition is characterized by repetitive urges or behaviours related to amassing or buying items. Difficulty discarding is characterized by a perceived need to save items and a distress associated with discarding them. The accumulation of possessions results in living spaces becoming cluttered to the point that their use or safety is compromised.

Although hoarding behaviours may be exhibited as a part of a broad range of mental and behavioural disorders and other conditions – including obsessive-compulsive disorder, depressive disorders, schizophrenia, dementia, autism spectrum disorders and Prader-Willi syndrome – there is sufficient evidence supporting hoarding disorder as a separate and unique disorder[38].

Individuals affected by hoarding disorder are underrecognized and undertreated, which argues from a public health perspective for its inclusion in the ICD-11[39].

Excoriation disorder

A new diagnostic subgrouping, body-focused repetitive behaviour disorders, has been added to the OCRD grouping. It includes trichotillomania (which was included in the grouping of habit and impulse disorders in ICD-10) and a new condition, excoriation disorder (also known as skin-picking disorder).

Excoriation disorder is characterized by recurrent picking of one's own skin, leading to skin lesions, accompanied by unsuccessful attempts to decrease or stop the behaviour. The skin picking must be severe enough to result in significant distress or impairment in functioning. Excoriation disorder (and trichotillomania) are distinct from other OCRDs in that the behaviour is rarely preceded by cognitive phenomena such as intrusive thoughts, obsessions or preoccupations, but instead may be preceded by sensory experiences.

Their inclusion in the OCRD grouping is based on shared phenomenology, patterns of familial aggregation, and putative etiological mechanisms with other disorders in this grouping[35,40].

Complex post-traumatic stress disorder

Complex post-traumatic stress disorder (complex PTSD)[41] most typically follows severe stressors of a prolonged nature, or multiple or repeated adverse events from which escape is difficult or impossible, such as torture, slavery, genocide campaigns, prolonged domestic violence, or repeated childhood sexual or physical abuse.

The symptom profile is marked by the three core features of PTSD (i.e., re-experiencing the traumatic event or events in the present in the form of vivid intrusive memories, flashbacks or nightmares; avoidance of thoughts and memories of the event or activities, situations or people reminiscent of the event; persistent perceptions of heightened current threat), which are accompanied by additional persistent, pervasive and enduring disturbances in affect regulation, self-concept and relational functioning.

The addition of complex PTSD to the ICD-11 is justified on the basis of the evidence that individuals with the disorder have a poorer prognosis and benefit from different treatments as compared to individuals with PTSD[42]. Complex PTSD replaces the overlapping ICD-10 category of enduring personality change after catastrophic experience[41].

Prolonged grief disorder

Prolonged grief disorder describes abnormally persistent and disabling responses to bereavement[41]. Following the death of a partner, parent, child or other person close to the bereaved, there is a persistent and pervasive grief response characterized by longing for the deceased or persistent preoccupation with the deceased, accompanied by intense emotional pain. Symptoms may include sadness, guilt, anger, denial, blame, difficulty accepting the death, feeling that the individual has lost a part of one's self, an inability to experience positive mood, emotional numbness, and difficulty in engaging with social or other activities. The grief response must persist for an atypically long period of time following the loss (more than six months) and clearly exceed expected social, cultural or religious norms for the individual's culture and context.

Although most people report at least partial remission from the pain of acute grief by around six months following bereavement, those who continue experiencing severe grief reactions are more likely to experience significant impairment in their functioning. The inclusion of prolonged grief disorder in the ICD-11 is a response to the increasing evidence of a distinct and debilitating condition that is not adequately described by current ICD-10 diagnoses[43]. Its inclusion and differentiation from culturally normative bereavement and depressive episode is important, because of the different treatment selection implications and prognoses of these latter disorders[44].

Binge eating disorder

Binge eating disorder is characterized by frequent, recurrent episodes of binge eating (e.g., once a week or more over a period of several months). A binge eating episode is a distinct period of time during which the individual experiences a subjective loss of control over eating, eats notably more or differently than usual, and feels unable to stop eating or limit the type or amount of food eaten.

Binge eating is experienced as very distressing and is often accompanied by negative emotions such as guilt or disgust. However, unlike in bulimia nervosa, binge eating episodes are not regularly followed by inappropriate compensatory behaviours aimed at preventing weight gain (e.g., self-induced vomiting, misuse of laxatives or enemas, strenuous exercise). Although binge eating disorder is often associated with weight gain and obesity, these features are not a requirement and the disorder can be present in normal weight individuals.

The addition of binge eating disorder in the ICD-11 is based on extensive research that has emerged during the last 20 years supporting its validity and clinical utility[45,46]. Individuals who report episodes of binge eating without inappropriate compensatory behaviours represent the most common group among those who receive ICD-10 diagnoses of other specified or unspecified eating disorder, so that it is expected that the inclusion of binge eating disorder will reduce these diagnoses[47].

Avoidant/restrictive food intake disorder

Avoidant/restrictive food intake disorder (ARFID) is characterized by abnormal eating or feeding behaviours that result in the intake of an insufficient quantity or variety of food to meet adequate energy or nutritional requirements. This results in significant weight loss, failure to gain weight as expected in childhood or pregnancy, clinically significant nutritional deficiencies, dependence on oral nutritional supplements or tube feeding, or otherwise negatively affects the health of the individual or results in significant functional impairment.

ARFID is distinguished from anorexia nervosa by the absence of concerns about body weight or shape. Its inclusion in the ICD-11 can be considered to be an expansion of the ICD-10 category "feeding disorder of infancy and childhood", and is likely to improve clinical utility across the lifespan (i.e., unlike its ICD-10 counterpart, ARFID applies to children, adolescents and adults) as well as maintaining consistency with DSM-5[45,47].

Body integrity dysphoria

Body integrity dysphoria is a rare disorder characterized by the persistent desire to have a specific physical disability (e.g., amputation, paraplegia, blindness, deafness) beginning in childhood or early adolescence[48]. The desire can be manifested in a number of ways, including fantasizing about having the desired physical disability, engaging in "pretending" behaviour (e.g., spending hours in a wheelchair or using leg braces to simulate having leg weakness), and spending time searching for ways to achieve the desired disability.

The preoccupation with the desire to have the physical disability (including time spent pretending) significantly interferes with productivity, leisure activities, or social functioning (e.g., the person is unwilling to have close relationships because it would make it difficult to pretend). Moreover, for a significant minority of individuals with this desire, their preoccupation goes beyond fantasy, and they pursue actualization of the desire through surgical means (i.e., by procuring an elective amputation of an otherwise healthy limb) or by self-damaging a limb to a degree in which amputation is the only therapeutic option (e.g., freezing a limb in dry ice).

Gaming disorder

As online gaming has greatly increased in popularity in recent years, problems have been observed related to excessive involvement in gaming. Gaming disorder has been included in a newly added diagnostic grouping called "disorders due to addictive behaviours" (which also contains gambling disorder) in response to global concerns about the impact of problematic gaming, especially the online form[49].

Gaming disorder is characterized by a pattern of persistent or recurrent Internet-based or offline gaming behaviour ("digital gaming" or "video-gaming") that is manifested by impaired control over the behaviour (e.g., inability to limit the amount of time spent gaming), giving increasing priority to gaming to the extent that it takes precedence over other life interests and daily activities; and continuing or escalating gaming despite its negative consequences (e.g., being repeatedly fired from jobs because of excessive absences due to gaming). It is differentiated from non-pathological gaming behaviour by the clinically significant distress or impairment in functioning it produces.

Compulsive sexual behaviour disorder

Compulsive sexual behaviour disorder is characterized by a persistent pattern of failure to control intense repetitive sexual impulses or urges, resulting in repetitive sexual behaviour over an extended period (e.g., six months or more) that causes marked distress or impairment in personal, family, social, educational, occupational or other important areas of functioning.

Possible manifestations of the persistent pattern include: repetitive sexual activities becoming a central focus of the individual's life to the point of neglecting health and personal care or other interests, activities and responsibilities; the individual making numerous unsuccessful efforts to control or significantly reduce the repetitive sexual behaviour; the individual continuing to engage in repetitive sexual behaviour despite adverse

consequences such as repeated relationship disruption; and the individual continuing to engage in repetitive sexual behaviour even when he or she no longer derives any satisfaction from it.

Although this category phenomenologically resembles substance dependence, it is included in the ICD-11 impulse control disorders section in recognition of the lack of definitive information on whether the processes involved in the development and maintenance of the disorder are equivalent to those observed in substance use disorders and behavioural addictions. Its inclusion in the ICD-11 will help to address unmet needs of treatment seeking patients as well as possibly reducing shame and guilt associated with help seeking among distressed individuals[50].

Intermittent explosive disorder

Intermittent explosive disorder is characterized by repeated brief episodes of verbal or physical aggression or destruction of property that represent a failure to control aggressive impulses, with the intensity of the outburst or degree of aggressiveness being grossly out of proportion to the provocation or precipitating psychosocial stressors.

Because such episodes can occur in a variety of other conditions (e.g., oppositional defiant disorder, conduct disorder, bipolar disorder), the diagnosis is not given if the episodes are better explained by another mental, behavioural or neurodevelopmental disorder.

Although intermittent explosive disorder was introduced in the DSM-III-R, it appeared in the ICD-10 only as an inclusion term under "other habit and impulse disorders". It is included in the ICD-11 impulse control disorders section in recognition of the substantial evidence of its validity and utility in clinical settings[51].

Premenstrual dysphoric disorder

Premenstrual dysphoric disorder (PMDD) is characterized by a variety of severe mood, somatic or cognitive symptoms that begin several days before the onset of menses, start to improve within a few days, and become minimal or absent within approximately one week following the onset of menses.

More specifically, the diagnosis requires a pattern of mood symptoms (depressed mood, irritability), somatic symptoms (lethargy, joint pain, overeating), or cognitive symptoms (concentration difficulties, forgetfulness) that have occurred during a majority of menstrual cycles within the past year. The symptoms are severe enough to cause significant distress or significant impairment in personal, family, social, educational, occupational or other important areas of functioning, and do not represent the exacerbation of another mental disorder.

In the ICD-11, PMDD is differentiated from the far more common premenstrual tension syndrome by the severity of the symptoms and the requirement that they cause significant distress or impairment[52]. The inclusion of PMDD in the research appendices of the DSM-III-R and DSM-IV stimulated a great deal of research that has established its validity and reliability[52,53], leading to its inclusion in both the ICD-11 and DSM-5. Although its primary location in the ICD-11 is in the chapter on diseases of the genitourinary system, PMDD is cross-listed in the subgrouping of depressive disorders due to the prominence of mood symptomatology.

SUMMARY OF CHANGES BY ICD-11 DISORDER GROUPING

The following sections summarize the changes introduced in each of the main disorder groupings of the ICD-11 chapter on mental, behavioural and neurodevelopmental disorders in addition to the new categories described in the previous section.

These changes have been made on the basis of a review of available scientific evidence by ICD-11 Working Groups and expert consultants, consideration of clinical utility and global applicability, and, where possible, the results of field testing.

Neurodevelopmental disorders

Neurodevelopmental disorders are those that involve significant difficulties in the acquisition and execution of specific intellectual, motor, language or social functions with onset during the developmental period. ICD-11 neurodevelopmental disorders encompass the ICD-10 groupings of mental retardation and disorders of psychological development, with the addition of attention deficit hyperactivity disorder (ADHD).

Major changes in the ICD-11 include the renaming of disorders of intellectual development from ICD-10 mental retardation, which was an obsolete and stigmatizing term that did not adequately capture the range of forms and etiologies associated with this condition[54]. Disorders of intellectual development continue to be defined on the basis of significant limitations in intellectual functioning and adaptive behaviour, ideally determined by standardized, appropriately normed and individually administered measures. In recognition of the lack of access to locally appropriate standardized measures or trained personnel to administer them in many parts of the world, and because of the importance of determining severity for treatment planning, the ICD-11 CDDG also provide a comprehensive set of behavioural indicator tables[55].

Separate tables for intellectual functioning and adaptive behaviour functioning domains (conceptual, social, practical) are organized according to three age groups (early childhood, childhood/adolescence and adulthood) and four levels of severity (mild, moderate, severe, profound). Behavioural indicators describe those skills and abilities that would be typically observed within each of these categories and are expected to improve the reliability of the characterization of severity and to

improve public health data related to the burden of disorders of intellectual development.

Autism spectrum disorder in the ICD-11 incorporates both childhood autism and Asperger's syndrome from the ICD-10 under a single category characterized by social communication deficits and restricted, repetitive and inflexible patterns of behaviour, interests or activities. Guidelines for autism spectrum disorder have been substantially updated to reflect the current literature, including presentations throughout the lifespan. Qualifiers are provided for the extent of impairment in intellectual functioning and functional language abilities to capture the full range of presentations of autism spectrum disorder in a more dimensional manner.

ADHD has replaced ICD-10 hyperkinetic disorders and has been moved to the grouping of neurodevelopmental disorders because of its developmental onset, characteristic disturbances in intellectual, motor and social functions, and common co-occurrence with other neurodevelopmental disorders. This move also addresses the conceptual weakness of viewing ADHD as more closely related to disruptive behaviour and dissocial disorders, given that individuals with ADHD are typically not intentionally disruptive.

ADHD can be characterized in the ICD-11 using qualifiers for predominantly inattentive, predominantly hyperactive-impulsive, or combined type, and is described across the lifespan.

Finally, chronic tic disorders, including Tourette syndrome, are classified in the ICD-11 chapter on diseases of the nervous system, but are cross-listed in the grouping of neurodevelopmental disorders because of their high co-occurrence (e.g., with ADHD) and typical onset during the developmental period.

Schizophrenia and other primary psychotic disorders

The ICD-11 grouping of schizophrenia and other primary psychotic disorders replaces the ICD-10 grouping of schizophrenia, schizotypal and delusional disorders. The term "primary" indicates that psychotic processes are a core feature, in contrast to psychotic symptoms that may occur as an aspect of other forms of psychopathology (e.g., mood disorders)[18].

In the ICD-11, schizophrenia symptoms have largely remained unchanged from the ICD-10, though the importance of Schneiderian first-rank symptoms has been de-emphasized. The most significant change is the elimination of all subtypes of schizophrenia (e.g., paranoid, hebephrenic, catatonic), due to their lack of predictive validity or utility in treatment selection. In lieu of the subtypes, a set of dimensional descriptors has been introduced[18]. These include: positive symptoms (delusions, hallucinations, disorganized thinking and behaviour, experiences of passivity and control); negative symptoms (constricted, blunted or flat affect, alogia or paucity of speech, avolition, anhedonia); depressive mood symptoms; manic mood symptoms; psychomotor symptoms (psychomotor agitation, psychomotor retardation, catatonic symptoms); and cognitive symptoms (particularly deficits in speed of processing,

attention/concentration, orientation, judgment, abstraction, verbal or visual learning, and working memory). These same symptom ratings can also be applied to other categories in the grouping (schizoaffective disorder, acute and transient psychotic disorder, delusional disorder).

ICD-11 schizoaffective disorder still requires the near simultaneous presence of both the schizophrenia syndrome and a mood episode. The diagnosis is meant to reflect the current episode of illness and is not conceptualized as longitudinally stable.

ICD-11 acute and transient psychotic disorder is characterized by a sudden onset of positive psychotic symptoms that fluctuate rapidly in nature and intensity over a short period of time and persist no longer than three months. This corresponds only to the "polymorphic" form of acute psychotic disorder in the ICD-10, which is the most common presentation and one that is not indicative of schizophrenia[56,57]. Non-polymorphic subtypes of acute psychotic disorder in the ICD-10 have been eliminated and would instead be classified in the ICD-11 as "other primary psychotic disorder".

As in the ICD-10, schizotypal disorder is classified in this grouping and is not considered a personality disorder.

Mood disorders

Unlike in the ICD-10, ICD-11 mood episodes are not independently diagnosable conditions, but rather their pattern over time is used as a basis for determining which mood disorder best fits the clinical presentation.

Mood disorders are subdivided into depressive disorders (which include single episode depressive disorder, recurrent depressive disorder, dysthymic disorder, and mixed depressive and anxiety disorder) and bipolar disorders (which include bipolar type I disorder, bipolar type II disorder, and cyclothymia). The ICD-11 subdivides ICD-10 bipolar affective disorder into bipolar type I and type II disorders. The separate ICD-10 subgrouping of persistent mood disorders, consisting of dysthymia and cyclothymia, has been eliminated[58].

The diagnostic guidelines for depressive episode are one of the few places in the ICD-11 where a minimal symptom count is required. This is due to the longstanding research and clinical tradition of conceptualizing depression in this manner. A minimum of five of ten symptoms is required rather than the four of nine possible symptoms stipulated in ICD-10, thus increasing consistency with the DSM-5. The ICD-11 CDDG organize depressive symptoms into three clusters – affective, cognitive and neurovegetative – to assist clinicians in conceptualizing and recalling the full spectrum of depressive symptomatology. Fatigue is part of the neurovegetative symptom cluster but is no longer considered sufficient as an entry-level symptom; rather, either almost daily depressed mood or diminished interest in activities lasting at least two weeks is required. Hopelessness has been added as an additional cognitive symptom because of strong evidence of its predictive value for diagnoses of depressive disorders[59]. The ICD-11 CDDG provide clear guidance on

the differentiation between culturally normative grief reactions and symptoms that warrant consideration as a depressive episode in the context of bereavement[60].

For manic episodes, the ICD-11 requires the presence of the entry level symptom of increased activity or subjective experience of increased energy, in addition to euphoria, irritability or expansiveness. This is meant to guard against false positive cases that might be better characterized as normative fluctuations in mood. ICD-11 hypomanic episodes are conceptualized as an attenuated form of manic episodes in the absence of significant functional impairment.

Mixed episodes are defined in the ICD-11 in a way that is conceptually equivalent to the ICD-10, based on evidence for the validity of this approach[61]. Guidance is provided regarding the typical contrapolar symptoms observed when either manic or depressive symptoms predominate. The presence of a mixed episode indicates a bipolar type I diagnosis.

The ICD-11 provides various qualifiers to describe the current mood episode or remission status (i.e., in partial or in full remission). Depressive, manic and mixed episodes can be described as with or without psychotic symptoms. Current depressive episodes in the context of depressive or bipolar disorders can be further characterized by severity (mild, moderate or severe); by a melancholic features qualifier that bears a direct relationship with the concept of the somatic syndrome in ICD-10; and by a qualifier to identify persistent episodes of more than two years' duration. All mood episodes in the context of depressive or bipolar disorders can be further described using a prominent anxiety symptoms qualifier; a qualifier indicating the presence of panic attacks; and a qualifier to identify seasonal pattern. A qualifier for rapid cycling is also available for bipolar disorder diagnoses.

The ICD-11 includes the category of mixed depressive and anxiety disorder because of its importance in primary care settings[62,63]. This category has been moved from anxiety disorders in the ICD-10 to depressive disorders in the ICD-11 because of evidence of its overlap with mood symptomatology[64].

Anxiety and fear-related disorders

The ICD-11 brings together disorders with anxiety or fear as the primary clinical feature in this new grouping[65]. Consistent with ICD-11's lifespan approach, this grouping also includes separation anxiety disorder and selective mutism, which were placed among the childhood disorders in the ICD-10. The ICD-10 distinction between phobic anxiety disorders and other anxiety disorders has been eliminated in the ICD-11 in favor of the more clinically useful method of characterizing each anxiety and fear-related disorder according to its focus of apprehension[66]; that is, the stimulus reported by the individual as triggering his or her anxiety, excessive physiological arousal and maladaptive behavioural responses. Generalized anxiety disorder (GAD) is characterized by general apprehensiveness or worry that is not restricted to any particular stimulus.

In the ICD-11, GAD has a more elaborated set of essential features, reflecting advances in the understanding of its unique phenomenology; in particular, worry is added to general apprehension as a core feature of the disorder. Contrary to ICD-10, the ICD-11 CDDG specify that GAD can co-occur with depressive disorders as long as symptoms are present independent of mood episodes. Similarly, other ICD-10 hierarchical exclusion rules (e.g., GAD cannot be diagnosed together with phobic anxiety disorder or obsessive-compulsive disorder) are also eliminated, due to the better delineation of disorder phenomenology in the ICD-11 and the evidence that those rules interfere with detection and treatment of conditions requiring separate specific clinical attention.

In the ICD-11, agoraphobia is conceptualized as marked and excessive fear or anxiety that occurs in, or in anticipation of, multiple situations where escape might be difficult or help not available. The focus of apprehension is fear of specific negative outcomes that would be incapacitating or embarrassing in those situations, which is distinct from the narrower concept in the ICD-10 of fear of open spaces and related situations, such as crowds, where an escape to a safe place may be difficult.

Panic disorder is defined in the ICD-11 by recurrent unexpected panic attacks that are not restricted to particular stimuli or situations. The ICD-11 CDDG indicate that panic attacks which occur entirely in response to exposure or anticipation of the feared stimulus in a given disorder (e.g., public speaking in social anxiety disorder) do not warrant an additional diagnosis of panic disorder. Rather, a "with panic attacks" qualifier can be applied to the other anxiety disorder diagnosis. The "with panic attacks" qualifier can also be applied in the context of other disorders where anxiety is a prominent though not defining feature (e.g., in some individuals during a depressive episode).

ICD-11 social anxiety disorder, defined on the basis of fear of negative evaluation by others, replaces ICD-10 social phobias.

The ICD-11 CDDG specifically describe separation anxiety disorder in adults, where it is most commonly focused on a romantic partner or a child.

Obsessive-compulsive and related disorders

The introduction of the OCRD grouping in the ICD-11 represents a significant departure from the ICD-10. The rationale for creating an OCRD grouping distinct from anxiety and fear-related disorders, despite phenomenological overlap, is based on the clinical utility of collating disorders with shared symptoms of repetitive unwanted thoughts and related repetitive behaviours as the primary clinical feature. The diagnostic coherence of this grouping comes from emerging evidence of the shared validators among included disorders from imaging, genetic and neurochemical studies[35].

ICD-11 OCRD include obsessive-compulsive disorder, body dysmorphic disorder, olfactory reference disorder, hypochondriasis (illness anxiety disorder) and hoarding disorder.

Equivalent categories that exist in the ICD-10 are located in disparate groupings. Also included in OCRD is a subgrouping of body-focused repetitive behaviour disorders that includes trichotillomania (hair-pulling disorder) and excoriation (skin-picking) disorder, both sharing the core feature of repetitive behaviour without the cognitive aspect of other OCRDs. Tourette syndrome, a disease of the nervous system in ICD-11, is cross-listed in the OCRD grouping because of its frequent co-occurrence with obsessive-compulsive disorder.

The ICD-11 retains the core features of ICD-10 obsessive-compulsive disorder, that is, persistent obsessions and/or compulsions, but with some important revisions. The ICD-11 broadens the concept of obsessions beyond intrusive thoughts to include unwanted images and urges/impulses. Moreover, the concept of compulsions is expanded to include covert (e.g., repeated counting) as well as overt repetitive behaviours.

Although anxiety is the most common affective experience associated with obsessions, the ICD-11 explicitly mentions other phenomena reported by patients, such as disgust, shame, a sense of "incompleteness", or uneasiness that things do not look or feel "right". ICD-10 subtypes of OCD are eliminated, because the majority of patients report both obsessions and compulsions, and because they lack predictive validity for treatment response. The ICD-10 prohibition against diagnosing obsessive-compulsive disorder along with depressive disorders is removed in the ICD-11, reflecting the high rate of co-occurrence of these disorders and the need for distinct treatments.

Hypochondriasis (health anxiety disorder) is placed in OCRD rather than among anxiety and fear-related disorders, even though health preoccupations are often associated with anxiety and fear, because of shared phenomenology and patterns of familial aggregation with OCRD[67]. However, hypochondriasis (health anxiety disorder) is cross-listed in the anxiety and fear-related disorders grouping, in recognition of some phenomenological overlap.

Body dysmorphic disorder, olfactory reference disorder, and hoarding disorder are new categories in ICD-11 that have been included in the OCRD grouping.

In OCRDs that have a cognitive component, beliefs may be held with such intensity or fixity that they appear to be delusional. When these fixed beliefs are entirely consistent with the phenomenology of the OCRD, in the absence of other psychotic symptoms, the qualifier "with poor to absent insight" should be used, and a diagnosis of delusional disorder should not be assigned. This is intended to help guard against inappropriate treatment for psychosis among individuals with OCRDs[35].

Disorders specifically associated with stress

The ICD-11 grouping of disorders specifically associated with stress replaces ICD-10 reactions to severe stress and adjustment disorders, to emphasize that these disorders share the necessary (but not sufficient) etiologic requirement for exposure to a stressful event, as well as to distinguish included disorders from the various other mental disorders that arise as a reaction to stressors (e.g., depressive disorders)[41]. ICD-10 reactive attachment disorder of childhood and disinhibited attachment disorder of childhood are reclassified to this grouping owing to the lifespan approach of the ICD-11 and in recognition of the specific attachment-related stressors inherent to these disorders. The ICD-11 includes several important conceptual updates to the ICD-10 as well as the introduction of complex PTSD and prolonged grief disorder, which have no equivalent in the ICD-10.

PTSD is defined by three features that should be present in all cases and must cause significant impairment. They are: re-experiencing the traumatic event in the present; deliberate avoidance of reminders likely to produce re-experiencing; and persistent perceptions of heightened current threat. The inclusion of the requirement for re-experiencing the cognitive, affective or physiological aspects of the trauma in the here and now rather than just remembering the event is expected to address the low diagnostic threshold for PTSD in ICD-10[42].

Adjustment disorder in the ICD-11 is defined on the basis of the core feature of preoccupation with a life stressor or its consequences, while in the ICD-10 the disorder was diagnosed if symptoms occurring in response to a life stressor did not meet definitional requirements of another disorder.

Finally, acute stress reaction is no longer considered to be a mental disorder in the ICD-11, but instead is understood to be a normal reaction to an extreme stressor. Thus, it is classified in the ICD-11 chapter on "factors influencing health status or contact with health services", but cross-listed in the grouping of disorders specifically associated with stress to assist with differential diagnosis.

Dissociative disorders

The ICD-11 dissociative disorders grouping corresponds to ICD-10 dissociative (conversion) disorders, but has been significantly reorganized and simplified, to reflect recent empirical findings and to enhance clinical utility. Reference to the term "conversion" is eliminated from the grouping title[68]. ICD-11 dissociative neurological symptom disorder is conceptually consistent with ICD-10 dissociative disorders of movement and sensation, but is presented as a single disorder with twelve subtypes defined on the basis of the predominant neurological symptom (e.g., visual disturbance, non-epileptic seizures, speech disturbance, paralysis or weakness). ICD-11 dissociative amnesia includes a qualifier to indicate whether dissociative fugue is present, a phenomenon that is classified as a separate disorder in ICD-10.

The ICD-11 divides ICD-10 possession trance disorder into the separate diagnoses of trance disorder and possession trance disorder. The separation reflects the distinctive feature in possession trance disorder wherein the customary sense of personal identity is replaced by an external "possessing" identity attributed to the influence of a spirit, power, deity or other spiritual

entity. In addition, a greater range of more complex behaviours may be exhibited in possession trance disorder, while trance disorder typically involves the repetition of a small repertoire of simpler behaviours.

ICD-11 dissociative identity disorder corresponds to the concept of ICD-10 multiple personality disorder and is renamed to be consistent with currently used nomenclature in clinical and research contexts. The ICD-11 also introduces partial dissociative identity disorder, reflecting the fact that the preponderance of ICD-10 unspecified dissociative disorders is accounted for by presentations in which non-dominant personality states do not recurrently take executive control of the individual's consciousness and functioning.

Depersonalization and derealization disorder, located in the other neurotic disorders grouping in the ICD-10, is moved to the dissociative disorders grouping in the ICD-11.

Feeding and eating disorders

The ICD-11 grouping of feeding and eating disorders integrates ICD-10 eating disorders and feeding disorders of childhood, in recognition of the interconnectedness of these disorders across the lifespan, as well as reflecting the evidence that these disorders can apply to individuals across a broader range of ages[45,47].

The ICD-11 provides updated conceptualizations of anorexia nervosa and bulimia nervosa to incorporate recent evidence, which eliminates the need for ICD-10 "atypical" categories. It also includes the new entities of binge eating disorder, which is introduced based on empirical support for its validity and clinical utility, and ARFID, which expands upon ICD-10 feeding disorder of infancy and childhood.

Anorexia nervosa in the ICD-11 eliminates the ICD-10 requirement for the presence of a widespread endocrine disorder, because evidence suggests that this does not occur in all cases and, even when present, is a consequence of low body weight rather than a distinct defining feature of the disorder. Furthermore, cases without endocrine disorder were largely responsible for atypical anorexia diagnoses. The threshold for low body weight in ICD-11 is raised from 17.5 kg/m^2 to 18 kg/m^2, but the guidelines accommodate situations in which the body mass index may not adequately reflect a worsening clinical picture (e.g., precipitous weight loss in the context of other features of the disorder). Anorexia nervosa does not require "fat phobia" as in the ICD-10, to allow for the full spectrum of culturally diverse rationales for food refusal and expressions of body preoccupation.

Qualifiers are provided to characterize the severity of underweight status, given that extremely low body mass index is associated with greater risk of morbidity and mortality. A qualifier describing the pattern of associated behaviours is included (i.e., restricting pattern, binge-purge pattern).

Bulimia nervosa in the ICD-11 can be diagnosed regardless of the current weight of the individual, as long as the body mass index is not so low as to meet definitional requirements for anorexia nervosa. In lieu of specific minimal binge frequencies that are, in fact, not supported by evidence, the ICD-11 provides more flexible guidance. A bulimia nervosa diagnosis does not require "objective" binges and can be diagnosed on the basis of "subjective" binges, in which the individual eats more or differently than usual and experiences a loss of control over eating accompanied by distress, regardless of the amount of food actually eaten. This change is expected to reduce the number of unspecified feeding and eating disorder diagnoses.

Elimination disorders

The term "non-organic" is removed from the ICD-11 elimination disorders, which include enuresis and encopresis. These disorders are differentiated from those that can be better accounted for by another health condition or the physiological effects of a substance.

Disorders of bodily distress and bodily experience

ICD-11 disorders of bodily distress and bodily experience encompass two disorders: bodily distress disorder and body integrity dysphoria. ICD-11 bodily distress disorder replaces ICD-10 somatoform disorders and also includes the concept of ICD-10 neurasthenia. ICD-10 hypochondriasis is not included and instead is reassigned to the OCRD grouping.

Bodily distress disorder is characterized by the presence of bodily symptoms that are distressing to the individual and an excessive attention directed toward the symptoms, which may be manifest by repeated contact with health care providers[69]. The disorder is conceptualized as existing on a continuum of severity and can be qualified accordingly (mild, moderate or severe) depending on the impact on functioning. Importantly, bodily distress disorder is defined according to the presence of essential features, such as distress and excessive thoughts and behaviours, rather than on the basis of absent medical explanations for bothersome symptoms, as in ICD-10 somatoform disorders.

ICD-11 body integrity dysphoria is a newly introduced diagnosis that is incorporated into this grouping[48].

Disorders due to substance use and addictive behaviours

The ICD-11 grouping of disorders due to substance use and addictive behaviours encompasses disorders that develop as a result of the use of psychoactive substances, including medications, and disorders due to addictive behaviours that develop as a result of specific repetitive rewarding and reinforcing behaviours.

The organization of ICD-11 disorders due to substance use is consistent with the approach in the ICD-10, whereby clinical syndromes are classified according to substance classes[70].

However, the list of substances in the ICD-11 is expanded to reflect current availability and contemporary use patterns of substances. Each substance or substance class can be associated with mutually exclusive primary clinical syndromes: single episode of harmful substance use or harmful pattern of substance use, which represents a refinement of ICD-10 harmful use; and substance dependence. Substance intoxication and substance withdrawal can be diagnosed either together with primary clinical syndromes or independently as a reason for delivery of health services when the pattern of use or possibility of dependence is unknown.

Given the extremely high global disease burden of disorders due to substance use, the grouping has been revised to optimally enable the capture of health information that will be useful in multiple contexts, support accurate monitoring and reporting, and inform both prevention and treatment[70]. The addition of ICD-11 single episode of harmful substance use provides an opportunity for early intervention and prevention of escalation of use and harm, whereas the diagnoses of harmful pattern of substance use and substance dependence suggest the need for increasingly intensive interventions.

The ICD-11 expands the concept of harm to health due to substance use to comprise harm to the health of other people, which can include either physical harm (e.g., due to driving while intoxicated) or psychological harm (e.g., development of PTSD following an automobile accident).

The ICD-11 includes substance-induced mental disorders as syndromes characterized by clinically significant mental or behavioural symptoms that are similar to those of other mental disorders but that develop due to psychoactive substance use. Substance-induced disorders can be related to substance intoxication or substance withdrawal, but the intensity or duration of symptoms are substantially in excess of those characteristic of intoxication or withdrawal due to the specified substances.

The ICD-11 also includes categories of hazardous substance use, which are not classified as mental disorders but rather are situated in the chapter on "factors influencing health status or contact with health services". These categories may be used when a pattern of substance use increases the risk of harmful physical or mental health consequences to the user or to others to an extent that warrants attention and advice from health professionals, but no overt harm has yet occurred. They are meant to signal opportunities for early and brief interventions, particularly in primary care settings.

ICD-11 disorders due to addictive behaviours include two diagnostic categories: gambling disorder (pathological gambling in ICD-10) and gaming disorder, which is newly introduced[49]. In ICD-10, pathological gambling was classified as a habit and impulse disorder. However, recent evidence points to important phenomenological similarities between disorders due to addictive behaviours and substance use disorders, including their higher co-occurrence as well as the common feature of being initially pleasurable followed by progression to loss of hedonic value and need for increased use. Moreover, disorders due to substance use and disorders due to addictive behaviours appear to share similar neurobiology, especially activation and neuroadaptation within the reward and motivation neural circuits[71].

Impulse control disorders

ICD-11 impulse control disorders are characterized by the repeated failure to resist a strong impulse, drive or urge to perform an act that is rewarding to the person, at least in the short-term, despite longer-term harm either to the individual or to others.

This grouping includes pyromania and kleptomania, which are classified in the ICD-10 under habit and impulse disorders.

The ICD-11 introduces intermittent explosive disorder and reclassifies ICD-10 excessive sexual drive to this grouping as ICD-11 compulsive sexual behaviour disorder[50,72,73].

Disruptive behaviour and dissocial disorders

The ICD-11 grouping of disruptive behaviour and dissocial disorders replaces ICD-10 conduct disorders. The new term better reflects the full range of severity of behaviours and phenomenology observed in the two conditions included in this grouping: oppositional defiant disorder and conduct-dissocial disorder. An important change introduced in the ICD-11 is that both disorders can be diagnosed across the lifespan, whereas the ICD-10 construes them as disorders of childhood. Additionally, the ICD-11 introduces qualifiers that characterize subtypes of disruptive behaviour and dissocial disorders intended to improve clinical utility (e.g., prognostically).

ICD-11 oppositional defiant disorder is conceptually similar to its ICD-10 equivalent category. However, a "with chronic irritability and anger" qualifier is provided to characterize those presentations of the disorder with prevailing, persistent irritable mood or anger. This presentation is recognized to significantly increase the risk for subsequent depression and anxiety. The ICD-11 conceptualization of this presentation as a form of oppositional defiant disorder is concordant with current evidence and diverges from the DSM-5 approach of introducing a new disorder, disruptive mood dysregulation disorder[74-76].

ICD-11 conduct disorder consolidates the three separate conduct disorder diagnoses classified in ICD-10 (i.e., confined to the family context, unsocialized, socialized). The ICD-11 acknowledges that disruptive behaviour and dissocial disorders are frequently associated with problematic psychosocial environments and psychosocial risk factors, such as peer rejection, deviant peer group influences, and parental mental disorder. A clinically meaningful distinction between childhood and adolescent onset of the disorder can be indicated with a qualifier, based on the evidence that earlier onset is associated with more severe pathology and a poorer course of the disorder.

A qualifier to indicate limited prosocial emotions can be assigned to both disruptive behaviour and dissocial disorders. In the context of an oppositional defiant disorder diagnosis, this presentation is associated with a more stable and extreme pattern of oppositional behaviours. In the context of conduct-dissocial disorder, it is associated with a tendency towards a more severe, aggressive and stable pattern of antisocial behaviour.

Personality disorders

Problems with the ICD-10 classification of ten specific personality disorders included substantial underdiagnosis relative to their prevalence among individuals with other mental disorders, the fact that only two of the specific personality disorders (emotionally unstable personality disorder, borderline type, and dissocial personality disorder) were recorded with any frequency in publicly available databases, and that rates of co-occurrence were extremely high, with most individuals with severe disorders meeting the requirements for multiple personality disorders[16,17].

The ICD-11 CDDG ask the clinician to first determine whether the individual's clinical presentation meets the general diagnostic requirements for personality disorder. The clinician then determines whether a diagnosis of mild, moderate or severe personality disorder is appropriate, based on: a) the degree and pervasiveness of disturbances in functioning of aspects of the self (e.g., stability and coherence of identity, self-worth, accuracy of self-view, capacity for self-direction); b) the degree and pervasiveness of interpersonal dysfunction (e.g., understanding others' perspectives, developing and maintaining close relationships, managing conflict) across various contexts and relationships; c) the pervasiveness, severity and chronicity of emotional, cognitive and behavioural manifestations of personality dysfunction; and d) the extent to which these patterns are associated with distress or psychosocial impairment.

Personality disorders are then further described by indicating the presence of characteristic maladaptive personality traits. Five trait domains are included: negative affectivity (the tendency to experience a broad range of negative emotions); detachment (the tendency to maintain social and interpersonal distance from others); dissociality (disregard for the rights and feelings of others, encompassing both self-centeredness and lack of empathy); disinhibition (the tendency to act impulsively in response to immediate internal or environmental stimuli without consideration of longer-term consequences); and anankastia (a narrow focus on one's rigid standard of perfection and of right and wrong and on controlling one's own and others' behaviour to ensure conformity to those standards). As many of these trait domains may be assigned as part of the diagnosis as are judged to be prominent and contributing to the personality disorder and its severity.

In addition, an optional qualifier is provided for "borderline pattern". This qualifier is intended to ensure continuity of care during the transition from the ICD-10 to the ICD-11 and may enhance clinical utility by facilitating the identification of individuals who may respond to certain psychotherapeutic treatments. Additional research will be needed to determine whether it provides information that is distinct from that provided by the trait domains.

The ICD-11 also includes a category for personality difficulty, which is not considered a mental disorder, but rather is listed in the grouping of problems associated with interpersonal interactions in the chapter on "factors influencing health status or contact with health services". Personality difficulty refers to pronounced personality characteristics that may affect treatment or provision of health services but do not rise to the level of severity to warrant a diagnosis of personality disorder.

Paraphilic disorders

The ICD-11 grouping of paraphilic disorders replaces the ICD-10 grouping of disorders of sexual preference, consistent with contemporary terminology used in research and clinical contexts. The core feature of paraphilic disorders is that they involve sexual arousal patterns that focus on non-consenting others[77].

ICD-11 paraphilic disorders include exhibitionistic disorder, voyeuristic disorder, and pedophilic disorder. Newly introduced categories are coercive sexual sadism disorder, frotteuristic disorder, and other paraphilic disorder involving non-consenting individuals. A new category of other paraphilic disorder involving solitary behaviour or consenting individuals is also included, which can be assigned when sexual thoughts, fantasies, urges or behaviours are associated with substantial distress (but not as a consequence of rejection or feared rejection of the arousal pattern by others) or confer direct risk of injury or death (e.g., asphyxophilia).

The ICD-11 distinguishes between conditions that are relevant to public health and clinical psychopathology and those that merely reflect private behaviour, and for this reason the ICD-10 categories of sadomasochism, fetishism, and fetishistic transvestism have been eliminated[26].

Factitious disorders

The ICD-11 introduces a new grouping of factitious disorders that includes factitious disorder imposed on the self and factitious disorder imposed on another. This grouping is conceptually equivalent to the ICD-10 diagnosis of intentional production or feigning of symptoms or disabilities, either physical or psychological (factitious disorder), but extended to include the clinical situation where an individual feigns, falsifies, or intentionally induces or aggravates medical, psychological or behavioural signs and symptoms in another individual (usually a child).

The behaviours are not solely motivated by obvious external rewards or incentives, and are distinguished on this basis from

malingering, which is not classified as a mental, behavioural or neurodevelopmental disorder, but rather appears in the chapter on "factors influencing health status or contact with health services".

Neurocognitive disorders

ICD-11 neurocognitive disorders are acquired conditions characterized by primary clinical deficits in cognitive functioning, and include most conditions that are classified among ICD-10 organic, including symptomatic, mental disorders. Thus, the grouping includes delirium, mild neurocognitive disorder (called mild cognitive disorder in ICD-10), amnestic disorder, and dementia. Delirium and amnestic disorder can be classified as due to a medical condition classified elsewhere, due to a substance or a medication, or due to multiple etiological factors. Dementia may be classified as mild, moderate or severe.

The syndromal characteristics of dementia associated with different etiologies (e.g., dementia due to Alzheimer disease, dementia due to human immunodeficiency virus) are classified and described within the chapter on mental, behavioural and neurodevelopmental disorders, whereas the underlying etiologies are classified using categories from the chapter on diseases of the nervous system or other sections of the ICD, as appropriate[78]. Mild neurocognitive disorder can also be identified in conjunction with an etiological diagnosis, reflecting improved detection methods for early cognitive decline, which represents an opportunity to provide treatment in order to delay disease progression. The ICD-11 therefore clearly recognizes the cognitive, behavioural and emotional components of neurocognitive disorders as well as their underlying causes.

CONCLUSIONS

The development of the ICD-11 CDDG for mental, behavioural and neurodevelopmental disorders and their underlying statistical classification represents the first major revision of the world's foremost classification of mental disorders in nearly 30 years. It has involved an unprecedented level and range of global, multilingual and multidisciplinary participation. Substantial changes have been made to increase scientific validity in the light of current evidence and to enhance clinical utility and global applicability based on a systematic program of field testing.

Now, both the version of the ICD-11 chapter to be used by WHO member states for health statistics and the CDDG for use in clinical settings by mental health professionals are substantively complete. In order for the ICD-11 to achieve its potential in the world, the WHO's focus will shift to working with member states and with health professionals on implementation and training.

The implementation of a new classification system involves the interaction of the classification with each country's laws, policies, health systems and information infrastructure. Multiple modalities must be developed for training a vast array of international health professionals. We look forward to continuing our very productive collaboration with the WPA and to working with member states, academic centers, professional and scientific organizations and with civil societies in this next phase of work.

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Internet-delivered psychological treatments: from innovation to implementation

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Internet interventions, and in particular Internet-delivered cognitive behaviour therapy (ICBT), have existed for at least 20 years. Here we review the treatment approach and the evidence base, arguing that ICBT can be viewed as a vehicle for innovation. ICBT has been developed and tested for several psychiatric and somatic conditions, and direct comparative studies suggest that therapist-guided ICBT is more effective than a waiting list for anxiety disorders and depression, and tends to be as effective as face-to-face CBT. Studies on the possible harmful effects of ICBT are also reviewed: a significant minority of people do experience negative effects, although rates of deterioration appear similar to those reported for face-to-face treatments and lower than for control conditions. We further review studies on change mechanisms and conclude that few, if any, consistent moderators and mediators of change have been identified. A recent trend to focus on knowledge acquisition is considered, and a discussion on the possibilities and hurdles of implementing ICBT is presented. The latter includes findings suggesting that attitudes toward ICBT may not be as positive as when using modern information technology as an adjunct to face-to-face therapy (i.e., blended treatment). Finally, we discuss future directions, including the role played by technology and machine learning, blended treatment, adaptation of treatment for minorities and non-Western settings, other therapeutic approaches than ICBT (including Internet-delivered psychodynamic and interpersonal psychotherapy as well as acceptance and commitment therapy), emerging regulations, and the importance of reporting failed trials.

Key words: Internet interventions, cognitive behaviour therapy, innovation, anxiety disorders, depression, moderators and mediators, negative effects, blended treatment, implementation

Modern information technology has changed the world and the way we interact with one another[1]. Computers were utilized early in psychotherapy research[2] and, with the advent of the Internet, use of computers in research and practice increased rapidly[3].

Clinical psychology and psychiatry have been influenced by these technological advances. Not only have Internet interventions become available, but so have websites providing information about psychiatric conditions[4], assessment procedures[5], and social forums related to psychiatric diagnoses[6]. More recently, modern mobile phones (smartphones) have facilitated data collection[7], increasing the reach and dissemination of therapeutic help. There are now literally thousands of smartphone apps dealing with mental health concerns, such as depression and stress[8,9].

The focus of this review is on Internet-delivered psychological treatments[10,11]. The first of these treatments were developed, evaluated and delivered as part of routine care in the mid-1990s[12]. Subsequently, the number of controlled trials of Internet-delivered psychological treatments has grown at a much faster rate than trials of psychotherapy in general. Most of the programs and research on Internet-delivered treatments have involved different forms of cognitive behaviour therapy (CBT), often referred to as ICBT[13].

TREATMENT APPROACH

There are numerous different versions of ICBT, but all require a treatment software platform to deliver and manage the intervention. This platform presents assessment instruments, treatment materials, and technology to facilitate interactions between a clinician and a client[14]. Treatment programs can deliver content in the form of text, video or audio, which are presented in the platform together with homework assignments, and interactions with a clinician and/or automated support functions (especially in the case of self-guided treatments). The layout of pages in the platform can be fully responsive, adapting to screen size and ensuring a fully-functional user experience regardless of whether the platform is accessed using a desktop computer, a mobile phone (smartphone) or a tablet[14].

Other important features of treatment software platforms include that they need to be able to regularly administer symptom questionnaires, which can be used to monitor progress, severity of symptoms, and possibly risk of self-harm[15]. Security of data is also crucial[16], in particular when there is an interaction between a client and a therapist via text or video chat and sensitive information is exchanged, and to record clinical notes.

The legal requirements for management of privacy of health-related data are rapidly evolving, but security requirements are generally similar to those for industries that involve electronic transmission of sensitive data, such as Internet banking (e.g., when bills are paid online), including encryption of data traffic and a double-authentication procedure at login[14].

Many programs include all components of an evidence-based psychological intervention[17]: for example, exposure instructions in the case of anxiety disorders and behavioural activation in the case of depression. Thus, some programs can include the equivalent of 150 pages of text, even if the material is presented online and with interactive features such as a quiz.

It has been possible to transfer a large proportion of common CBT techniques to the Internet format, with early programs sharing close similarities with bibliotherapy[18], and current ones being more easily readable on the screen or in the form of slide shows that present the principles of CBT via text and images[19].

While CBT has been the dominant model of therapy used in Internet interventions so far, different models have been and are being explored, including acceptance and commitment therapy[20], psychodynamic approaches[21], interpersonal psychotherapy[22], physical activity[23], mindfulness[24], and programs based on attention bias modification training[25].

A large proportion of studies and several implementations involve a clinician who guides the client through the program, provides feedback on homework assignments and also general support and answers to questions from the client[17]. The role of the clinician in ICBT has been investigated in many studies: overall, guided ICBT programs tend to be more effective than self-guided ICBT[26], even if some studies in which administrative contact is included tend to show that self-guided treatments can also produce clinically significant improvements[27,28].

While there are still few studies, there are indications that a practical and technical support may be sufficient[29], and that novice clinicians can be as effective as clinicians who have more experience with ICBT[30]. On the other hand, studies also show that what the therapist does is not irrelevant[31], and that a lenient therapist response to uncompleted homework assignments can be associated with less improvement in ICBT for generalized anxiety disorder[32]. Moreover, affirming responses to client e-mails can be associated with better outcomes in ICBT for depression, and the same seems to happen if the therapist is self-disclosing[33], just to give two examples. To increase fidelity and therapist efficacy, guidelines can be developed and followed which facilitate both research and clinical training[34].

Several studies have investigated the role of therapeutic alliance in ICBT[35], with a focus on agreement with regard to tasks and goals as well as the bond between the therapist and the client[36]. While some studies show a small but statistically significant association between early alliance ratings and outcome in ICBT[37], other studies fail to find this[38]. Overall, high alliance ratings have been reported, suggesting that clients do develop a relationship with their online therapist. However, there are problems with this research, in that it is likely that alliance is rated in relation to the whole program and not just to the relatively minor interactions between the client and the therapist[39]. Further, with the exception of a study on blended face-to-face and ICBT[40], studies have not involved observer-rated alliance.

INNOVATION

One aspect of Internet-delivered interventions, including ICBT, is the possibility of rapid clinical innovation, a hallmark of science as there is often room for improvement in treatment research[41]. Psychotherapy research has most likely suffered from the high costs involved with running controlled trials, and one advantage of conducting studies online is lower costs and shorter study periods.

First, recruitment is usually much faster than in ordinary clinical trials, in part because it is not geographically confined. Second, diagnostic procedures are often performed from a distance, with structured telephone interviews complementing the self-reported data gathered through the use of validated online questionnaires[42]. Third, by using online materials that provide a significant proportion of the therapeutic content, the actual time devoted to each client is much less than in face-to-face treatment research, with an average of 10 min per client and week versus the traditional 45 min weekly sessions. There is no need for a therapy room, and clients do not need to wait to the same extent as in a face-to-face study. Further advantages are the possibility to repeat a lesson/module and the faster access to support if needed.

Researchers in this field often start by conducting a randomized controlled trial (RCT), sometimes referred to as a "pilot RCT"[43], but not necessarily having smaller samples than in older psychotherapy trials, which were often underpowered[44]. Some researchers perform open pilot studies before running a controlled trial[45], but, as a controlled trial is more likely to give clearer answers regarding effects, and still does not cost more than a pilot trial, there is a tendency to skip this open testing once a treatment has been developed.

Phase IV open studies with no control groups have an important role to play in clinical effectiveness research[46], when it is not feasible or even possible to randomize clients. Investigations of Internet interventions can also use qualitative methods, including interviews of individuals who have completed the treatment[47]. Such studies are on the increase. What is lacking, however, are detailed case descriptions and, to the best of our knowledge, there are very few case studies on Internet interventions[48].

Given the large sample sizes that can be obtained in Internet interventions research, the possibility has emerged to conduct factorial design trials instead of the ordinary treatment versus control trials. In factorial research designs, it is possible to answer more than one question, as two or more independent variables (or factors) are tested within the same study, leading to two or more main effects and possible interaction effects between conditions. At a minimum, this leads to a design with four experimental conditions (or groups). For example, two different forms of ICBT for depression (behavioural activation vs. cognitive therapy) could be compared as well as two different ways to provide support (scheduled vs. on request).

There are various versions of factorial designs[49], and several such studies are in progress[50,51]. The use of factorial designs is likely to speed up the development of new interventions and treatment components. However, even current Internet interventions research can be viewed as an engine for innovation, with treatments being developed and tested directly for Internet delivery instead of first being tested as a face-to-face treatment. One such example is a recently developed treatment for procrastination[52].

The possibility to recruit patients without geographical barriers also presents opportunities for testing psychotherapy for people with conditions and problems (e.g., spinal cord injury, epilepsy) that can be highly disabling while also having a relatively low prevalence, making them very difficult to study feasibly in face-to-face trials[53].

EVIDENCE BASE TO DATE

The evidence base for ICBT, and for Internet interventions in general, has increased rapidly, making separate systematic reviews for different conditions necessary. There are now as many as 300 controlled trials of Internet interventions (including unpublished studies), for different disorders and target populations, and the number continues to increase.

Early reviews tended to focus more broadly on the effects of ICBT[54], or on computerized interventions in general[55]. It is still common to mix different technologies in reviews, which can be problematic, as there are differences between computerized treatments delivered in a clinic and ICBT involving contact from a distance.

Some contemporary reviews focus on the effects of Internet interventions for specific disorders or conditions, different target populations, and on specific forms of psychological treatments, such as, for example, acceptance and commitment therapy[56]. Another recent trend is to conduct individual participant data meta-analyses, by pooling the raw data from different research groups, which facilitates moderator analyses[57].

A common problem when reviewing the literature on Internet interventions, including ICBT, is the use of different terms to describe the interventions, for example digital therapy, Internet interventions, and computerized psychotherapy. Other terms, such as web-based psychotherapy and online psychotherapy, are also commonly used. This has been referred to as "terminology chaos"[58], and there are no signs that it will be solved since, for example, smartphone delivery and virtual reality are now sometimes being seamlessly combined with the more standard Internet format[59].

Concerning anxiety disorders, several systematic reviews and meta-analyses are available, with a Cochrane review on therapist-delivered ICBT being one of the most recently updated[60]. This included randomized controlled trials of therapist-supported ICBT compared to a waiting list, attention, information or online discussion group; unguided CBT; or face-to-face CBT. Studies on adults with panic disorder, agoraphobia, social phobia, post-traumatic stress disorder (PTSD), acute stress disorder, generalized anxiety disorder, obsessive-compulsive disorder, or specific phobia, defined according to DSM-III/III-R/IV/IV-TR or ICD-9/10, were included. The standardized mean difference (SMD) for disorder-specific anxiety symptoms (22 studies, 1,573 participants) and general anxiety symptoms (14 studies, 1,004 participants) at post-treatment favored therapist-supported ICBT over waiting list, attention, information, or online discussion group only (respectively, SMD=−1.12, 95% CI: −1.39 to −0.85 for disorder-specific anxiety symptoms; and SMD=−0.79, 95% CI: −1.10 to −0.48 for general anxiety symptoms). The quality of the evidence, however, was rated as low. There was no significant difference between therapist-supported ICBT and face-to-face CBT for either disorder-specific anxiety symptoms (6 studies, 424 participants, SMD=0.09, 95% CI: −0.26 to 0.43) or general anxiety symptoms (5 studies, 317 participants, SMD=0.17, 95% CI: −0.35 to 0.69) at post-treatment. Again, the quality of the evidence was rated as low.

This is in line with a more recent review by Andrews et al[61], in which the Hedges' g for ICBT or computerized CBT (cCBT) compared to care as usual, waiting list, information control, psychological placebo or pill placebo was 1.31 (95% CI: 0.85 to 1.76; 12 studies) for panic disorder, 0.92 (95% CI: 0.76 to 1.08; 11 studies) for social anxiety disorder, and 0.70 (95% CI: 0.39 to 1.01; 9 studies) for generalized anxiety disorder. Nine studies compared ICBT to face-to-face CBT (568 subjects in total), and the difference was found to be not significant (g=0.14 in favor of face-to-face CBT, 95% CI: −0.04 to 0.32).

Overall, these data seem to suggest that therapist-supported ICBT is more efficacious than control conditions for anxiety disorders, and not significantly different from face-to-face CBT, although further evidence of a better quality is needed.

Several separate reviews have been published on, for example, PTSD[62], in which the pooled between-group effect size with treatment against waiting list control was g=0.71, based on 10 studies and 1,139 participants. There is also a recent review on the effects of ICBT for children and adolescents[63], which included 24 studies and found a moderate effect size against control conditions (g=0.62).

Concerning depression, Andrews et al[61] found an Hedges' g for ICBT or cCBT compared to care as usual, waiting list, information control, psychological placebo or pill placebo of 0.67 (95% CI: 0.51 to 0.81), based on 32 studies. Josephine et al[64], in a systematic review and meta-analysis focusing on Internet- and mobile-based interventions in adults with diagnosed depression, compared with waiting list or attention placebo, found that only 19 studies were eligible for inclusion (i.e., included patients with diagnosed major depression). Internet- and mobile-based interventions had a significantly greater impact on depression severity compared to waiting list at the end of treatment (g=−0.90, 95% CI: −1.07 to −0.73).

A recent meta-analysis of individual participant data[65] managed to get the raw data from 13 randomized controlled trials (3,876 participants) in which self-guided ICBT was compared with a control condition (usual care, waiting list or attention control) in individuals with symptoms of depression. Self-guided ICBT was significantly more effective than control conditions on depressive symptoms severity (g=0.27) and treatment response (odds ratio=1.95, 95% CI: 1.52 to 2.50). These effect sizes seem to confirm the results of older reviews suggesting that self-guided ICBT tends to be less effective than therapist-guided ICBT[66].

One approach to ICBT is to tailor the intervention according to the patient profile, which is a way to handle comorbidity

between disorders. An alternative is to use a transdiagnostic approach targeting the underlying mechanisms of several disorders (e.g., avoidance). Both approaches have been tested in ICBT research, and a meta-analysis of studies dealing with anxiety and depression, including 19 controlled trials and 2,952 participants, found an average effect size against control conditions of g=0.82 (95% CI: 0.58 to 1.05) for anxiety and g=0.79 (95% CI: 0.59 to 1.00) for depression. There were no substantial differences between transdiagnostic and disorder-specific treatments[67].

In addition to studies on psychiatric conditions, there is a large literature on various health problems, such as chronic pain[68], insomnia[69], tinnitus[70], and stress[71], just to mention a few examples. There are also studies on addictions[72].

Many studies point in the direction of equivalent effects of guided Internet interventions and face-to-face treatments, but this question can only be addressed by direct comparisons. In an updated meta-analysis of a previous review[73], 20 studies in which participants had been randomly assigned to guided ICBT for psychiatric and somatic conditions or to face-to-face CBT were included[74]. The pooled between-group effect size at post-treatment was g=0.05, suggesting that ICBT and face-to-face treatment produce equivalent effects.

While early studies of unguided ICBT suffered from high dropout rates (a weighted average of 31% of the participants dropped out of treatment in 19 studies of Internet-based treatment programs for psychological disorders)[75], a recent meta-analysis of ICBT for adult depression[76], including 24 studies, found that participants in guided ICBT completed on average 80.8% of their treatment, which did not differ significantly from participants in face-to-face CBT (83.9%, p=0.59). However, the percentage of completers (total intervention) was significantly higher in face-to-face CBT (84.7%) than in guided ICBT (65.1%, p<0.001).

There are also studies in which the long-term effects of ICBT have been investigated. A recent review included 14 trials in which data had been collected for a follow-up period of two years or longer after completion of treatment. The included studies had an average follow-up period of three years[77]. There were long-term outcome studies on panic disorder, social anxiety disorder, generalized anxiety disorder, depression, mixed anxiety and depression, obsessive-compulsive disorder, pathological gambling, stress, and chronic fatigue. The pre- to follow-up effect size was g=1.52.

In sum, the literature on Internet interventions and ICBT is growing, guided ICBT tends to be as effective as face-to-face CBT, and the effects are likely to be sustained over time.

HARMFUL EFFECTS

While hardly being noticed (and perhaps even dismissed for a long time), the possibility of negative effects during and following psychotherapy has more recently been investigated in relation to ICBT[78]. Negative effects are increasingly documented in association with controlled trials of ICBT, but there are also separate reports of negative effects.

One example is a patient-level meta-analysis[79], which included 2,866 patients from 29 clinical trials of ICBT. Using the Reliable Change Index, the deterioration rate was 5.8% in the treatment and 17.4% in the control conditions (odds ratio=3.10, 95% CI: 2.21 to 4.34). Being in a relationship, being older and having at least a university degree were associated with lower odds of deterioration, but only in patients assigned to the treatment condition.

Another patient-level meta-analysis focused on self-guided Internet treatments for depression[80], and found that, of the 3,805 participants analyzed, 5.8% in the treatment groups and 9.1% in the control groups had deteriorated (odds ratio=0.62, p<0.001). No examined moderators were significantly associated with the deterioration rate.

In a similar patient-level analysis on guided ICBT[81] (18 studies, 2,079 participants), the deterioration rate was 3.36% in the treatment groups and 7.60% in the control groups (relative risk=0.47, 95% CI: 0.29 to 0.75). Patients with lower education presented a higher risk for deterioration than those with higher education.

Overall, these rates of deterioration appear similar to those reported in face-to-face treatments[78]. However, it is important to note that our methods for exploring negative effects are still limited and, for example, relatively little is known about the causes (e.g., the intervention itself, factors outside of the intervention) of the negative effects observed during Internet interventions. Negative effects other than symptom deterioration may also occur in ICBT and should be documented, for example by using open-ended questions or self-report measures covering adverse and unwanted events[79].

MECHANISMS OF CHANGE AND PREDICTORS OF OUTCOME

As would be expected from the literature on face-to-face psychotherapies[82], there are no consistent predictors or change mechanisms reported in Internet interventions research. We have reviewed above the literature on therapeutic alliance, in which the results have been inconsistent. In addition, studies have been conducted on genetic variables, but findings have not been promising[83].

One study[84] hypothesized that a greater cognitive flexibility would provide a better foundation for learning and implementing the cognitive restructuring techniques used in ICBT, leading to better treatment outcomes. Data from three samples including patients with depression, social anxiety disorder and tinnitus were used. The 64-card Wisconsin Card Sorting Test (WCST) was administered prior to treatment. There was no significant association between perseverative errors on the WCST and treatment gains in any group.

However, another study[85], conducted on 66 older adults with mixed anxiety depression randomized to ICBT or control conditions, who were administered the WCST (perseverative errors) and the Cognitive Failures Questionnaire before treatment, reported a moderate between-group effect on the main

outcome measure, the Beck Anxiety Inventory (d=0.50), favoring the treatment group. The authors concluded that the role of cognitive functioning in the outcome of ICBT should be further investigated.

Perhaps more promising, but still very preliminary, are studies on brain imaging. One study[86] showed that the long-term outcome of ICBT for social anxiety disorder could be predicted by blood oxygen level-dependent (BOLD) responses to self-referential criticism in the fear-expressing dorsal anterior cingulate cortex and amygdala regions at pre-treatment, analyzed using a support vector machine learning approach. Another study[87] found that larger pre-treatment right rostral anterior cingulate cortex volume was a significant predictor of greater depressive symptom improvement on ICBT, even after controlling for demographic and clinical variables previously linked to treatment response.

Various demographic characteristics have been investigated as well, with mixed findings. It is common to find that variables such as age, gender, marital status, computer skills, educational level, and having children have no significant predictive value[88].

There are other possible mediators of outcome more directly related to the actual treatment process, and factors that are likely to influence uptake and adherence to treatment. For instance, it has been reported that Internet therapy is more effective when the treatment is user friendly and not overly technically advanced, and a clear deadline is provided for the duration of the treatment[89]. Furthermore, sudden gains (i.e., large and stable improvements occurring between two consecutive treatment sessions) have been found to predict larger improvements at both post-treatment and one-year follow-up in patients receiving ICBT for severe health anxiety[90]. Design features of ICBT could also be important: a systematic review[91] found that "persuasive technology" elements (such as more extensive employment of dialogue support) significantly predicted better adherence to treatment.

ICBT has been also conceptualized as a form of patient education. Studies have investigated whether ICBT influences knowledge acquisition in social anxiety disorder[30], eating disorders[92] and, most recently, adolescents with depression[93]. The studies show that improvements in knowledge occur following ICBT. More research is needed in this domain, for example, to test if knowledge acquisition can be influenced directly in treatment (by using methods from educational science).

Another recent and related body of work indicates that client's use of CBT skills may predict change in symptoms and satisfaction with life[94]. This promising direction of work indicates that practice of such skills may be an important mechanism of change, but requires large scale replication.

In sum, while there are observational studies on mechanisms of change in ICBT, there are few consistent findings regarding both moderators and mediators. Theory-driven and experimental research with repeated measure of process variables might help to identify what to look for, as much research has been informed by traditional psychotherapy research rather than the unique aspects of ICBT.

IMPLEMENTATION

ICBT and Internet interventions at large have been around for about 20 years[3], but implementation efforts have had mixed success. Moreover, these efforts have rarely been well documented from an implementation science perspective.

However, several effectiveness studies, with data from routine clinical practice settings, have been published for a number of disorders and conditions[95]. One early application in general health care was the tinnitus clinic in Uppsala, Sweden, which began delivering CBT for tinnitus via the Internet by the end of 1999, and published effectiveness data early on[96]. Another early example was the Interapy program from the Netherlands, which started in the 1990s and subsequently published effectiveness data on adult patients with symptoms of depression, panic disorder, PTSD or burnout[97]. The publicly available Moodgym from Australia is another early example with published data from community users[98].

Two contemporary examples of effectiveness reports come from the MindSpot Clinic in Australia[19] and the Internet psychiatry unit in Sweden[46,99]. Both groups have published data from their routine clinical practice, indicating that ICBT works when delivered as a regular intervention with ordinary clients. A recent study described the implementation of ICBT in five countries: Australia, Canada, Norway, Sweden and Denmark[100]. The authors also included references to published effectiveness studies of outcomes from their clinics, which all demonstrated large clinical improvement, low rates of deterioration, and high levels of patient satisfaction.

While still being at an early stage, published data clearly suggest that ICBT can work in regular settings, even as a stepped-care approach[101]. However, in most cases, the implementation has been handled by specialist and centralized clinics as opposed to wide-scale dissemination across a whole country with several clinics involved.

One potential obstacle when implementing Internet interventions and ICBT is negative attitudes among clients, clinicians and other stakeholders (such as insurance companies). One stakeholder survey was conducted in eight European countries with 175 organizations participating[102]. Results showed greater acceptability of blended treatment (the integration of face-to-face and Internet sessions within the same treatment protocol) compared to stand-alone Internet treatments. For example, for mild depression, 46.5% would recommend ICBT only and 69.8% blended treatment, but for moderate depression the corresponding figures were 15.7% and 57.2%, a marked difference. The same discrepancy was found for severe depression, with 1.9% recommending ICBT and 27% blended treatments. Thus, stakeholders are still hesitant to recommend ICBT as a stand-alone intervention, in particular for more severe depression. Another example is a study from the US conducted in a primary care setting, which showed that patients were less interested in taking part in ICBT than face-to-face treatment[103].

This literature should be interpreted with some caution, as there are likely differences both between and within countries

and settings. Given the observation that clinicians may not know what ICBT is, there is also a role for education in order to facilitate dissemination[104]. Nevertheless, the benefit of Internet interventions is likely to be that they provide an opportunity to care for people who cannot or do not want to access face-to-face care, rather than for people presenting for and wanting face-to-face care.

FUTURE DIRECTIONS

It is hard to predict how technology will develop, and also if new technology will be adapted for clinical use. One example is the use of sensors to measure physiological activity and behaviours such as sleep through smartphones[8]. Such technology already exists, but there is a need to investigate if it can advance treatment in any way. Another example is serious gaming and other delivery formats than just text and pictures[105]. Virtual reality is another technique that has become less expensive and can be integrated with ICBT[106]. Finally, in light of the ability to generate large amounts of data, the role of machine learning can possibly increase, with one initial study suggesting that prediction of treatment outcome may benefit from this approach[107].

A second possible future direction of research is to expand the reach of ICBT to other languages and cultures than are usually targeted in psychotherapy research (for example, immigrants). As an example of this, controlled studies have been conducted in the Arabic language[108] as well as in Chinese[109]. One project aimed at disseminating treatment across languages and cultures involved translation of a Swedish ICBT program for social anxiety disorder into Romanian[110].

A third development, already mentioned earlier, is the development and testing of Internet-delivered psychotherapies other than CBT. Examples include psychodynamic therapy[21], interpersonal therapy[111], and treatment programs involving attention training[112]. This is likely to increase, along with the possible integration of therapeutic techniques. We also expect more research into models of blended care, as described earlier.

A fourth development has to do with research designs and publication bias. With regards to research designs, we believe that the standard treatment versus control design may be less needed as compared to more sophisticated factorial designs testing several research questions simultaneously[51]. Publication bias is a problem in both basic and applied research, but we believe that change will happen. "Failed" trials of ICBT are already being reported[113], as well as trials with negative findings[25].

A fifth likely development is the creation of regulations and standards governing the delivery of ICBT in routine care. We recognize that health services delivered via the Internet should meet the same safety and quality standards as traditional models, but must also meet appropriate standards for the safety and security of sensitive health-related data. As a consequence of increasing interest in ICBT by health funders and regulators, we expect considerable future debate about how best to regulate such services, what standards they should meet, and how they should be accredited[114,115].

CONCLUSIONS

ICBT and other forms of Internet interventions hold promise as a way to increase access to evidence-based psychological treatment. They can also serve as vehicles for innovation, which may subsequently inform face-to-face treatments.

Even if ICBT is gradually being implemented, the process is slow and needs to be better documented. While the intervention has proved to be cost-effective[116], there are several professional challenges when moving from traditional service models. Most likely, blended approaches, which retain advantages from both face-to-face and technology-driven methods, will gain more popularity in the future.

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Personal growth in psychosis

Recovery is a new paradigm for mental health systems globally. One implication is a greater emphasis on subjective experience – what is it like to live with schizophrenia and other psychoses?

A systematic review of the experience of recovery found that the impact of psychosis is more mixed than traditional illness models would imply[1]. The process of recovery was characterized as an active and life-changing experience, involving struggle and occurring both with and without professional intervention. However, clinical practice often remains focussed on deficit amelioration through treatment, rather than on supporting these active processes of change which are involved in developing an identity as a "person in recovery".

Trauma is both a cause[2] and effect of psychosis, and trauma research has identified a range of post-traumatic growth and adaptation processes which are relevant to people living with psychosis. Post-traumatic growth research focuses on the extent to which the struggle to overcome trauma can act as a catalyst for personal growth and development.

In the process of adapting to distressing experiences, including making sense of and attributing meaning to these experiences, individuals may challenge and change some of their pre-trauma beliefs. For example, aspects of personality, relationships with others and beliefs about the world can all change in a manner that the individual views as positive and reflective of personal growth.

The profile of these positive changes varies across individuals, but a consensus has emerged about five post-traumatic growth domains in which these changes typically occur: heightened feelings of personal strength; more intimate relationships with loved ones; recognition of new possibilities or directions in one's life purpose; greater appreciation of life; and engagement with spiritual and existential questions about the nature and meaning of life[3].

Post-traumatic growth has clinical relevance. A meta-analysis of populations experiencing a diverse range of traumatic events found that engaging in post-traumatic growth was an adaptive and clinically beneficial process[4]. Higher post-traumatic growth was associated with lower levels of depression and higher levels of well-being. Post-traumatic growth can, therefore, be considered as a process that aids recovery by enabling the individual to find meaning from a painful struggle and to recalibrate his/her identity and purpose in life in light of his/her experiences.

Post-traumatic growth in psychosis is both possible and supportive of recovery. A scoping review of evidence relating to first-episode psychosis identified several forms of post-traumatic growth: developing positive character traits, making positive lifestyle changes, developing stronger relationships, greater appreciation of life and spirituality, and integrating one's experience of first-episode psychosis into one's identity[5].

Predictors of post-traumatic growth in psychosis are emerging. A study of 34 first-episode psychosis participants in England found that higher levels of post-traumatic growth were predicted by lower levels of post-traumatic stress disorder symptoms, greater levels of self-disclosure behaviour, and higher self-reported recovery[6]. Similarly, a study of 121 community rehabilitation service users with psychosis in Israel found that post-traumatic growth is mediated by coping self-efficacy appraisal and meaning-making[7].

In relation to meaning-making, an important aspect of post-traumatic growth in psychosis is the opportunity for validation and collective identity offered by peer-support networks. For example, the International Hearing Voices Movement (HVM) has worked in partnership with academics and clinicians for the past 30 years to promote more accepting and empowering perspectives on what has traditionally been an extremely stigmatized and marginalized experience.

One aspect of this approach is helping members to develop a positive identity as someone who hears voices. A central philosophy of the HVM has been that the ownership and interpretation of one's voices always belongs to the individual voice hearer. Correspondingly, a great emphasis is placed on personal testimony and meaning-making, in which distressed individuals are supported to find explanatory frameworks that are subjectively useful and significant. Thus, while psychosocial models have been strongly promoted within the HVM, including the links between trauma and voice hearing[8], they are not privileged; alternative explanatory frameworks, such as spiritual or cultural, are seen as equally valid.

The HVM perspective is that even the most devastating periods of mental ill-health can ultimately be a source of personal development. Many narratives from HVM members show how psychiatric crisis has prompted, for example, a greater capacity for political activism, emotional insight, creativity, courage, and compassion for self and others.

The idea of relocating voice hearing from being a meaningless disease symptom to a personally significant event that can inform and guide one's recovery journey has resonated with many mental health service users. There has been a rapid expansion of HVM networks across Europe, Australasia and North America, with initiatives currently emerging in Asia, Africa and South America: "the HVM appear[s] to offer an attractive alternative for voice-hearers who have not been fully helped by traditional approaches, who are searching for greater understanding and acceptance of their experiences, or who feel that their stories have not been heard or acknowledged"[9].

We identify three clinical implications. First, clinical assessment should include trauma and its effects. An insight offered by the HVM is that it may be as useful to find out "What's happened to you?" as opposed to "What's wrong with you?". Second, promoting post-traumatic growth is an approach to supporting recovery. The five established domains of strengths, relationships, life possibilities, appreciation and spirituality provide an assessment framework which may have clinical utility, both for

encouraging therapeutic optimism that a more positive future is possible and for identifying points of intervention.

Finally, supporting people who live with psychosis to make personally-meaningful sense of their experiences is a different skill to promoting insight, and may require new clinical approaches which avoid imposing explanatory clinical models. The expertise of organizations such as the HVM may be needed in the mental health system.

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Assessment and determinants of patient satisfaction with mental health care

How satisfied patients are with the care they are receiving is widely regarded as an important process variable and quality indicator in mental health care.

It is a process variable, as it predicts to what extent the aim of care, i.e. the alleviation or overcoming of mental distress, may be achieved. Various studies have shown that more satisfied patients are more adherent to treatment and – even if there is no difference in adherence – benefit more from care than less satisfied patients. Furthermore, patient satisfaction predicts outcomes right from the initial stages of treatment, e.g. when assessed within the first two days of hospital care[1]. It is also a quality indicator, because all treatments should be as patient friendly as possible, independently of any impact on health and social outcomes.

Since the 1960s, numerous scales have been used to measure patient satisfaction with mental health care, also termed treatment satisfaction, service satisfaction or consumer satisfaction. A recent systematic review indicates that scales vary significantly in their structure, length, focus and quality[2]. There is no consensus on how exactly patient satisfaction should be measured and, across scales, patients are asked to rate their satisfaction with 19 different aspects of care. Despite an extensive literature, the review identified only four scales that have been used in more than 15 studies and may therefore be regarded as more established.

The Client Satisfaction Questionnaire[3] for outpatient treatment and the Client Assessment of Treatment Scale[4] for inpatient treatment are brief scales of 8 and 7 items respectively and provide global scores. The Verona Service Satisfaction Scale[5] and the Self-Rating Patient Satisfaction Questionnaire[6] are much longer and have subscales on different care aspects in addition to a global score.

Satisfaction with care, as measured on such scales, can be influenced by characteristics of the patients and by aspects of the care they are receiving[7].

A number of socio-demographic characteristics such as gender, ethnicity, socio-economic and marital status have been suggested as determinants of satisfaction with care, but the associations are usually weak and the findings across studies are inconsistent. The only socio-demographic feature that is consistently linked with higher patient satisfaction with care is older age, which however is also associated with higher satisfaction with life in general.

More substantial correlations have been found with clinical characteristics and patient reported outcomes, such as subjective quality of life. Patients with higher symptom levels, especially more depressive symptoms, with personality disorders and with lower subjective quality of life tend to express less satisfaction with their care[8].

Only a few aspects of care have consistently been found to impact on patient satisfaction. Coercive treatment and the perception of a negative therapeutic relationship are strongly associated with lower satisfaction with care, which might however be regarded as highly expected findings. There also seems to be a tendency for patients to be more satisfied with treatment in the community than in hospitals[9].

When satisfaction scores are obtained for the evaluation of different treatments and services, one should consider the above determinants – e.g., age, the legal status of the treatment, and severity of illness or symptoms, in particular depressive symptoms – as potential confounders. Adjusting scores for these confounders minimizes the risk that positive or negative ratings get falsely attributed to a specific form of care when in fact they reflect general tendencies of a patient group with specific characteristics. For instance, patients with marked depressive mood are more likely to express lower satisfaction with any form of care.

Adjusting for age and the legal status of treatment should usually be feasible in mental health services, as such data are available in most routine data documentation systems. In many research studies, one can also obtain observer or self ratings of symptoms, including depressive symptoms. When patients rate their satisfaction in routine care, however, it is often not possible

to assess their symptom levels at the same time. Still, considering some global rating of symptom severity would be helpful.

How patient satisfaction with mental health care should be assessed in research and practice depends mainly on the scope and purpose of the assessment. Quantitative scores as provided by the established scales can be helpful, if an adjustment for confounders is possible. Some scales are short and simple to use, and provide helpful scores for research studies and broader evaluations of services or treatments. When using the scales, one might, however, also want to be aware of their limitations.

When satisfaction scores are obtained to evaluate services, substantial differences of such scores between services or significant changes over time are unlikely, when all confounders are considered. Frequent measurement of satisfaction scores may, therefore, not be very informative. Also, differences on quantitative scores alone will not be a precise guide for which aspects of care should be improved to raise the satisfaction of patients. For this, one may want to analyze subscales or single items of scales. Even these scores, however, have limitations, as no scale covers all aspects of care, and low satisfaction scores do not necessarily indicate what exactly should be done to make patients more satisfied.

Better than quantitative scales, open questions on what specifically patients are satisfied or dissatisfied with can elicit information on a wide range of aspects of care that may be relevant in a given context and that professionals can potentially act on. For example, if patients express dissatisfaction with the behaviour of one particular staff member or with the timing of home visits or with the dose of their medication, clinicians may change these aspects of care and thus directly improve patient satisfaction.

Finally, no scale or survey can replace the most important procedure to assess patient satisfaction with care in practice, which is a direct and open communication between patients and clinicians about patients' experiences, appraisals and wishes. This can facilitate ongoing consideration of these experiences and views in shared treatment planning and service development.

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Community alternatives to inpatient admissions in psychiatry

The aim of treating people experiencing a mental health crisis in settings other than hospital inpatient wards is not new[1]. A system of family foster care for people with mental health problems at times of need was established in Geel, Belgium, 700 years ago. In the 1930s, A. Querido set up a home treatment admission-diversion system in Amsterdam, The Netherlands. In the 1970s, P. Polak developed in Colorado a network of crisis services including family placements, crisis beds, an acute day unit and treatment by mobile mental health teams. The first recognizable modern multi-disciplinary crisis resolution home treatment team was founded by L. Stein in Colorado in the 1970s.

The attractions of averting hospital admission where possible are obvious. Inpatient care is very costly. Potential harms to patients from hospital admission include: institutionalization and dependency; distress from enforced social proximity to others, or from separation from friends and family; harm from other patients or staff; loss of employment or housing tenure; the development of unhelpful coping strategies; stigma[2]. Some of these harms may be mitigated by alternative residential crisis provision. Treatment at home during a crisis offers positive opportunities: to identify and modify social and environmental precipitants of crisis, enlist family support, develop coping skills applicable to people's normal social context, and offer a more equal basis for collaborative relationships between staff and patients.

Patients tend to strongly advocate alternatives to admission being available. The provision of a range of crisis services, from which patients and staff could collaboratively choose the best option, appears evidently desirable. A number of community service models now have trial evidence as viable alternatives to inpatient admission for many patients. Acute day hospitals may be able to treat as many as one in five patients who would otherwise be admitted to acute wards, with comparable outcomes[3]. Crisis resolution teams can reduce inpatient admissions and increase satisfaction with acute care[4]. Residential crisis houses may have greater patient satisfaction and lower costs than inpatient admission, with comparable effectiveness[5].

Despite this promising evidence, community crisis alternatives have struggled to become fully embedded in national acute care systems. Crisis resolution teams are probably the most widely adopted model, but have only been implemented nationally in England and Norway. Community crisis models, even where they do act effectively as an alternative to admission, risk being labeled as a luxury and vulnerable to cuts.

Community alternatives are unlikely ever to replace psychiatric hospitals completely: some patients may always be un-

willing to accept treatment, or pose such a high risk that secure accommodation is required. No crisis alternative has demonstrated any impact on rates of compulsory hospital admission.

Four challenges can be identified for community crisis alternatives to thrive in modern mental health systems, as detailed below.

Rapid response. In many countries, lack of bed availability can lead to delays in admissions, or patients being admitted far from home. In principle, though, referral routes to inpatient wards are clear and new patients can be accepted rapidly at any time. Community alternatives, in order to provide a genuine crisis service, must seek to match this. Yet in England, for example, crisis resolution teams' response time targets for initial assessment of patients referred in crisis vary from one hour to one week[6].

Managing acuity. While community alternatives must set responsible limits on levels of risk which can be safely managed, an ability to accept acutely ill and distressed patients, even where some risks are present, is essential. Referral processes, staffing levels and skill mix, the physical environment, and organizational culture have been identified as modifiable barriers to successful management of acuity in community crisis services[7].

Role clarity. Community alternatives may offer either comparable treatment to inpatient wards in an alternative setting, or distinctly different care from psychiatric hospital. Crisis resolution teams typically emphasize the former, providing clinical treatment from a multi-disciplinary team to all those for whom hospital admission might be averted. Residential crisis houses may seek a more niche role, to provide different, innovative and potentially more appropriate care for a specific demographic or clinical group. The Soteria model of crisis houses provides the best known example of this. Developed in California in the 1970s, Soteria houses offer a minimum medication-use, non-hierarchical residential treatment setting for people with first-onset psychosis in crisis[8]. Being perceived by local commissioners and service planners as having a clearly defined role is a key factor influencing the sustainability and survival of crisis alternatives[7].

Implementation. Community crisis alternatives face the common challenge of replicating the benefits observed from early adopters and initial evaluations, when scaled up. The English experience of implementing crisis resolution teams nationally exemplifies this. Reductions in inpatient admissions anticipated from trials have not been consistently reproduced[9] and implementation of national policy guidelines has only been partial[6]. High model specification, rigorous assessment of adherence, and programmes to support implementation may be required to maximize the benefits of crisis alternatives.

Potential unintended consequences of crisis alternatives should also be considered. Outcomes for rare adverse events, such as suicides, are poorly evaluated by individual studies. Community alternatives may attract skilled staff away from inpatient wards and, by accepting the more compliant, less high-risk patients, may raise the overall levels of disturbance and acuity on acute wards. Increasing the complexity of local acute care systems presents challenges to maintaining continuity of care. Overall length of stay in acute care could be increased, if crisis alternatives were commonly used as a "step down" provision from inpatient wards.

Community crisis alternatives, which offer a cheaper alternative to inpatient admission, as well as a potentially less frightening, stigmatizing and socially dislocating experience, have a positive role to play in sustaining deinstitutionalization. Yet, there is little consensus within or across countries about optimal acute service configurations. The next challenge for researchers is to move beyond evaluating individual service models to system level evaluation, which can identify service components and configurations which provide the best outcomes for patients within mental health acute care systems.

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Drop-outs in psychotherapy: a change of perspective

Research including almost 84,000 adult psychotherapy patients from 669 randomized controlled and uncontrolled trials shows that almost 20% of patients prematurely terminate psychotherapeutic treatments, with no differences in drop-out rates among the different approaches (e.g., cognitive-behavioral, humanistic or psychodynamic)[1].

No differences between diagnostic groups seem to exist, except for personality and eating disorders showing higher drop-out rates. Rates were also found to be higher in patients not receiving their preferred treatment, in treatments that are not time-limited or manualized, in psychotherapy performed by trainees, in effectiveness studies (as opposed to efficacy studies) and in younger patients[1]. A recent meta-analysis found that almost 29% of children and adolescents dropped out from cognitive-behavioral therapy[2].

There are different ways to operationalize and measure drop-out[1]. In randomized controlled trials, for example, patients who unilaterally do not finish the prescribed treatment

protocol are usually considered as drop-outs. More generally, premature termination or drop-out occurs when a patient decides to discontinue treatment before reaching a sufficient reduction of the problems that initially led him/her to seeking therapy[1,3].

When compared with completers, patients who drop out of psychotherapy show poorer treatment outcomes[4]. Thus, it is important to address this phenomenon.

Taking research findings into account[1,3,5], several strategies may be helpful to address the issue of drop-outs. Most of these strategies not only apply to psychotherapy, but to pharmacotherapy as well. A first group of strategies includes measures which psychotherapists can already apply at present. A second group encompasses issues to be addressed in future research.

First of all, dropping out of treatment is related to problems in patient expectations and the therapeutic alliance[5]. Thus, better preparing the patient for psychotherapy may help to reduce drop-out rates. In a socialization interview, for example, patients should be informed about the disorder and the treatment, including the roles of patient and therapist. These are important steps for establishing and fostering a therapeutic alliance. Shared decision making also contributes to fostering the alliance. Ruptures in the alliance need to be adequately addressed[6].

Several additional strategies fostering the therapeutic alliance may help to prevent dropping out of treatment, such as conveying a sense of understanding, acceptance and respect, setting goals, conveying realistic hope, reviewing what has already been achieved, recognizing that the patient has made some progress towards the jointly set goals, or that he/she is becoming more and more able to use the "tools" of the treatment (e.g., challenging cognitions in cognitive-behavior therapy or core conflictual relationship themes in psychodynamic therapy)[7].

Addressing ambivalence, doubts and resistance towards therapy early in treatment is another promising strategy, an approach consistent with motivational interviewing. In addition, patient preferences for treatments need to be taken into account[5]. Risk for non-response and drop-out may also be reduced by continuous feedback on patient progress[5].

All of these strategies may be particularly important for younger patients, trainees, and patients with personality or eating disorders. In the psychotherapeutic work with children and adolescents, it is essential to take the concept of the dual working relationship (i.e., the relationship of the therapist with the patients as well as their parents) into account, to prevent inappropriate expectations from parents as well as a conflict of loyalties for the patients, factors that may increase drop-out from psychotherapy.

For younger patients, it is also important to take into account the adaptability and competence of parents to support the child's development during psychotherapeutic treatment – parents may justify a drop-out by arguing that it is a "good decision" and "in favor" of the family even though the consequences for the patient may be negative. Thus, addressing potential fears, ambivalence and resistance of parents is an important aspect of psychotherapy with younger patients. In the case of adolescent patients, wishes for increasing autonomy may also be a reason for dropping out.

Further research is needed in this area. The reasons for dropping out need to be further explored, and patient characteristics associated with dropping out need to be more comprehensively identified. For this purpose, qualitative interviews may be useful. Furthermore, up to date, it is unknown what happens to patients who drop out of treatment, as they are usually lost from follow-up assessments. Future trials may be designed offering alternative treatments (so-called switch trials) to participants not responding to treatments or at risk of dropping out[8,9].

Up to now, dropping out of treatment has had a negative connotation. A shift in perspective may be helpful: in research, unexpected results are sometimes of particular interest. Dropouts both inspire and force us to develop treatments that work for a broader range of patients. Further, as only about 50% of patients respond to psychotherapy and even less patients show a remission, at least some patients may have made a good decision when discontinuing a treatment that does not seem to be helpful to them. In addition, examining the relationship between drop-outs and side effects can be useful – the latter represent another neglected issue in psychotherapy.

Drop-outs represent a challenge for psychotherapy (and pharmacotherapy). Seen from a different perspective, they provide a chance to learn more about our treatments, for whom they work and for whom they do not, why and how they work and why not. They can inform us about limitations and *non-curative* factors of psychotherapy. For these reasons, a paradigm shift may be needed, regarding drop-outs (and non-responders) as important informants.

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"Capacity", "best interests", "will and preferences" and the UN Convention on the Rights of Persons with Disabilities

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The United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD) is the most up-to-date international legal instrument concerning the rights of persons with disabilities. Such persons are taken to include those with serious mental disorders. According to an authoritative interpretation of a crucial Article (Article 12 - Equal recognition before the law) by the UN CRPD Committee, involuntary detention and treatment of people with mental health disabilities are prohibited under the Convention. Both conventional mental health law and "capacity-based" law are deemed to violate the Convention. However, some other UN bodies are not in full agreement (for example, the UN Human Rights Committee and the Subcommittee on Prevention of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment), while others are less explicitly absolutist (for example, the Human Rights Council). Furthermore, strong criticisms of the position of the CRPD Committee have been mounted from a number of academic quarters. These criticisms center on whether the role of a person's ability to make a decision can be ignored, no matter the circumstances. Much of the above debate turns on the concept of "legal capacity" and the now often-repeated precept that one must always respect the "will and preferences" of the person with a disability. However, "will and preferences" remains undefined. In this paper, I offer an analysis of "will and preferences" that can clarify interventions that may be acceptable or non-acceptable under the terms of the UN Convention.

Key words: UN Convention, human rights, persons with disability, UN CRPD Committee, mental disorders, involuntary treatment, mental health law, legal capacity, mental capacity, will, preferences, best interests, substitute decision-making

The United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD)[1] is the most up-to-date international legal instrument specifically tailored to stipulate the rights of persons with disabilities. Such persons are taken to include those with serious mental disorders.

Recent authoritative interpretations issued by the UN Committee set up to monitor the implementation of the Convention (CRPD Committee) lead to an insistence that involuntary detention and treatment of people with mental health (or "psychosocial") disabilities are prohibited.

For example, the Committee's General Comment No. 1 on Article 12 (Equal recognition before the law) of the Convention[2] includes the following statements:

"Support in the exercise of legal capacity must respect the rights, will and preferences of persons with disabilities and should never amount to substitute decision-making." (para. 17)

"States parties must review the laws allowing for guardianship and trusteeship, and take action to develop laws and policies to replace regimes of substitute decision-making by supported decision-making, which respects the person's autonomy, will and preferences." (para. 26)

"The denial of the legal capacity of persons with disabilities and their detention in institutions against their will, either without their consent or with the consent of a substitute decision-maker... constitutes arbitrary deprivation of liberty and violates articles 12 and 14 of the Convention." (para. 40)

Furthermore, the Committee's Statement on Article 14 (Liberty and security of person) of the Convention[3] argues that:

"The Committee has called on States parties to protect the security and personal integrity of persons with disabilities who are deprived of their liberty, including by eliminating the use of forced treatment, seclusion and various methods of restraint in medical facilities, including physical, chemical and mechanic restraints." (para. 12)

"The involuntary detention of persons with disabilities based on risk or dangerousness, alleged need of care or treatment or other reasons tied to impairment or health diagnosis is contrary to the right to liberty, and amounts to arbitrary deprivation of liberty." (para. 13)

These challenging assertions follow from the Committee's position that Article 12 of the Convention entails that all persons, regardless of their decision-making capabilities, must enjoy "legal capacity" on an "equal basis with others". Legal capacity involves the right to be recognized as a person before the law, as well as the right to legal agency, that is, to have one's decisions – for example, concerning health or social care, where and how to live, finances – legally recognized. "Legal capacity" is considered fundamental to personhood, equal human dignity, and full citizenship[4,5].

The Committee's interpretation[2] states that "legal capacity" and "mental capacity" are distinct: the former is a legal concept, the latter a psychological one. Contrary to the virtually universal provisions in mental health law and capacity-based law, the Committee maintains that the existence of a disability (based on a physical, mental, sensory or psychosocial impairment) must never be grounds for denying legal capacity and the imposition of "substitute decision-making" – that is, a

decision made by another person in the place of the person with a disability (not appointed by the person, done against his or her will, and not based on his or her own "will and preferences").

The Committee insists that the preservation of "legal capacity" means that we "must respect the rights, will and preferences of persons with disabilities". With the appropriate support (strictly speaking for the exercise of "legal capacity", and that the State is obligated to provide), people with disabilities will be able to express their "will and preferences". Where a person has difficulty in communicating this directly, the Committee states that one should achieve a "best interpretation" of the person's "will and preferences", involving those who know the person.

Article 14 of the CRPD states that "the existence of a disability shall in no case justify a deprivation of liberty"[1]. On the Committee's interpretation[2], even where there is a risk to the person or to others in association with a disability, involuntary measures are nevertheless in breach of the Convention. Thus, conventional mental health law, based on a diagnosis of some form of "mental disorder" plus risk to self or others, is clearly ruled out.

This interpretation of Article 12 (together with that of Article 13 - Access to justice) has also important implications for forensic practice, including a possible prohibition of the "mental condition" defenses – "unfitness to stand trial" and "not guilty by reason of insanity" – on the grounds that defenses must be "disability-neutral"[6-9].

An important background factor in the emphasis on legal capacity in the CRPD is the widespread abuse of the rights of persons with disabilities. In many places this has amounted to a loss of nearly all civil rights, sometimes termed a "civil death".

WHY IS THE CONVENTION IMPORTANT?

The Convention, adopted in 2006, came into force in 2008. Although it does not create rights not already existing in universal human rights treaties, it specifies how the principles of human dignity,

equality, non-discrimination, autonomy and full social participation and inclusion apply in the case of persons with disabilities. It aims to ensure that such persons are treated on an equal basis with others.

The Convention can be regarded as representing a "paradigm shift" in the legal concept of "disability"[10,11]. Persons with disabilities are characterized as "including those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others". This is not an exhaustive definition. Most authorities (but not all service users) accept that persons with a mental disorder treated within the mental health system are included. The Convention puts forward a "social model" of disability: it is the level of accommodations made by a society that determines the degree to which a person's impairment becomes a disability. It is in this sense that "supported decision-making" may be necessary for a person with a mental health disability to facilitate the person's expression of his or her "will and preferences".

At the time of this writing, 177 States have ratified the Convention. Ratification signals the willingness of a State to foster the specified legal rights and obligations. Depending on the jurisdiction, the Convention may or may not be automatically incorporated into national law upon ratification. In many common law countries (like the UK), it is incorporated into national law only when directly legislated.

OTHER UN INTERPRETATIONS

The UN currently has ten "treaty-based" bodies set up to monitor specific human rights legal instruments such as the CRPD. There is also the UN "charter-based" Human Rights Council, with its various "special procedures", such as reports by "special rapporteurs", "independent experts", and working groups. A "flat" overall structure means that there may be significant differences in the interpretation of similar issues across these essentially independent bodies.

The CRPD Committee's absolute prohibition on involuntary detention and treatment is supported by the Special Rapporteur on Disability[12], the first Special Rapporteur on the Rights of Persons with Disabilities[13], the UN Working Group on Arbitrary Detention[14], and the UN High Commissioner on Human Rights[15].

However, there are statements from other UN bodies that do not support the Committee's interpretation, at least in its absolutist form.

Some positions are clearly at variance. In 2014, the Human Rights Committee published a General Comment (No. 35) on Article 9 of the International Covenant on Civil and Political Rights, which states[16]:

"The existence of a disability shall not in itself justify a deprivation of liberty but rather any deprivation of liberty must be necessary and proportionate, for the purpose of protecting the individual in question from serious harm or preventing injury to others. It must be applied only as a measure of last resort and for the shortest appropriate period of time, and must be accompanied by adequate procedural and substantive safeguards established by law. The procedures should ensure respect for the views of the individual and ensure that any representative genuinely represents and defends the wishes and interests of the individual."

A similar position has been taken by the Subcommittee on Prevention of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment[17].

Other UN bodies' positions are less explicit about an absolute prohibition on involuntary interventions, but are framed in terms that support a central role for "will and preferences". They call for an urgent need to develop alternatives to coercive interventions.

An important Resolution on Mental Health and Human Rights from the UN Human Rights Council[18] calls upon States to "abandon all practices that fail to respect the rights, will and preferences of all persons, on an equal basis" and to "provide mental health services for persons with mental health conditions or psychosocial disabilities on the same basis as to

those without disabilities, including on the basis of free and informed consent".

A report of the UN Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health[19] notes the lack of consensus on compulsion within the UN bodies. The Rapporteur offers to work with others to achieve one. He notes that discrimination is still evident in mental health services, for example, in depriving users of the rights to refuse treatment, to legal capacity and to privacy, as well as other civil and political rights. He insists that action is required to radically reduce coercion and to facilitate a move towards an eventual end to all forced psychiatric treatment.

A report from the UN Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment[20] seems ambiguous on whether involuntary measures can ever be justified.

Worth noting at this point is a recent decision by the European Court of Human Rights[21] which, whilst addressing Article 12 of the CRPD, concluded that it was justified not to accede to the expressed "preference" of a man with an intellectual disability concerning where he should live, since "the disability was of a kind that, in terms of its effects on the applicant's cognitive skills, rendered the applicant unable to adequately understand the significance and the implications of the specific decision he wished to take", and that, therefore, "the applicant's well-being and interests require that the mentor [in effect, a substitute decision-maker] arrangement be maintained". Thus, the Court's interpretation of Article 12 did not concur with that of the CRPD Committee.

CRITICISMS OF THE CRPD COMMITTEE'S INTERPRETATION OF ARTICLE 12

It is no surprise that the absolutist position of the CRPD Committee, so dramatically at odds with centuries of legal acceptance of involuntary detention and treatment, should receive harsh criticism.

An international group of clinicians[22] argues that the Committee's interpretation threatens to undermine hard-won, critical rights of people with mental health disabilities – the right to the highest attainable standard of health, to life, or access to justice. Furthermore, they fear that the rights of others, the family and the public, are similarly threatened, with a consequent increase in mental illness stigma. A central necessary role for a person's decision-making capacity is described (though, of course, in the majority of jurisdictions, capacity plays no formal role in civil commitment regimes). The authors bemoan the Committee's apparent limited expertise in relation to mental illness, the lack of clinician input, and the Committee's failure to consider the views of a broad population of service users, a significant proportion of whom support involuntary treatment, at least as a last resort.

Dawson[23], from a legal perspective, criticizes the Committee's interpretation for failing to offer adequate guidance on how, when situations arise where rights articulated in the CRPD are in conflict, this can be resolved. This is especially important since the relevant text of the CRPD, he maintains, is ambiguous. A key concept in many legal systems, in settling the balance between competing imperatives, is a functional test of decision-making capacity. This points to whether – in a particular instance – autonomy, on the one hand, or protection of the interests of a vulnerable person, on the other, should prevail.

Furthermore, Dawson notes that the law in general is riddled with mental concepts, deprecated by the Committee as not objective, like intention, understanding or foresight. A denial of legal capacity in a specific domain, he argues, is not necessarily a denial of intrinsic human rights. Blind persons are not allowed to drive; the key consideration is whether the person has an impairment of the relevant functions, physical or mental, necessary to act safely in that domain. Dawson criticizes the Committee's understanding of the meaning of "discrimination", arguing that it is not necessarily improper to treat people differently if relevant differences exist between their situations even after adequate support has been provided and reasonable accommodations made.

Scholten and Gather[24] argue that the Committee's standpoint, if accepted, would result in a number of serious adverse consequences for persons with mental health disabilities. Important would be a serious effect on "autonomy" and well-being. By "autonomy" they mean "the ability to live one's life according to one's own conception of the good". They state: "When a person's decision-making competence is substantially impaired, the person is often not in the best position to assess which treatment option will be most conducive to her well-being and consistent with her conception of the good. In such cases, the practice of informed consent loses its point".

They further argue that the Committee's proposals would make it difficult to determine whether "undue influence" had been exerted by a supporter of the disabled person: "It will be more difficult for the medical staff to monitor the actions of support persons because the distinction between the interests of the patient and those of the support person becomes diffuse". Related to this problem, they maintain, would be the formal allocation of responsibility for a decision exclusively to the person with a mental disability. Support persons are presumably to be left without any formal accountability.

All three critiques above have in common a key objection. They ask whether the role of a person's ability to make a decision can be ignored, no matter the circumstances. If all efforts at support have failed, or if the person refuses support, but there is still an inability to understand the facts pertinent to the decision in question, or to appreciate their relevance, or to use, weigh, or reason with that information in terms of what is important to that person, to his or her beliefs and values, to his or her personal life goals or personal conception of the good, is his or her choice to be nevertheless accepted?

Decision-making ability is currently widely constructed as the crux around which justifications are sought for interfering in a person's life in the interests of restoring that person's ability to decide and thus his or her well-being. Or, as Dawson proposes, the basis on which we

work to resolve serious situations where rights contradict each other – for example the right to self-determination versus the right to life, or to the highest standard of health care, or to be free of violence and exploitation.

All three critiques also raise the related question of how we are to understand "advance directives". At Time 1, a person with unquestioned decision-making ability may predict that, because of an anticipated future episode involving what that person recognizes as an impairment in that ability (Time 2), he or she will express a different, contradictory preference, which the person states is not to be regarded as what he or she truly or "autonomously" desires. If the feared episode occurs, which preference should be respected? The CRPD Committee provides no explicit guidance on this question. Is it the Time 2 preference, disavowed at Time 1, that is to be followed? If so, what is the point of such an advance directive?

Since significant criticisms of the Committee's interpretation turn on the notion of decision-making ability, I suggest that an examination of how this concept might relate to the CRPD's "respect for rights, will and preferences" may be fruitful. Such a discussion will have a strong bearing on two key principles underlying the CRPD: support for autonomy and the elimination of discrimination.

DECISION-MAKING ABILITY, A DISABILITY-NEUTRAL LAW, AND DISCRIMINATION

Before the CRPD Committee had issued its interpretation, colleagues and I presented an argument that a "disability-neutral" law could be formulated that was non-discriminatory towards people with mental health disabilities[25,26]. Such a law would permit involuntary treatment when all attempts at support had failed in helping the person to make a decision that could be considered autonomous.

Such a law, we proposed – as do the critics discussed above – would be squarely based on decision-making ability. This is not a "blanket" inability but is specific to a particular treatment decision at a par-

ticular time. People with mental illness do not have an impairment of such an ability for most, or indeed all decisions, and for most or all of the time. If there was a significant impairment of this ability, involuntary treatment would only be justified if it were in the person's "best interests". We qualified the term "best interests" as "subjective" best interests – that is, one that gives paramount importance to the person's deep beliefs and values, or what might be termed the person's "will and preferences".

We also suggested that decision-making ability itself might be construed in terms of a person's beliefs and values. An assessment of the person's decision-making ability would go beyond the more conventional, so-called "cognitive" elements, by examining the coherence of a person's treatment decision with his or her relevant deep beliefs, values, and commitments. A similarity was noted to Bach and Kerzner's influential account of how "will and preferences" could be assessed in the light of a person's ability to express an intention (or will) and its coherence with a sense of a personal identity through time[27,28].

Further, we argued it was essential that the law be "generic". To avoid discrimination, it had to apply to all persons on an equal basis, no matter the cause of the impairment of their decision-making ability, whether it was a "mental" or "physical" disorder, nor whether they had a "disability" or not. Decision-making ability, we argued, is conceptually distinct from a "disability" and may occur in people with or without a disability.

Dawson and I had earlier proposed such a generic law, which we termed a "fusion law", as a riposte to conventional mental health legislation. We argued that conventional law was unfairly discriminatory against people with a mental illness, in that their autonomy or right to self-determination was not accorded the same respect as given to all other patients in general medicine or surgery.

Some, including the CRPD Committee, criticize capacity-based law – even a generic law applicable to all – as discriminatory, because a disproportionate number of people with mental health dis-

abilities would be judged to lack decision-making capability, even if such a lack is specific to a time and decision. Certainly, this would constitute a "disproportionate effect". However, a disproportionate effect does not automatically entail discrimination – in such cases, "indirect discrimination". For example, a person with an intellectual disability is rarely accepted for training as a doctor. As entry qualifications do not explicitly exclude people with an intellectual disability, there is no "direct discrimination". However, the entry criteria, usually requiring top class examination results in academic subjects, do have a disproportionate impact on people with an intellectual disability. Yet, we do not claim these criteria discriminate unfairly against people with an intellectual disability.

This is because it is accepted, certainly in international law, that a disproportionate effect does not amount to indirect discrimination provided its basis has three attributes: a) it has a legitimate aim, b) the criteria leading to the effect are objective, and c) the criteria are reasonable in the light of that aim[29].

The "aim", in the instances that interest us, should be seen in the terms of the fundamental principles of the CRPD: respect for the "inherent dignity of the person, and individual autonomy, including the freedom to make one's own choices". The aim is essentially to ensure that people experiencing a serious difficulty in making an important decision are supported in acting autonomously (according to their deeply held personal beliefs and values, their personal conception of the "good", or "will and preferences'"), and that those values are given effect through facilitation from others until the person's autonomy is restored.

A substantial body of research on the standard criteria for "decision-making capacity" – as defined, for example, in the work of Grisso and Appelbaum[30] – show a level of agreement between independent assessors, a strong index of "objectivity", that is very high[31].

"Reasonableness" turns on whether the basis of the differential treatment advances the legitimate aim. Is it a reasonable and proportionate means to achieve

that aim? A person's "autonomy" – in the sense above – is necessarily related to some kind of decision-making ability. If a person is unable to make a decision reflecting or furthering his or her conception of the good, despite all measures of support, this poses an obstacle to acting autonomously.

Under what circumstances might a person have difficulties in making a treatment decision that is coherent with his or her individual conception of the good, or his or her deep beliefs and values? What the CRPD Committee has not directly considered is a common situation for people with a serious mental illness, such as a psychosis: that is, a significant, often dramatic, change in the person's preferences. Indeed, the same may occur in people without a mental illness, for example, with an organic brain syndrome caused by a brain injury or adverse drug reaction.

An examination of the terms "will and preferences" can perhaps help to clarify the elements entering into such situations; and how we might respond to them in a manner arguably consistent with the CRPD, yet sometimes allowing for an "involuntary" intervention.

THE MEANING OF "WILL AND PREFERENCES": "WILL" VERSUS "PREFERENCE"

According to the CRPD Article 12, Clause 4, "States Parties shall ensure that all measures that relate to the exercise of legal capacity provide for appropriate and effective safeguards to prevent abuse in accordance with international human rights law. Such safeguards shall ensure that measures relating to the exercise of legal capacity respect the rights, will and preferences of the person, are free of conflict of interest and undue influence, are proportional and tailored to the person's circumstances, apply for the shortest time possible and are subject to regular review by a competent, independent and impartial authority or judicial body."

There appears to be ambiguity in this text, born of compromise. Some authorities have interpreted this clause as permitting substitute decision-making, but only

with the safeguards stated[11]. However, as we have seen, the CRPD Committee maintains that the exercise of legal capacity prohibits substitute decision-making and insists that we must at all times "respect the rights, will and preferences" of persons with disabilities (as we presumably do for everyone else)[2]. The expression "will and preferences", as noted earlier, appears in many UN bodies' statements, even in those that do not explicitly prohibit substitute decision-making.

Though the expression "will and preferences" is frequently repeated, no authority has provided a definition of its meaning. I have not found one in the "travaux préparatoires". Why were these two words, "will" and "preference", chosen? "Preference" has a relatively straightforward meaning: the Oxford English Dictionary defines it as "a greater liking for one alternative over another". On the other hand, the meaning of "will" moves us into a much more difficult territory.

In ordinary language, "will" has a stronger sense of force or resolve to act in a particular way than does a "preference". Furthermore, the "will" has a long history in the philosophy of mind. It is no surprise that the views expressed by philosophers concerning its meaning reveal significant differences. Indeed, in a recent volume dealing with the subject, the author describes the "incomplete demise" of the "modern theory of the will" that held sway from Descartes to the 19th century and came under fierce attack in the 20th century[32].

A 17th century account might see the "will" as occupying a kind of causal role between the desire and the act aimed at fulfilling the desire. A distinction between the "will" and a desire (or wish or "preference") is generally drawn in the philosophical literature. Influential has been Kant's concept of the "will", helpfully summarized as: "The will, then, as distinct from the ability to choose, is the capacity to transform felt urges or desires with causal force into motivating reasons for action with justifying validity. To possess a will is therefore also to be able to test desires to see whether or not they can be validated as reasons"[33]. Kant's "will" forms part of a larger account including

the choice of "ends", but this is not relevant for our purposes.

Pertinent to this discussion, and shared with a number of recent accounts, is the idea of the "will" as a kind of higher-order motivating structure that determines which desires are to be translated into acts. It may be seen as having a special "reason-giving force"[34], or as a higher-order self-governing mechanism, one in which "values" play a key role and where desires are subject to forms of deliberation within higher-order "policies" extending over time and expressing commitments towards ends that embody values[35].

Consistent with this framework, we can develop an account of "will" and "preference" that proves helpful in understanding when we may become concerned that a person's decision-making is undermined[36]. A distinction may be drawn between the "will" – as a higher-order, self-governing function – as opposed to desires or inclinations or "preferences", expressed in the present. The "will", on this view, is a manifestation of a person's deeply held, reasonably stable and coherent personal beliefs, values, commitments and conception of the good. It is what we may understand as characterizing personal "autonomy". In this sense, it is not the same as a desire, inclination, or a currently held "preference", even a strongly expressed one.

Normally, "will" and "preferences", by and large, run together. It is when the "will" and a "preference" diverge or are contradictory, and a person needs to make a serious decision, that a problem may arise.

WHERE A "PREFERENCE" IS INCONSISTENT WITH THE "WILL": ALL PREFERENCES ARE NOT CREATED EQUAL

For an instructive model we can return to "advance directives", cited as problematic in the critiques of the CRPD Committee's interpretation of Article 12. Noting the difference between the "will" of the person (and its associated preferences) at Time 1, as against the "preferences" that the person anticipates will be expressed at

Time 2 – and which the person asks to be ignored – it is explained why we generally respect the person's Time 1 "will" and not the Time 2 "preference". If the person were to "will" at Time 1 that treatment on an involuntary basis in the face of a predicted persistent refusal at Time 2 (as a last resort, all attempts at support having failed), the argument is strong that the Time 2 refusal should be overridden. We favor the Time 1 instruction as it reflects the person's "will" – his or her relatively stable, deeply held beliefs and values, and personal conception of the good.

To honor the preference at Time 2 is to undermine the "will" or, in essence, the "autonomy", of the person. It is hard to see how this would be consistent with the first "General Principle" of the CRPD: "Respect for [the] inherent dignity, individual autonomy including the freedom to make one's own choices, and independence of persons".

If this analysis is accepted, it would follow that we would act similarly if the person had not made a written advance directive, but had expressed, through various statements and life choices, the same values (or "will") and associated "preferences", as evidenced by people who know the person well, for example, relatives and friends. Even if the person had not previously expressed clear treatment wishes, his or her previously manifest "will", as evident from his or her value commitments, life choices and goals, would have to count heavily in deciding whether or not to respect a present "preference".

Consistent with the spirit of the CRPD would be – despite an involuntary intervention – the necessity of developing a relationship aimed at facilitating the person's expression of his or her will as soon as possible[27].

This analysis of "will and preferences" adds a further dimension in the conceptualization of "decision-making capacity" and "best interests", if not a major reformulation. Treatment decision-making capacity is undermined when there is a serious divergence between the person's "will" and a currently expressed treatment "preference"; while a person's "best interests" are served by acting so as to

give effect to the person's "will". An advance directive offers the clearest model. The case for an involuntary intervention is stronger, the greater the threat to the person's "will" that would result from the person enacting a contradicting "preference".

How well are we able to determine what are a person's deep beliefs, values or personal conception of the good? The tool we use is called, by philosophers, "interpretation"[37-39], not to be confused with the psychoanalytic version. Interpretation involves a form of "folk" or "common-sense" psychology we use to understand and predict others' behaviour in everyday terms of mental states such as beliefs and desires. Dennett[40] characterized this ability as follows: "For all of its blemishes, warts and perplexities, folk psychology is an extraordinarily powerful source of prediction. It is not just prodigiously powerful but remarkably easy for human beings to use. We are virtuoso exploiters of not so much a theory as a craft". When employed collaboratively with the patient, and with people who know the patient well, one would expect an appropriate degree of "objectivity" in the assessment.

No doubt the reader will have seen some potential difficulties in this "will and preferences" approach. Here, I point to some briefly.

Can a person's "will" (and associated preferences) change without it being a sign of that "will" being undermined? Although there are accounts of a sudden, "quantum" change in a person's deep beliefs and values, these appear to be rare[41]. They are usually in the nature of spiritual revelations, and the result of the change appears to be an overall largely coherent conception of the "good", often of a religious nature. More commonly, a change in the "will" is gradual and understandable, usually involving a working through of value conflicts: "coherence" in an interpretive sense is maintained. Another instance where a new "will" may be seen as "authentic" may occur in a person with a long-standing psychosis, where the person has changed significantly, but where there is a sufficient degree of stability and coherence in the person's new beliefs, values,

and conception of the good, with a reasonable correspondence with the real world.

Should one always privilege the "will" over a conflicting "preference"? When the impairment of decision-making is due to a reversible cause, it is usually straightforwardly so. However, when irreversible, for example in dementia, it is arguable that the person now is not the "same person" having the previous "will". Whether that "will" should be respected rather than a strongly held but divergent "preference" in the present, I suggest, should be determined on a case-by-case basis, involving those with a close interest in the well-being of the person[39].

There are situations where it may be impossible to know what a person's "will" might be – for example, a person who is unconscious or is in an organic confusional state where no-one is available who knows the person; or a person with a severe intellectual disability who may not have been able to clearly express a coherent "will" (though there may be fragments of observed behaviour and utterances pointing to what has been important to the person that offer an indication). In such cases, it has been proposed that the default position might be to consider the human rights relevant to the situation as the guide for the decision to be made[42].

RESPECT FOR "RIGHTS" AS WELL AS "WILL" AND "PREFERENCES"?

Just as "will" and "preferences" may point in different directions, so may "will" and "rights". When a "right" should override a clearly formulated "will" constitutes a predicament more familiar to us, usually framed as "protection" versus "autonomy".

An example is whether a right to enjoy freedom from exploitation should override a person's "will" to live alone in a situation where such a right is threatened. Its resolution might depend on a "best interpretation" of whether the person's "will" to live independently – as judged on the basis of his or her beliefs, values and conception of the good – would be consistent with accepting the level of risk to which the person would be exposed (af-

ter appropriate support services were provided).

From the previous discussion, it will be evident that the word "respect" in the phrase "one must respect the rights, will and preferences" of the person cannot mean that one must comply or accede to all those three elements. If they point in different directions, that is logically impossible.

CONCLUSIONS

The UN CRPD is an important legal instrument clearly specifying the rights of persons with disabilities. If given effect by ratifying States, it will dramatically transform the standing in society of such persons. This is to be strongly welcome.

However, the CRPD Committee's interpretation of Article 12 prohibiting "substitute decision-making", while supported in some quarters, has not been fully endorsed in statements from some other UN bodies, and has drawn strong criticism from legal and clinical scholars.

An absolute prohibition on involuntary treatment is, at least at present, not credible. Nevertheless, States parties are constantly reminded of the Committee's position in its Concluding Observations, published following regular examinations of each State's progress in implementing the Convention[43]. Almost invariably, States are asked to replace regimes of "substitute decision-making" with regimes of "supported decision-making".

While it is probable that service innovations aiming to reduce coercive measures can substantially reduce their frequency, there will always be cases – for example, due to organic confusional states or neurodegenerative disorders – where ethically persuasive justifications can be made for such measures, at the very least in circumstances carrying grave consequences. Furthermore, surveys reveal that a significant proportion of people who have been involuntarily treated for a mental illness state that such a measure can be appropriate as a last resort[44-46]. This indicates that law reform must involve those most directly

affected and take into account the diversity of views in this group[47].

It would be an unhappy state of affairs if regard for the CRPD were undermined by the Committee's interpretation. It should be noted that, while this interpretation is "authoritative", it is nevertheless not "legally binding" in international law[29].

Despite these concerns, the Committee's role in drawing attention to involuntary detention and treatment is welcome. Sadly, this has been a neglected area in mental health care. We prefer not to linger on what can be a profoundly distressing and humiliating experience for patients (and a disturbing one for clinicians). The discrimination against people with a mental illness in conventional mental health law is being increasingly recognized, raising fundamental questions about justifications for compulsion.

The Committee's objective to eliminate the obvious discrimination against persons with mental health disabilities and to pay special or paramount regard to such persons' deeply held beliefs and values (or personal conception of the good, or "will" and "preferences") is to be highly commended. However, by failing to analyze the meaning of the regularly endorsed phrase "respect for will and preferences", especially in cases where there is a radical change in a person's "preferences", the Committee's interpretation is incomplete.

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Mental health and human rights in the 21st century

Mental health is emerging from the shadows. Human rights are on the agenda, and advocates are increasingly calling for parity with general health funding and a reduction of the treatment gap for people in crisis, particularly in low- and middle-income countries. There is high-level agreement on key components of good mental health policy, from promotion to prevention, treatment and rehabilitation.

However, important disagreements remain about how to invest resources. An impasse has emerged, and it risks hardening into a dispute. The controversy relates to complex connections between mental health and human rights, and coalesces around a single question: do involuntary psychiatric interventions violate international human rights law?

Coercion in psychiatry and broader mental health services is rising worldwide. This fact demands not merely discussion but action. The Convention on the Rights of Persons with Disabilities (CRPD) offers a chance for all stakeholders to rethink conventional wisdoms, address long-standing power imbalances and implement innovative practices.

Anxieties about the change must not obstruct dialog or political action. The CRPD provides a unique opportunity to liberate not just users of mental health services but the entire field of mental health from a legacy of stigma, hopelessness and discrimination. The directive of the CRPD to embrace a social or "human rights" model of disability and move away from a "medical model" of disability has strategic advantages, including shining a light on the many social, political and economic factors that create grave disparities for people with mental health conditions or psychosocial disability.

It may be tempting to focus on the most exceptional cases, which seem unmanageable without coercion. More important, however, is the need to substantially reduce coercion by implementing alternative, human rights compliant ways of providing support. Psychiatry can and must be among the leaders in this direction, not just among those resisting change.

Human rights violations in the mental health context remain significant throughout the world, including in high-, middle- and low-income countries. The prevalence of rights abuse cannot be explained by a mere lack of resources. In the relatively wealthy European region, for example, funds continue to be invested in the renovation and expansion of large scale residential and psychiatric institutions[1,2]. These sites perpetuate a vicious cycle of exclusion and despair. The rise elsewhere of involuntary psychiatric intervention in hospitals and homes also suggests that something is wrong.

We recognize the serious arguments of professionals who warn against a prohibition of forced treatment. They insist on retaining legal permission to treat individuals with serious mental health conditions involuntarily in exceptional circumstances in ways that preserve dignity and autonomy, even the right to life. Those against argue that the non-consensual imposition of mind- and body-altering drugs based on narrow conceptions of impairment, poorly evidenced claims about "risk" and "necessity", and a limited range of alternatives, is incompatible with dignity and autonomy.

Scholars in diverse fields, including philosophy, neuroscience, psychology and economics, are increasingly challenging the grounds for the "exceptions" that legitimize coercion in mental health care. The CRPD has elevated this challenge to the level of international human rights law. Indeed, the CRPD challenges centuries of legally sanctioned prejudice. However, "exceptions" remain at the domestic level, in law, policy and practice, and they filter into the norm, fostering power asymmetries, the overuse of biomedical interventions, and the disempowerment of an already marginalized population. Systemic violations follow. This *status quo*, which can be observed on a global scale, is no longer acceptable.

For psychiatrists and all healing professions, a pivot toward human rights would require setting aside "substitute decision-making" and offering support according to a person's "will and preferences", and where unknown, the "best interpretation" of her/his will, preferences and rights.

Szmukler's paper[3] makes a substantial contribution to this effort. He elucidates some of the practical and conceptual requirements involved in a move toward a "will and preferences framework" and asks seriously what the CRPD means for the future of psychiatry, and for global health governance more generally.

One of his claims, however, raises some concerns: namely, the proposal to assess decision-making inability in the form of functional assessments of mental capacity when a person's will and preferences are unclear or appear to be in conflict.

On this point, caution is warranted. Szmukler mentions the many critics of functional assessments of mental capacity, to whom the authors of the World Health Organization's QualityRights Framework[4] could be added. Yet, his efforts to assure against discrimination or a replication of long-standing power imbalances will fail to convince many (including ourselves). He is right, however, insofar as emergency responses are needed and the dialog must continue to find grounds for intervening in ways that are just.

This Forum in *World Psychiatry*, and the WHO QualityRights Framework, are exemplary of this ongoing search. Creative responses are needed that foster therapeutic relationships based on trust and empowerment, in ways that avoid the pitfalls of the past. Moving in this direction opens space and creates urgency to develop innovative practices, some of which emerge organically when involuntary interventions are suspended or greatly restricted (as appears to have occurred in Germany, for example)[5].

Academic psychiatry – as Szmukler's own work makes eminently clear – will be essential to this shift. Clinical researchers can continue this effort by calling for the reinvestment of the vast resources currently spent on narrow biomedical research, shifting funds instead to social, clinical and community studies within

a humanistic frame[6]. Ties between psychiatry, public health and social sciences need to be strengthened.

There are no simple solutions. Debates may be uncomfortable, but they could open new opportunities and roles for psychiatry. The shift would diminish the "formal power" currently afforded to psychiatrists. Yet, there could be multiple benefits in shifting the profession from a tutelary to a facilitative role, including unlocking funds currently used for coercion and addressing important issues of image and reputation. It should be in the interests of psychiatry as a medical profession to substantially reduce its reliance on coercion, and to spread such a message to its members worldwide.

A rights-based approach can provide a pathway to the future of mental health care we want for all. The CRPD can be used to promote the investment of human and financial resources into a broad spectrum of support to drastically reduce non-consensual measures with a view to their elimination. It offers a framework to achieve social justice, attain the highest standard of health care, and strengthen governance of health and social services.

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Practical strategies to end coercive practices in mental health services

Mental health has become a global imperative. Increasing coverage of treatment options and support services is crucial. However, without deep reflection and change in paradigm about the types of services being provided, we risk reproducing some of the poor outcomes and dissatisfaction that we see in high-income countries, stemming from overmedicalization, overuse and inappropriate use of medications (and their negative impacts, for example, in terms of metabolic disturbance, sexual dysfunction, premature mortality) and human rights violations associated with involuntary admission, forced treatment, seclusion and restraint[1-3].

Promoting human rights in mental health *must* go hand-in-hand with efforts to scale-up services in countries, and mental health strategies and interventions must be firmly grounded in a human rights approach[4].

The Convention on the Rights of Persons with Disabilities (CRPD) sets out key obligations on countries to end practices based on force, coercion and substitute decision making in mental health, and instead requires that practices be based on people's will and preferences or on the best interpretation of their will and preferences[5,6].

Coercive practices are particularly challenging to change, since they are commonly accepted in society, seen as necessary to protect persons from harm, and are firmly cemented and sanctioned in law and policy across all countries. This despite the absence of evidence for their effectiveness, and the available evidence demonstrating that practices such as seclusion and restraint actively cause harm to physical and mental health, and can lead to death[7].

G. Szmukler[8] argues that there are exceptions where, in the interest of promoting people's autonomy, it becomes necessary to utilize involuntary interventions, and that a person's ability to make a decision should be a decisive factor in determining whether forced admission and treatment is a legitimate response. Below, we set out our disagreement with this position and also address some specific points raised by the author.

First, denying a person who is blind the right to drive is not the same as denying a person, whose decision making capacity is impaired, the right to decide on his/her admission and treatment. A person who is blind is objectively so, and cannot drive a car. On the other hand, determining that a person's decision making is impaired is subjective. Furthermore, there is no objective way that a health or other professional can know what is best for the person, because preferences are themselves subjective. The professional does not have the same history, experience or knowledge as the person concerned about what he/she finds helpful in his/her recovery.

The underlying issue in the scenario outlined by Szmukler is not the denial of the right to drive, but rather understanding that the function of driving is first and foremost the possibility to get from A to B. A person who is blind will be primarily interested in the freedom of movement that driving affords, rather than the act of driving itself. Thus, while the act of driving may not be a guaranteed right, creating the necessary accommodations to enable him/her to get from A to B, on an equal basis with others, is an obligation under international human rights law.

Similarly, in the case of someone whose decision making is affected, the obligation is to support him/her to make his/her own decisions on an equal basis with

others. This support may mean helping the person to access relevant information, understand and weigh up the benefits and negative effects of treatment, and support him/her to assert and communicate his/her decisions and choices.

If a person is unable to communicate his/her decisions directly, these should be based on the best interpretation of his/her will and preferences. Best interpretation can be determined, for example, by drawing upon a trusted support person or network to help interpret what the person would want in the current situation, based on what is already known about him/her (e.g., his/her views, beliefs, values in life)[9].

Alternatively, one can refer to a person's advance directive, containing information about his/her will and preferences should he/she be unable to communicate decisions sometime in the future. However, there are cases in which a person, who expressed a particular wish at Time 1, expresses a contrary will and preference at a later time. In such scenarios, Szmukler questions which preference should be respected. In fact, advance directives can include an "Ulysses clause", which enables people to state that any objections they may express "in the moment" should be overruled in favor of the written directive. This also allows options for people using services who report that they are in favor of involuntary treatment. However, even with a Ulysses clause, it is important to consult a support network to validate the final decision where discrepancies have arisen.

In situations where there are no support persons or advance directive available (or when an advance directive is not clear), sufficient time should be allowed for a person to make his/her decision in a safe, non-coercive environment. If there is no life threatening urgency to the situation, then decisions can be deferred to such a time that the person is able to express his/her will and preference. And even if there is urgency, one is still obliged to interpret what the person's will and preference might be, based on information that one has at hand.

In these situations it is possible that errors are made, and that decisions based on the best interpretation turn out not to be in line with a person's will and preferences. In these situations it is essential that the experience serves as a learning opportunity to gain a deeper understanding of the person's wishes, how best to support him/her moving forward, and to prevent such incidents from re-occurring. In the aftermath of such situations, it is useful to encourage the person to develop or update advance directives and to help him/her to identify trusted persons/networks to support him/her by interpreting his/her will and preferences in the future if necessary.

In addition to achieve long-term sustainable change, policy and law will need to reflect the practice changes described above. Many recently formulated laws around mental health contain substantial provisions about "managing" the "exceptional" use of involuntary admission and treatment, as well as seclusion and restraint. However, the system of exceptions has not worked even when there have been stringent rules and restrictions about their use. Furthermore, the endless debate about what is "exceptional" has served to hinder progress and productive dialogue both at national and international levels. Energies should instead be concentrated on looking at a way forward and at strategies and solutions to promote the right of people to receive quality care and support in line with the CRPD.

Change will be required at multiple levels, including knowledge, attitudes and practices of professionals, families and others towards supporting people in their decision making, providing services that operate without force, that promote rights, recovery, and people centered care and support, and redefining policy and law so that these move beyond a narrowly focused biomedical approach in order to fully embrace a human rights approach that addresses the social determinants of mental health, and emphasizes support instead of coercion.

WHO QualityRights has developed training and guidance tools to enable national stakeholders to integrate CRPD rights into their practices[10]. The initiative is also developing best practice guidance identifying and providing the evidence for community based services that operate without coercion, respond to people's needs, support recovery, and promote autonomy and inclusion. The initiative is also at the early stages of discussing new guidance for human rights oriented policy and law in line with the CRPD.

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The UN Committee's interpretation of "will and preferences" can violate human rights

In the controversies with the United Nations (UN) Committee for the implementation of the Convention on the Rights of Persons with Disability (CRPD), G. Szmukler[1] highlights an important point in focusing on what the manifold cited notion of a person's "will and preferences" actually means.

He sets forth that the "will" should be considered as "some kind of higher-order motivating structure that determines which desires are to be translated into acts", reflecting the person's "deeply held beliefs", while "preferences" should be considered as more superficial, momentary wishes which can undergo rapid change, e.g. by mental illness. Correspondingly, the "will" as stated in an advance directive should be overriding later expressed "preferences", because otherwise advance directives would not make sense.

I am not really convinced that this interpretation adds "a further dimension in the conceptualization of decision-making capacity and best interests", as he states. I doubt that "will" and "preferences" can be differentiated without using either psychiatric or normative concepts, both of which would be rejected from the Committee's radical perspective as discriminatory.

I have tried to reconcile psychiatric ethics with the UN CRPD[2]. However, I think that to find a common ground with the Committee's radical interpretation is not possible, since the clinical and legal consequences are irreconcilable.

Let us consider two clinical examples. The first is the case of a patient with delusional depression and a strong suicidal intention; the second the case of a patient with severe anorexia nervosa and a life-threatening body mass index. The first patient wants to commit suicide because he is deeply convinced to be the devil himself and to be able to save the world only by his death. The other patient has demonstrated over years that her highest value seems to be eating as little as possible, even at the price of her death.

How can we affirm that these wishes are only "preferences" and not the patients' "real" will? Either by pointing out that we know a significant number of people with similar conditions who had changed their intentions completely after psychiatric treatment, maybe with some initial coercion, and continued to live for decades even without treatment and without any intention to die. This is the "mental illness" concept. If one denies this concept and wants to deter these people from dying nonetheless, he has to suppose that their "real" will is to live, sharing the wishes of most people – living in good mental and physical health, under good conditions and with good relations to the people next to them. In other words, it means to enjoy their human rights. However, this is normative and very closely related to the "best interest" concept.

According to the Committee's position, both the above concepts are misleading. The Committee invokes a new legislation which for these two patients would result in the consequence of death. This would certainly violate some of their most important human rights: the right to life (UN CRPD, para. 10), and the right of health (UN CRPD, para. 25).

Similar to ethical principles, human rights are individually not absolute, but their degree of fulfillment is subject to their compatibility with other human rights. A typical example is circumcision of new-born boys, inducing a conflict between (the parents') freedom of religion and (the baby's) right to physical integrity. Similar deliberations are necessary in our cases. For example, in cases of patients with psychotic disorders who can live in the community with medication but end up in a seclusion room or a forensic hospital without medication, it seems short-sighted to focus only on para. 12 of the UN CRPD (equal recognition before the law), without taking into account para. 19 (living independently and being included in the community), which is likewise important for such extremely vulnerable people.

In my country (Germany), we do not have common law but a constitution, with the Federal Constitutional Court (FCC) as the highest and widely respected institution. This has the advantage that a renowned legal authority is available that is competent to clarify controversial legal issues as last instance. In 2011, the FCC published two seminal decisions on the issue of involuntary treatment[3]. According to the FCC, treatment with use of coercion is only admissible under very restrictive conditions. However, the FCC pointed out that, in case of lack of capacity, involuntary treatment can be even required to protect the patient's right to freedom. In this context, the FCC made clear distinctions between the "free will" (corresponding to "will" in Szmukler's paper) and the "natural will" (corresponding to "preference" in Szmukler's paper).

Moreover, the FCC dealt in detail with the question whether the concept of involuntary treatment is in accordance with the UN CRPD, and confirmed that it is. In addition, the FCC made in 2017 a decision in the case of a woman with breast cancer and a psychotic disorder who had refused the necessary operation because she denied being ill. Since involuntary treatment was only legal in combination with involuntary detention in a psychiatric hospital, her decision to stay voluntarily entailed that she could not be treated, and she consequently died. Retrospectively, the FCC decided that the state had a "duty to protect" in such cases and required the law to be changed, allowing treatment against a patient's will also in general hospitals. This is a careful deliberation of conflicting human rights and is completely in line with medical ethics[2].

Human rights belong to the most universal and precious ideas of mankind. If the UN CRPD Committee says they are unique advocates of the human rights perspective and all of us psychiatric professionals together with our domestic laws should, at least morally, stand in the dock because of torture, this is not only

an "incomplete" view, as Szmukler says, but it is shocking and inacceptable.

We should dare to express that. Exaggerations may be sometimes necessary to achieve political goals, but exaggerations in morality and medicine can have deadly consequences. Nonetheless, the UN CRPD itself, as Szmukler emphasized, is highly welcome, and deserves high efforts to be realized in a reasonable manner.

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The CRPD Article 12, the limits of reductionist approaches to complex issues and the necessary search for compromise

The United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD)[1] was received with high expectations by all those concerned with the protection of the human rights of people with mental disorders and psychosocial disabilities. For most sectors of the mental health community, it appeared to be a unique opportunity to take a leap forward in the development of laws promoting the rights of this group of people and facilitating the development of community-based and human rights-oriented mental health care.

Is it possible that the UN Committee's General Comment No. 1 on Article 12 of the Convention[2] has created a situation in which all these expectations are in danger? Unfortunately, the danger is real. A large number of States Parties that have ratified the Convention have also expressed their disagreement with the Committee's interpretation, in particular regarding the absolute prohibition of substitute decision-making. An increasing number of human rights experts, scholars and clinicians have stated their conviction that this interpretation, if accepted, would result in serious adverse consequences for people with mental health disorders and psychosocial disabilities, and would undermine some of the hard-won critical rights of these people[3]. Although many mental health service users' organizations support the prohibition of involuntary admission and treatment, there are indicators showing that this view is not shared by all people with mental disorders nor by the majority of family members. In this context, we have to conclude that the possibility that governments will change their mental health laws in accordance with the directives of the Committee seems rather remote.

How did we get into this situation? The limited involvement of some relevant sectors (e.g., clinicians) in the drafting of the Committee's Comment, and an insufficient debate about the implications and the implementation of the CRPD, were important factors. However, in my opinion, the ambiguity of the text of clause 4 of Article 12, pointed out by Szmukler[4], has certainly had a very strong influence in this process. It was this ambiguity, in which it is difficult not to see an imperfect compromise between conflicting approaches, that the Committee has tried to overcome, alas, at the cost of a radical and reductionist interpretation, that is not compatible with the complexity of the issue at stake.

According to the Committee's interpretation, any form of substitute decision-making is considered a violation of the Convention's guarantee of legal capacity on an equal basis. This means that, faced with a person with a mental disorder who does not accept a treatment considered indispensable and has a severe lack of decision-making skills, a psychiatrist would not be allowed to resort to involuntary treatment in any circumstance. Because, in order to preserve legal capacity, it is necessary to respect the person's rights, will and preferences, in such a situation the psychiatrist would have to rely solely on the support that the State is obliged to provide for the person to become able to express his/her will and preferences.

This approach suffers from several fragilities and contradictions. One of these has to do with the arguments used by the Committee to justify why the lack of decision-making skills cannot be the basis for any form of substitute decision. In fact, one of these arguments – that the assessment of these skills would be impossible – is not confirmed by the available evidence[5], while the other – that its determination would be discriminatory – has been refuted by several experts, who have argued that the assessment of decision-making capacity does not need to be discriminatory in nature and can be applied to all people equally[4,6].

Another example is the idea according to which, with the appropriate support, most persons with disabilities will be able to express their will and preferences, a presumption which ignores the fact that, in many situations, it is not possible to guarantee this support, while in many other situations this support will not be effective. Finally, denying persons with severe mental disorders the treatment they need, in cases where it has been proved that they lack the ability to make decisions regarding their treatment needs, and doing so in the name of "the freedom to take risks", is, in my opinion, highly debatable from the ethical point of view.

Despite all the objections that may be leveled against the Committee's Comment, we should not forget, as Szmukler[4] rightly underlines, that the publication of this Comment has had several important merits. It has stimulated a debate, although this has been manifestly insufficient so far. It has called attention to the fact that, for many people with mental disorders and psychosocial disabilities,

involuntary admission and treatment may be a very painful and traumatic experience. Finally, it has represented a strong challenge to be met by the development of new contributions that may help to build a much-needed consensus.

The proposal of Szmukler and Dawson[4,7] goes in that direction and proves that it is possible to formulate a law that is generic, non-discriminatory towards people with mental health disabilities, based on decision-making ability in relation to a particular treatment decision at a particular time, and that permits involuntary treatment when all attempts at support have failed in helping the person to make a decision that could be considered autonomous.

The proposal of a more subjective approach to both the concept of best interests and the assessment of the person's decision-making ability could also help to ensure that the deep beliefs and values (in other words, the will and preferences) of the person are taken into consideration[4]. Although differing from this approach in several specific aspects, the proposals put forward by Freeman et al[3]

and Scholten and Gather[8] share some of its principles.

Important differences remain between these proposals and the Committee's view. However, they all represent valuable contributions to the construction of a formulation that will take into account the complexity of what is at stake and will have real chances of being incorporated into the mental health laws of most countries.

For this to happen, several things are necessary: a) to promote all forms of debate that may help to build a new consensus; b) to ensure the participation in the discussion of a much broader range of stakeholders (e.g., different groups of people with mental disabilities, family members, mental health professionals with clinical experience, and experts in mental health legislation and policy); c) to clarify the definition of and the relations between relevant concepts (e.g., mental disorders, disabilities, psychosocial disabilities); d) to admit that, rather than concentrating our efforts on "an absolute prohibition on involuntary treatment (that) is, at least at present, not credible"[4],

we should "devote more time to thinking about how to make the essential practice of substitute decision-making as respectful as possible"[9]; and e) to invest more on the reform of services and practices, without which no meaningful change in protection of the human rights of people with mental disorders will ever occur.

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The UN Convention on the Rights of Persons with Disabilities: great opportunities and dangerous interpretations

G. Szmukler's paper[1] provides an in-depth analysis of some critical aspects of the United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD) that make its implementation problematic in mental health care laws and provisions.

Out of 177 States Parties that ratified the Convention, only 92 signed the Optional Protocol, and several of them expressed reservations on the Convention or explicitly put forward their interpretation of some articles[2].

Actually, as correctly pointed out in Szmukler's paper[1], the most critical aspects do not stem directly from the text of the Convention, but from the interpretations provided by the UN Committee set up to monitor the implementation of the Convention (CRPD Committee)[3].

Articles 12 and 14 represent the best examples. The text of these articles requires appropriate measures by States Parties to guarantee persons with disabilities the support they may require in exercising their legal capacity. However, in the interpretation provided by the Committee, these articles would preclude all non-consensual treatment and substitute decision making on behalf of persons with mental disorders.

Szmukler focuses on three concepts likely to underlie misinterpretations of several articles of the Convention and generate problems in its implementation in mental health laws: legal capacity, will and preferences.

The position taken by the Committee on the issue of legal capacity is a challenge for common sense. It is based on

the assumption that mental capacity and legal capacity are independent from each other, though both of them (in particular, legal capacity in terms of legal agency) involve decision making processes. As a result, a person may lack the capability of making decisions, but will be considered able to do so from a legal point of view, in order to avoid discrimination and denial of human rights.

This assumption entails multiple risks for multiple entities. The recognition of full legal capacity would deprive the person with mental disorder of any right to benefit from the acknowledgement of a mental condition as a source of defense. In the absence of decisional capacity, a person with a severe mental disorder (e.g., psychotic disorder or dementia) may be unable to protect her/his own in-

terests, and may be victim of exploitation by others. Those who care for people with mental disorders know that this happens and, unfortunately, it is not a rare event.

It is also worth reminding all of us that several people are willing to take their own life when deeply depressed. However, when recovered from depression, the same people are very thankful to doctors who treated them (even under a coercive treatment regimen) for being still alive.

Of course, the need to support people in being actively involved in decisions relevant to their treatments, housing or finances is not questioned, and efforts aimed at identifying and disseminating the best relevant practices should be encouraged. Indeed, the shift from a classical welfare approach to one focusing on autonomy and full inclusion in the society of people with disabilities is more than welcome, as demonstrated by the ratification of the Convention by so many States Parties.

However, a rigid approach, as the one advocated by the Committee's General Comment No. 1 on Article 12, would not provide any safeguard in case support fails to enable the person's active and informed participation in the decisional process, and would leave room for exploitation and extreme irreversible decisions. As highlighted in Szmukler's paper, rigid interpretations of the Convention may result in a paradoxical situation in which both the person with mental disability and her/his unofficial carers may experience more disadvantages than advantages.

The reliance on will and preferences of the person in ensuring the exercise of legal capacity suggests a lack of clinical expertise and input in the writing of the Convention. In several neurological, psychiatric and internal medicine conditions, such as those involving quantitative and qualitative alterations of consciousness, the possibility to assess the person's will and preferences "coherent with a sense of personal identity"[1] is very limited. During a manic episode, for instance, a person may prefer to behave in ways that, outside that episode, would make her/him deeply ashamed, or concerned, or even guilty. When recovered, the person might ask those around her/him why no one did anything to prevent her/him from causing so many troubles. When acutely delusional, a person might wish to donate all her/his goods to someone else, and later on, when no more delusional, feel desperate for having ruined her/himself and the whole family. Conflicts between different wills in different moments, and even among different rights, are clearly present here: in these cases, should, as noted by Szmukler, the right to enjoy freedom from exploitation override the right to act according to one's own current preferences?

In spite of the drawbacks underlined by Szmukler, advance directives might be an important resource. However, an in-depth discussion among all stakeholders is needed in order to identify the best relevant procedures and validate them in different cultural contexts.

In the light of the potentially harmful consequences of rigid interpretations, it is not surprising that several States Parties, while ratifying the UN Convention, expressed reservations on some of its articles (in particular on Articles 12, 14 and 19) and did not sign the Optional Protocol. It is also not surprising that, as highlighted by Szmukler, other UN bodies do not support the interpretations provided by the CPRD Committee[4]. The issue of mental disabilities is very complex, and requires high ethical standards, appropriate training, as well as mental health care services with adequate structural and human resources.

In spite of the critical aspects highlighted in Szmukler's paper, the Convention has fueled a lively debate on inappropriately neglected hot topics which, at odds with the tendency to shortcuts and oversimplifications characteristic of the CPRD Committee and Special Rapporteur's report, seem to require accurate testing of different models and a neutral evaluation of their outcomes.

For the time being, a general agreement could and should be reached on the following aspects: a) the determination of incapacity should never be based upon diagnosis alone, as no mental disorder impairs the capability of making decisions by definition; b) in each State Party, procedures for advance directives should be identified and included in mental health laws after adequate validation; c) a careful documentation of attempts made to establish a therapeutic alliance and to support the patient in the process of making decisions relevant to her/his treatment, housing, finances, etc., should be provided in patients' clinical records.

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Will and preferences in the overall CRPD project

G. Szmukler's paper[1] needs to be understood in the context of the Convention on the Rights of Persons with Disabilities (CRPD) as a whole, and what the CRPD endeavors to achieve.

The motivation for the CRPD was an acknowledgement that existing legal and policy approaches, both at the international and the national levels, were not delivering human rights for people with disabilities[2]. As that relates to people with mental disabilities, that is unlikely to be contested by the readers of this journal. We are all aware of institutional systems in which people with mental disabil-

ities may spend most of their lives in conditions that are frankly deplorable. Countries of the global North sometimes portray themselves as somehow above this, but a perusal of the reports of the European Committee for the Prevention of Torture suggests that none of us has much to crow about[3].

Life in the community is often not much better. Poverty is endemic, no doubt in part reflecting the risible employment rates of people with mental disabilities. Community housing is often substandard. There is little evidence of meaningful social integration, but certainly evidence of being the victims of violence, exploitation and abuse[4]. These problems are international: we all have to own them as they relate to our own countries, wherever we are.

In that sense, the CRPD is an attempt to hit the reset button. It tries to create a fresh start in international human rights law, envisaging a world where people with disabilities do get to enjoy the rights and the meaningful lives that the rest of us take for granted[2]. When commentators speak of the CRPD introducing a "new paradigm", that is what is meant: it is an acknowledgement that the way we have approached human rights of people with disabilities since the Second World War (and perhaps for centuries before) needs a fundamental rethink.

Fundamental to that is a challenge to rethink the role of the state, and its relationship to people with disabilities. Traditionally, the role of the state has been one of control. Mental disabilities provide a particularly clear example of this: we have locked up people with mental disabilities because of perceived dangerousness, or "for their own good", or to remove them from the public gaze, or to allow their family carers to work. When we have established community programmes for them, social workers and similar professionals have been expected to keep a close eye on their lives. Usually this has been done with good intentions; but it has created a second class citizenship, where rights are contingent in a way not experienced by the rest of society.

The CRPD is not anti-state or libertarian. Instead, it re-casts the state, not as a manager of people with disabilities, but in a support role. If people with disabilities are to enjoy the meaningful lives the rest of us expect, supports have to be put in place to bring this about, and that requires either service provision by states, or services provided under state regulation. The services do need to be what people with disabilities want, however: these people should not be required as a matter of state policy to take what is on offer, any more than any other citizen should. The CRPD envisages a world where people with disabilities get to make the same choices as the rest of us.

Szmukler is correct that a number of international human rights bodies have been slow to pick this up, but that is appropriately a criticism of those bodies. It is difficult to see how the existing human rights systems that those bodies perpetuate can provide the legal, cultural, policy and ideological shifts that are required to make human rights real for people with disabilities. The failure of these existing systems for people with disabilities was, after all, the reason why the CRPD was perceived as needed, and the international human rights bodies noted by Szmukler need to own that truth.

That is not necessarily to say that the position of the CRPD Committee is to be taken uncritically or as unassailable. It is to say that the problems the CRPD is intended to address are real, and critics of the CRPD position should be challenged to provide positive alternatives, rather than to trot out the approaches of the past that have proven insufficient.

What does all this mean for Szmukler's analysis? Three points are of particular relevance.

The first is that in Szmukler's analysis, as elsewhere in the literature, the debates about capacity, supported vs. best interests decision-making, and the CRPD Committee's General Comment No. 1[5] take place in isolation from the bigger pictures of what needs to change for people with disabilities. Unsurprisingly, physicians view these issues through the lens of medicine and the effects on their prac-

tice. Almost certainly, this will only be a small piece of what is required.

Further, decision-making is only relevant if there are options to choose between. The changes needed to realize the CRPD ambition will no doubt include provision of the best available standards of health, but provisions for example concerning the structures of social care and benefits, housing, and community integration will also be pivotal. We should all be working with people with disabilities to articulate those broader changes in ways relevant to our own countries. The discussion of how decisions should be taken in "hard cases" needs to occur in that broader set of contexts, not just within clinical treatment.

The second issue is how far Szmukler's analysis actually diverges from the CRPD Committee's approach in General Comment No. 1. He does seem to suggest that the influence of the will and preferences of a person with disability in determining a decision should be directly proportional to the clarity and reliability of those will and preferences. That already seems to be moving a considerable distance from the hard capacity/incapacity divide of current law.

Szmukler might well be agreeable to proper support being offered to the person with disability in reaching and articulating views. While he does not use the phrase, his view would appear to be that, in hard cases, decisions should be taken based on the "best approximation" of the person's will and preferences – the CRPD Committee's approach. There is admittedly some divergence on what constitute hard cases, but the similarity of Szmukler's position to that of the Committee is notable. Certainly, versions of Szmukler's approach could mean a considerable move from the managerial ethos of the current system – and that is very much consistent with the CRPD.

Finally, there is the question of who should support the person with disability in articulating his/her will and preferences, and deciding what weight should be given to divergent views expressed by the person. Psychiatrists, like many other care professionals, have for generations

been at the centre of the culture that people with disabilities are to be managed by the state – the old paradigm. If a will and preferences approach is to be provided by psychiatrists in a non-managerial way, and if psychiatrists are to have the trust of people with disabilities in providing the support in articulating will and preferences, psychiatry will have to break from the old, controlling paradigm. It is not clear whether psychiatry as a profession is ready to make that break.

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The rejection of capacity assessments in favor of respect for will and preferences: the radical promise of the UN Convention on the Rights of Persons with Disabilities

G. Szmukler[1] argues for an interpretation of "will and preferences" that allows for determinations of decision-making ability, in the form of functional assessments of mental capacity, to be used to interpret the decisions of those who appear to display conflicting will and preferences.

In this commentary, I will focus on three core issues which arise from Szmukler's approach: the issue of indirect discrimination in functional assessments of mental capacity, the dilemma of advance decisions, and the need for a human rights compliant response in a situation where the individual's preference(s) appears to conflict with his/her will.

Concerning the first issue, Szmukler argues that the application of functional assessments of decision-making ability should not be regarded as unlawful discrimination, because these serve a legitimate aim, the assessments are objective in nature, and meet the criteria of reasonableness and proportionality in pursuit of their legitimate aim.

Even if the notion of a legitimate aim – protecting the totality of the person's human rights – is accepted, it is far less certain whether functional assessments of capacity can be considered objective in nature, or a reasonable and proportionate response to resolving a perceived conflict of rights. Szmukler cites Grisso and Appelbaum's review of measures used to assess competence[2] in support of the argument for objectivity, but this is by no means an uncontested position in the literature.

For example, Morgan and Veitch[3] criticize the purported objectivity of mental capacity assessments. They argue that "the real point of legal tests for mental capacity seems not to be to assess some projected future or, indeed, past ability to make a choice... but to assess whether the person making that decision can construct a convincing case why he or she reaches the standard of the 'ability' that law expects in such circumstances".

In support of this argument, Haidt[4] and Iyengar and Lepper[5] showed that individuals only conjure up reasons for their decisions when called upon to do so, and these reasons rarely correlate with their actual decision-making process at the time of the original decision, but rather reflect the most persuasive explanation the person can find for his/her decision.

These studies suggest that the process of assessing an individual's mental capacity, even on a functional basis, is an inherently subjective and value-laden one. Therefore, the use of such assessments to restrict or deny legal capacity violates the requirement of objectivity demanded by human rights norms in order to avoid the categorization of disability-based discrimination.

It is also clear that the use of functional assessments of mental capacity to reconcile perceived conflicts of rights, will and preferences does not meet the criteria of reasonableness and proportionality. With increasing evidence of the effectiveness of alternatives to substitute decision-making[6], a reliance on mental capacity assessments as a trigger for (potentially coercive) interventions seems less and less reasonable. As long as alternative, less intrusive measures exist which could be used to reconcile perceived conflicting will and preferences, it cannot be proportionate to impose substitute decision-making based on an external decision-maker's functional assessment of an individual's mental capacity to make a particular decision.

The second issue I wish to address relates to advance directives. Such directives – which are listed in the Committee on the Rights of Persons with Disabilities' General Comment No. 1[7] as an important example of support to exercise legal capacity – can easily be reframed away from the capacity/incapacity paradigm, to give the directive-maker much greater flexibility to determine when the directive becomes operational. In other words, the perceived absence of functional mental capacity should not be the automatic legal trigger for a directive entering into force. Instead, the directive-maker should specify the circumstances in which he/she wishes his/her directive to take effect.

A directive-maker could, for example, specify that the directive should be activated once he/she starts exhibiting certain behaviors, or when he/she is admitted to hospital, or when a number of trusted supporters named in the directive all agree that he/she is now in crisis or unable to communicate. This ensures that the power remains with the directive-maker

to set the conditions under which the directive will take legal effect.

As for the thorny question of Ulysses clauses, in my view it should be possible for individuals to include these in directives if they so choose. In practice, I anticipate that the use of such clauses would be very rare, as most people will not want to bind their future selves to a situation that they would not then be able to reverse. But, as this is an important support option which some individuals wish to have, it should be available to persons with disabilities on an equal basis with others.

The final issue I wish to address is how a human rights compliant response can be developed where we perceive an individual's will and preferences to be in conflict and incapable of reconciliation. As I have previously argued[8], where will and preferences conflict, a number of strategies can be employed. First of all, what an outsider might perceive as a conflict between will and preferences may not be perceived by the individual decision-maker as problematic – it might reflect a change of approach from past decisions based on experience, a new perspective, or simply the fact that the person has changed his/her mind.

A human rights compliant approach to resolving these perceived conflicts involves engaging in all forms of communication with the person, and speaking with those the person indicates are trusted supporters to inform the interpretation of his/her will and preferences in this specific situation. It may happen during this process that the will and preferences of the person become clear. If the will and preferences of the person remain unclear following all efforts, and a decision still needs to be made, the interpreter will have to make a decision informed by the "best interpretation" of the person's will and preferences he/she arrives at, given all the information available about the person's wishes.

Others have suggested that a "best interpretation" means "the interpretation of an adult's behaviour and/or communication that seems most reasonably justified in the circumstances", and that "decision-making supporters must be able to provide a reasonable account of how this interpretation was arrived at"[9].

The process of arriving at a "best interpretation" of will and preferences is inevitably challenging and fraught with uncertainty, but, if the new paradigm heralded by the Convention on the Rights of Persons with Disability (CRPD) is to mean anything, it must be understood that this process is radically different from how determinations of decision-making ability have been undertaken in the past.

Therefore, contrary to what Szmukler proposes, it is my contention – in keeping with the jurisprudence of the CRPD Committee – that functional assessments of mental capacity cannot be used to determine whether a particular preference should take precedence over what others perceive to be the individual's will, or whether third parties' interpretation of a person's will can justify ignoring the individual's clearly expressed preference.

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The UN Convention: a service user perspective

The United Nations (UN) Convention on the Rights of Persons with Disabilities (CRPD)[1] has sparked quite a global debate around Articles 12 (Equal recognition before the law) and 14 (Liberty and security of the person), and their relation to involuntary hospitalization and treatment.

In light of this controversy, the South African Federation for Mental Health (SAFMH) has conducted an engagement exercise with mental health care users who had experienced involuntary hospitalization. Seventy-one percent of participants indicated that they were in favor of involuntary treatment, and specified that their preference was due to acknowledging that there had been intervals during a relapse where they were unable to act in their own best interest.

The participants felt that the practice of involuntary treatment "protected" them from their own behaviour at a time of relapse where they may not have control over their actions, and which may consequently result in personal harm or harm to others (harm not specifically defined as physical harm but including psychological harm).

Participants, however, emphasized that they had more often not been involved in decision-making when it came to treatment options. They noted that their experiences with involuntary hospitalization had happened without consultation, and that they became aware of what was going on only when the ambulance and/or police arrived. They further noted that involuntary hospitalization would in most instances not have been necessary should they have been consulted and would have agreed to voluntarily go to hospital for treatment.

Paternalism has a long history in psychiatry[2], sometimes with the best of intentions, but it is a disempowering component of the mental health care system, where others instinctively tend to take on a decision-making role. Paternalism

denies the opportunity to make an informed decision through a consultative process (or through a supported decision-making process when necessary) to allow for the will and preferences of mental health care users to be acknowledged, respected and executed.

Assumptions are often made instinctively as to the decision-making capacity of a mental health care user, without any determination on whether the person is in fact unable/able to make an informed decision or needs support to make a decision. Moreover, paternalistic decision-making may reinforce self-stigma and lead to poorer health outcomes[3].

Mental health care systems need to take bold steps and strategically redesign the way in which services are provided, to ensure alignment with international human rights standards and evidence-based interventions, with an emphasis on empowerment, recovery and mental health care user involvement in the evaluation of the system. An example of a mental health care system that achieved considerable transformation is the "Open Door – No Restraint" system in Italy[4], focusing on recovery and citizenship, where mental health care users are at the centre of service delivery.

Apart from reverting away from abruptly dismissing the will and preferences of service users when it comes to treatment options, the change should pay serious attention to the environment in which services are delivered. Psychiatric facilities often look and function more like prisons than places of care and recovery. The dilapidated state of such facilities impacts on bioethical principles that should promote respect for autonomy, non-maleficence, beneficence, and justice.

Psychiatric facilities and mental health services have been noted as environments in which human rights violations are most likely to take place[5], and where service users' voices are often silenced. It is, therefore, a logical expectation that a person will refuse admission to such psychiatric facilities if the environment which should help and care for him/her exposes him/her to degrading and undignified treatment, adding to the psychological distress that he/she may experience at the time.

In South Africa, persons refusing hospital treatment may be resistant not because of diminished legal or mental capacity (however perceived), but because of the knowledge of what happens in those facilities.

In the engagement exercise conducted by SAFMH, the word "dignity" came up several times where participants explained how the mental health care system had violated their rights. Words describing their experiences included "devastated", "frightened", "confused", "undignified", "violated", "criminalized", "treated as less than human", "Nazi concentration camp", "tied down like a dog".

My own experience of involuntary hospitalization was more traumatic than the devastating symptoms I experienced with my diagnosed schizophrenia. I refused voluntary hospitalization based on past experience of unconducive and abusive conditions within the hospital. Even though my will and preference was aimed at obtaining treatment, just not in such an environment, yet I was considered to have diminished decision-making capacity and to be unable to acknowledge what was in my own best interest.

On the other hand, the CRPD Committee's interpretation of the Convention's Articles 12 and 13, which would mean that the "insanity plea" would be scrapped as far as "unfitness to stand trial" and "not guilty by reason of insanity" are concerned, may have consequences that impact on a person with a mental disorder who enters the justice system. A case study in South Africa that I have dealt with in my advocacy work gives insight into this.

A person with a diagnosis of schizophrenia who in a psychotic state caused damage to property, in response to voices that instructed him to do so, was arrested and stood trial without his diagnosis at any point being introduced as a defense. Consequently, he was found guilty and served a prison sentence. Upon release, he failed to obtain employment merely because of his criminal record. In the alternative scenario where he could have been found "not guilty by reason of insanity", he would not have had a criminal record that now prevents him from obtaining employment and ultimately independence. The question is: was it a fair trial if the circumstances surrounding his actions on the day of the damage to property were not considered?

Prison systems may often not be equipped or sufficiently resourced to care for and protect people with mental disorders from victimization and abuse, or may not be able to provide an adequate standard of mental health care and services to this population. Even in a more resourced country like the US, prisoners with mental disorders are "more likely than other prisoners to be held in solitary confinement, be financially exploited, physically and sexually assaulted, commit suicide, or be intentionally self-destructive"[6].

Any person, whether he/she has a mental disorder, a disability or not, may at some point be unable to make an informed decision (for whatever reason) and, where will and preference are in contradiction, there must be a mechanism that protects the individual.

To avoid stigmatization and discrimination, I support Szmukler's suggestion[7] of a law that is solely based on decision-making ability, with a clear definition of will and preference, human rights and best interest processes to be considered on an individual case basis, opposed to a law that is specifically aimed at persons with mental disorders.

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The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials

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We summarized and compared meta-analyses of pharmacological and non-pharmacological interventions targeting physical health outcomes among people with schizophrenia spectrum disorders. Major databases were searched until June 1, 2018. Of 3,709 search engine hits, 27 meta-analyses were included, representing 128 meta-analyzed trials and 47,231 study participants. While meta-analyses were generally of adequate or high quality, meta-analyzed studies were less so. The most effective weight reduction interventions were individual lifestyle counseling (standardized mean difference, SMD=–0.98) and exercise interventions (SMD=–0.96), followed by psychoeducation (SMD=–0.77), aripiprazole augmentation (SMD=–0.73), topiramate (SMD=–0.72), d-fenfluramine (SMD=–0.54) and metformin (SMD=–0.53). Regarding waist circumference reduction, aripiprazole augmentation (SMD=–1.10) and topiramate (SMD=–0.69) demonstrated the best evidence, followed by dietary interventions (SMD=–0.39). Dietary interventions were the only to significantly improve (diastolic) blood pressure (SMD=–0.39). Switching from olanzapine to quetiapine or aripiprazole (SMD=–0.71) and metformin (SMD=–0.65) demonstrated best efficacy for reducing glucose levels, followed by glucagon-like peptide-1 receptor agonists (SMD=–0.39), dietary interventions (SMD=–0.37) and aripiprazole augmentation (SMD=–0.34), whereas insulin resistance improved the most with metformin (SMD=–0.75) and rosiglitazone (SMD=–0.44). Topiramate had the greatest efficacy for triglycerides (SMD=–0.68) and low-density lipoprotein (LDL)-cholesterol (SMD=–0.80), whereas metformin had the greatest beneficial effects on total cholesterol (SMD=–0.51) and high-density lipoprotein (HDL)-cholesterol (SMD=0.45). Lifestyle interventions yielded small effects for triglycerides, total cholesterol and LDL-cholesterol (SMD=–0.35 to –0.37). Only exercise interventions increased exercise capacity (SMD=1.81). Despite frequent physical comorbidities and premature mortality mainly due to these increased physical health risks, the current evidence for pharmacological and non-pharmacological interventions in people with schizophrenia to prevent and treat these conditions is still limited and more larger trials are urgently needed.

Key words: Schizophrenia, psychosis, physical health, body weight, blood pressure, glucose, insulin, tryglicerides, cholesterol, lifestyle counseling, exercise interventions, dietary interventions, metformin, topiramate, antipsychotic switching

People with schizophrenia have substantially poorer physical health than the general population[1-4], which is often attributed to an interaction between social circumstances, lifestyle factors and treatment effects[5]. For instance, behavioral research has demonstrated that people with schizophrenia are less physically active and exhibit more sedentary behavior than the general population[6], have a higher quantity but lower quality of dietary food intake[7], and increased adverse health behaviors, such as smoking[8]. Additionally, psychiatric treatment with antipsychotics and other commonly prescribed agents, such as mood stabilizers and antidepressants, further increases the risk of physical health conditions[9,10]. Consequently, people with schizophrenia more frequently have cardio-metabolic diseases[11-13], respiratory diseases[14], chronic pain[15], fractures[16], and lower physical fitness[17,18] than the general population.

This increased somatic risk is associated with a lower physical health related quality of life[19,20], but, despite this increased risk, access to monitoring, physical health care and intervention for those with schizophrenia are suboptimal compared to the general population[21,22]. Resultantly, people with schizophrenia experience a 10-20 year gap in life expectancy, primarily driven by this poorer physical health[13,23]. Furthermore, the physical health inequalities experienced by people with schizophrenia have been observed across the globe[24] and have not improved over time[25].

Given this gross inequality, there has been a substantial increase in efforts to improve the physical health of this at-risk population[5,26]. To address the physical health disparity, a number of individual meta-analyses have led to national and international evidence-based recommendations for or against specific pharmacological and non-pharmacological intervention options[27-34].

Despite this rapid expansion of meta-analytic evidence on interventions for tackling poor physical health in people with

schizophrenia, no summary of this top-tier of evidence exists, nor is there a direct quantitative comparison of the evidence between all individual and/or combined pharmacological and non-pharmacological strategies. Moreover, the quality of these meta-analyses and the included trials has not been comprehensively evaluated, which is an indispensable step before more rigorous treatment recommendations can confidently be made.

In order to address this gap within the literature, we set out to aggregate the existing top-tier evidence from the most recent/largest published meta-analyses of randomized trials of physical health interventions, in order to determine the comparative quality of evidence and magnitude of efficacy for pharmacological and non-pharmacological interventions targeting physical health outcomes among people with schizophrenia spectrum disorders.

METHODS

Searches

Four authors searched independent from each other MEDLINE/PubMed, PsycINFO, EMBASE and the Cochrane databases, from their respective inception dates until June 1, 2018, without language restriction, for meta-analyses of randomized controlled trials in people with schizophrenia spectrum disorders where physical health improvements were the primary outcome.

The search terms included ("meta-analysis" OR "systematic review") AND ("random*" OR "placebo" OR "control*") AND ("schizophrenia" OR "schizoaffective" OR "schizophreniform" OR "psychosis" OR "psychotic" OR "severe mental illness") AND ("physical health" OR "cardio*" OR "metabol*" OR "respir*" OR "*weight" OR "pain" OR "somatic"). We searched the reference lists of all included articles.

Inclusion criteria

Inclusion criteria were organized in accordance with the population, interventions, comparisons, outcomes and setting/study design (PICOS) reporting structure (see Table 1).

Data extraction, outcomes, and data synthesis

Regarding efficacy and adverse drug reactions, we manually extracted effect size data (with 95% confidence intervals, CI) for all relevant outcomes, and the number of participants in the intervention and control arms for each effect size. Specifically, data for effect sizes of continuous outcomes were extracted or recalculated as standardized mean difference (SMD), which expresses the mean difference between the intervention and control groups in standard deviation units, with 95% CI. Generally, an SMD less than 0.2 is considered negligible, an SMD

Table 1 Application of the PICOS search strategy

Population – People with schizophrenia spectrum disorders, including schizophrenia, schizoaffective or schizophreniform disorder or first episode psychosis, confirmed through validated assessment measures (e.g., DSM, ICD). Studies conducted with a severe mental illness subgroup (e.g., also including bipolar disorder or major depressive disorder) were only included if the schizophrenia spectrum disorder sample was ≥70%.

Interventions – We included all pharmacological interventions that had a primary aim to improve physical health outcomes. Non-pharmacological interventions included all educational, psychotherapeutic, social and physical interventions, excluding alternative therapies. Specifically, we included lifestyle interventions (e.g., physical activity, diet, smoking cessation).

Comparisons – All relevant control interventions were included (e.g., placebo, treatment as usual/usual care, waiting list, no treatment).

Outcomes – We considered any physical health outcomes explored, including the following: a) any physical health markers, such as body weight, proportion with overweight or obesity, random or fasting levels of glucose and lipid metabolism parameters, proportion with abnormalities in glucose and lipid metabolism parameters, cardiovascular illness (e.g., myocardial infarction, stroke, transient ischemic attack, pulmonary embolism), respiratory illness (lung cancer, chronic obstructive pulmonary disease); b) parameters of physical fitness (e.g., maximal or peak oxygen uptake, muscle strength); c) any biomarkers investigated (hemoglobin A1c, C-reactive protein or other blood and serum markers); d) any physical health behavior researched (physical activity levels, smoking behavior, diet patterns, attending physical health appointment, attendance rates); e) physical health related quality of life; f) side effects (e.g., adverse drug reactions).

Setting – We considered any setting: hospital (inpatient or outpatient), community, or remote (e.g., using digital technology).

Study design – Meta-analyses informed by a systematic review that included randomized controlled trials (RCTs) were included. A paper was classified as a systematic review and meta-analysis if the following criteria were met: clear inclusion criteria, a systematic search strategy, a screening procedure to identify relevant studies, systematic data extraction and meta-analysis procedures for RCTs. Meta-analyses meeting the inclusion criteria were removed if there was a more recently updated meta-analysis for that same combination strategy and outcome as long as more than 75% of the meta-analyzed trials overlapped and the pooled sample was larger for that specific intervention and outcome. Conference abstracts were excluded.

between 0.2 and less than 0.5 is small, an SMD between 0.5 and less than 0.8 is medium, and an SMD of at least 0.8 is large[35]. Risk ratios (RRs) were used for categorical outcomes. If odds ratios were present, they were recalculated as RRs. For both types of outcomes, we followed the decisions of the original authors concerning fixed vs. random effects models.

Quality assessment of the meta-analyzed studies

Included meta-analyses were assessed using "A Measurement Tool to Assess Systematic Reviews" (AMSTAR) (range 0-11, with a score of 8 or higher indicating high quality)[36].

While AMSTAR is a reliable and valid tool for measuring the methodological quality of meta-analyses, its score does not capture quality indicators of the meta-analyzed trials, which

could bias pooled results. For instance, a meta-analysis that meets all methodological quality criteria, but that meta-analyzes potentially biased studies would have a good methodological quality but poor content quality.

Thus, for a more comprehensive assessment of the content validity of included meta-analyses, we used a set of six additional, previously developed quality items, each ranging between 0 and 1 or 2, that capture the content quality of the meta-analyzed trials (AMSTAR-Plus Content, range 0-8, with a score of 4 or higher indicating high quality)[37].

Statistical analysis

We analyzed data as they were directly extracted from the published meta-analyses or, if necessary, after they were converted to standardized outcomes using comprehensive meta-analysis (CMA, version 3) (Biostat). To compare the SMDs of the experimental pharmacological and non-pharmacological interventions vs. the control interventions, we conducted separate random-effects meta-analyses for each variable using CMA.

The AMSTAR and AMSTAR-Plus Content scores and sample size were used where possible in meta-regression analyses, which were done separately for pharmacological and non-pharmacological strategies. Where possible, we also performed meta-regression and subgroup analyses to examine putative factors which may influence effect sizes for each individual physical health outcome, including participant characteristics (e.g., average age, gender distribution) and interventional design (treatment duration in weeks, delivered by mental health vs. physical health staff, clinical setting, percent of sessions attended/adherence, group vs. individual treatment).

Heterogeneity was quantified using the Q and I^2 statistic, with scores of <25%, 25-50% and >50% indicating low, moderate and high heterogeneity, respectively[38]. If it was not possible to extract effect size data for the comparative meta-analysis, we reported individual review level results in a narrative synthesis.

RESULTS

Systematic search results

Of 3,709 search engine hits, 27 meta-analyses were included[39-65], representing a total of 128 meta-analyzed trials and 47,231 study participants.

There were meta-analytic data for 17 different pharmacological interventions: aripiprazole augmentation[43,47,53,55], fluoxetine[55], metformin[46,48,49,54,55,61,62], nizatidine[54,55], NMDA receptor antagonists including amantadine and memantine [45,55,57,60], ranitidine[42], topiramate[39], dextroamphetamine[64], d-fenfluramine[64], famotidine[64], metformin in combination with sibutramine[64], orlistat[64], rosiglitazone[64], fluvoxamine[64], glucagon-like peptide-1 receptor agonists (GLP-1 RAs)[40], and switching from olanzapine to quetiapine or aripiprazole[65].

Meta-analytic data were available for six different non-pharmacological interventions: individual lifestyle counseling[58,59,63], group lifestyle counseling[58,59,63], cognitive behavioral therapy[58,59], psychoeducation[58], exercise[50,56,58], and dietary interventions[44,58]. One meta-analysis investigated the pooled effect of a combined lifestyle and metformin intervention[41].

In total, 17 different physical health outcomes were investigated: weight, body mass index, waist circumference, waist to hip ratio, diastolic and systolic blood pressure, fasting glucose, insulin, homeostatic model assessment of insulin resistance, hemoglobin A1c, fasting triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, android/gynoid ratio (i.e., percent fat ratio defined as android fat divided by gynoid fat), visceral fat, and functional exercise capacity.

The control interventions included placebo, continued psychotropic treatment, or care as usual for pharmacological trials, and care as usual for non-pharmacological trials.

The number of trials for a specific health outcome ranged from one to 29, with a median of five trials (interquartile range = 5). Trials lasted six to 72 weeks. When reported, the mean age of participants was 34.9±2.0 years, and 58.4% were men.

Quality assessment of the included meta-analyses

The AMSTAR mean score was 8.8±1.0 in the whole sample, 8.9±0.9 in the pharmacological interventions, and 8.7±1.0 in the non-pharmacological interventions. Twenty-four (89%) meta-analyzed studies had an AMSTAR score of 8 or higher, but only two[42,65] (4%) had the maximum AMSTAR score of 11. The AMSTAR-Plus Content mean score was 3.4±1.5 in the whole sample, 3.2±1.6 in the pharmacological interventions, and 3.7±1.1 in the non-pharmacological interventions. None had the maximum score of 8.

Only eleven meta-analyses (41%) were rated as high-quality based on the meta-analyzed studies. Seven of the 27 meta-analyses included only double-blind trials (26%). In 16 meta-analyses (59%), the total pooled sample was less than 500 cases, while only five meta-analyses (18%) had a total sample of more than 1,000 participants. Only two meta-analyses[49,53] (7%) had one included trial with at least 200 participants. Finally, following the AMSTAR-Plus Content criteria, a significant heterogeneity was found for 12 meta-analyses (44%), and 18 (67%) could not disprove the presence of a publication bias.

Further, we examined the relationship between the effect size for both the non-pharmacological and pharmacological interventions versus the control conditions with the quality assessment measures (AMSTAR and AMSTAR-Plus Content). The SMDs for pharmacological and non-pharmacological interventions did not correlate significantly with the methodological quality of the meta-analysis as measured by AMSTAR (p=0.37 to 0.52) nor with the content quality of the meta-analysis as measured by AMSTAR-Plus Content (p=0.17 to 0.97).

Table 2 Anthropometric physical health outcomes of pharmacological and non-pharmacological interventions in people with schizophrenia

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR	AMSTAR Plus Content	Effect size	Between-group p
Weight reduction									<0.001
	Individual lifestyle counseling	–0.98***	–1.15 to –0.81	14	411	8.3	3.7	Large	
	Exercise interventions	–0.96***	–1.27 to –0.66	4	183	8.0	2.5	Large	
	Psychoeducation	–0.77***	–0.98 to –0.55	8	345	8.0	3.0	Medium	
	Aripiprazole augmentation	–0.73***	–0.97 to –0.48	9	813	8.3	3.0	Medium	
	Topiramate	–0.72***	–1.56 to –0.33	15	783	10.0	3.0	Medium	
	d-Fenfluramine	–0.54***	–1.07 to –0.02	1	16	7.0	6.0	Medium	
	Metformin	–0.53***	–0.69 to –0.38	29	1,279	8.2	3.6	Medium	
	Dietary interventions	–0.50***	–0.66 to –0.34	22	1,576	8.5	3.5	Medium	
	NMDA receptor antagonists	–0.47***	–0.62 to –0.32	5	309	8.0	4.5	Small	
	Metformin + lifestyle intervention	–0.44***	–0.69 to –0.19	3	122	9.0	1.0	Small	
	GLP-1 RAs	–0.44***	–0.60 to –0.28	3	168	9.0	1.0	Small	
	Group lifestyle counseling	–0.39***	–0.54 to –0.23	19	883	8.3	3.7	Small	
	Amantadine	–0.30*	–0.57 to –0.03	3	205	8.5	3.5	Small	
	Cognitive behavioral therapy	–0.37*	–0.55 to –0.18	11	546	8.3	3.7	Small	
	Nizatidine	–0.12*	–0.24 to 0.00	4	357	8.0	3.0	Negligible	
	Ranitidine	–0.24	–0.67 to 0.20	4	260	11.0	1.0	Non-significant	
	Metformin + sibutramine	–0.24	–0.62 to 0.13	1	28	7.0	6.0	Non-significant	
	Orlistat	–0.21	–0.46 to 0.04	1	63	7.0	6.0	Non-significant	
	Rosiglitazone	0.14	–0.21 to 0.52	1	29	7.0	6.0	Non-significant	
	Fluoxetine	0.14	–0.09 to 0.36	2	60	7.0	3.0	Non-significant	
	Dextroamphetamine	0.11	–0.33 to 0.56	1	20	7.0	6.0	Non-significant	
	Switching from olanzapine to quetiapine or aripiprazole	–0.11	–0.23 to 0.03	2	287	11.0	3.0	Non-significant	
	Famotidine	–0.02	–0.48 to 0.43	1	14	7.0	6.0	Non-significant	
Body mass index reduction									<0.001
	Topiramate	–0.56***	–1.54 to –0.22	11	449	10.0	3.0	Medium	
	Individual lifestyle counseling	–0.49***	–0.77 to –0.22	4	202	8.3	3.7	Small	
	GLP-1 RAs	–0.41***	–0.57 to –0.26	3	168	9.0	1.0	Small	
	Cognitive behavioral therapy	–0.34*	–0.67 to –0.07	6	308	8.0	3.7	Small	
	Group lifestyle counseling	–0.28*	–0.54 to 0.00	4	202	8.3	3.7	Small	
	Metformin	–0.41	–0.93 to 0.10	23	1,228	9.0	3.7	Non-significant	
	Exercise interventions	–0.25	–0.56 to 0.06	8	231	8.0	2.5	Non-significant	
	Ranitidine	–0.23	–0.44 to 0.00	5	312	11.0	1.0	Non-significant	

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR	AMSTAR Plus Content	Effect size	Between-group p
	Switching from olanzapine to quetiapine	–0.12	–0.29 to 0.05	1	129	11.0	3.0	Non-significant	
Waist circumference reduction									<0.001
	Aripiprazole augmentation	–1.10**	–1.42 to –0.79	3	174	10.0	2.0	Large	
	Topiramate	–0.69*	–0.93 to –0.45	8	310	10.0	3.0	Medium	
	Dietary interventions	–0.39***	–0.56 to –0.22	11	858	8.5	3.5	Small	
	Lifestyle interventions	–0.37**	–0.60 to –0.13	10	705	8.0	5.0	Small	
	GLP-1 RAs	–0.34***	–0.50 to –0.18	3	167	9.0	1.0	Small	
	Metformin	–0.01	–0.68 to 0.65	12	721	9.0	6.0	Non-significant	
Waist to hip ratio reduction									0.07
	Topiramate	–0.69**	–0.90 to 0.27	5	123	10.0	3.0	Medium	
	Metformin	–0.32	–1.15 to 0.51	3	133	8.0	5.0	Non-significant	
	GLP-1 RAs	0.03	–0.13 to 0.18	3	163	9.0	1.0	Non-significant	
Android/gynoid ratio									
	GLP-1 RAs	–0.03	–0.20 to 0.13	3	131	9.0	1.0	Non-significant	
Visceral fat reduction									
	GLP-1 RAs	–0.37*	–0.46 to –0.06	3	97	9.0	1.0	Small	

*p<0.05, **p<0.01, ***p<0.001

SMD – standardized mean difference, GLP-1 RAs – glucagon-like peptide-1 receptor agonists, AMSTAR – A Measurement Tool to Assess Systematic Reviews mean scores

Physical health outcomes of pharmacological and non-pharmacological interventions

An overview of the different physical health outcomes of pharmacological and non-pharmacological interventions in people with schizophrenia based on the SMDs and the quality of the meta-analyzed studies as assessed by the AMSTAR and AMSTAR-Plus scores is presented in Table 2 (anthropometric results) and Table 3 (blood pressure, metabolic and exercise capacity results).

Body weight

Non-pharmacological interventions

Six meta-analyses investigated non-pharmacological interventions for body weight (78 trials, N=3,944). The mean AMSTAR score was 8.2±0.2 and the mean AMSTAR-Plus Content was 3.3±0.4.

Individual lifestyle counseling was the most effective intervention (SMD=–0.98, 95% CI: –1.15 to –0.81, p<0.001; 14 trials, N=411, I^2=0%, Q=0.5, i.e., large effect), followed by exercise interventions alone (SMD=–0.96, 95% CI: –1.27 to –0.66, p<0.001; 4 trials, N=183, I^2=0, Q=0, i.e., large effect).

Psychoeducation interventions focusing on promoting a healthy lifestyle showed a medium effect (SMD=–0.77, 95% CI: –0.98 to –0.55, p<0.001; 8 trials, N=345, I^2=0, Q=0). This was also the case for dietary interventions alone (SMD=–0.50, 95% CI: –0.66 to –0.34, p<0.001; 22 trials, N=1,576, I^2=94%, Q=15.8).

A small effect was observed for cognitive behavioral therapy focusing on promoting a healthy lifestyle (SMD=–0.37, 95% CI: –0.55 to –0.18, p=0.022; 11 trials, N=546, I^2=0%, Q=0.2) and group lifestyle counseling (SMD=–0.39, 95% CI: –0.54 to –0.23, p<0.001; 19 trials, N=883, I^2=28%, Q=2.8).

With regards to prevention of weight increase, multidisciplinary lifestyle/behavioral counseling showed a medium effect (SMD=–0.69, 95% CI: –0.84 to –0.54, p<0.001; 14 trials, N=694, I^2=0%, Q=1.4).

Table 3 Blood pressure, metabolic and exercise capacity physical health outcomes of pharmacological and non-pharmacological interventions in people with schizophrenia

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR	AMSTAR Plus Content	Effect size	Between-group p
Systolic blood pressure reduction									0.14
	Metformin	−0.24	−0.53 to 0.05	3	176	9.0	4.0	Non-significant	
	Lifestyle interventions	−0.22	−0.49 to 0.05	7	615	8.0	5.0	Non-significant	
	GLP-1 RAs	−0.09	−0.24 to 0.06	3	160	9.0	1.0	Non-significant	
	Dietary interventions	0.05	−0.18 to 0.28	7	655	8.5	3.5	Non-significant	
Diastolic blood pressure reduction									<0.001
	Dietary interventions	−0.39**	−0.56 to −0.22	6	654	8.5	3.5	Small	
	Metformin	−0.24	−0.53 to 0.05	3	176	9.0	4.0	Non-significant	
	GLP-1 RAs	−0.12	−0.28 to 0.03	3	160	9.0	1.0	Non-significant	
	Lifestyle interventions	−0.08	−0.57 to 0.41	3	171	8.0	5.0	Non-significant	
Glucose level reduction									<0.001
	Switching from olanzapine to quetiapine or aripiprazole	−0.71***	−0.85 to −0.58	2	280	11.0	3.0	Medium	
	Metformin	−0.65***	−0.94 to −0.35	17	1,281	9.6	3.7	Medium	
	GLP-1 RAs	−0.39***	−0.54 to −0.23	3	166	9.0	1.0	Small	
	Dietary interventions	−0.37*	−0.69 to −0.05	6	422	8.5	3.5	Small	
	Aripiprazole augmentation	−0.34***	−0.47 to −0.20	10	710	9.3	3.5	Small	
	Topiramate	−0.43	−1.00 to 0.14	6	369	10.0	3.0	Non-significant	
	Lifestyle interventions	−0.27	−0.59 to 0.05	8	688	8.0	5.0	Non-significant	
Insulin level reduction									<0.001
	Rosiglitazone	−0.42*	−0.80 to 0.00	1	29	7.0	6.0	Small	
	Lifestyle interventions	−0.28*	−0.55 to 0.00	6	481	8.0	5.0	Small	
	Metformin	−0.37	−0.81 to 0.07	15	1,007	9.5	4.5	Non-significant	
	Dietary interventions	−0.19	−0.42 to 0.04	11	787	8.5	3.5	Non-significant	
HOMA-IR improvement									<0.001
	Metformin	−0.75***	−1.10 to −0.40	11	680	9.0	6.0	Medium	
	Rosiglitazone	−0.44*	−0.82 to −0.06	1	29	7.0	6.0	Small	
	GLP-1 RAs	−0.08	−0.23 to 0.08	3	163	9.0	1.0	Non-significant	
HbA1c reduction									
	Metformin	−0.38*	−0.69 to -0.07	4	383	9.0	6.0	Small	
	GLP-1 RAs	−0.38*	−0.53 to −0.22	3	166	9.0	1.0	Small	
Triglycerides reduction									<0.001
	Topiramate	−0.68*	−1.23 to −0.13	5	268	10.0	3.0	Medium	
	Lifestyle interventions	−0.37***	−0.54 to −0.20	8	659	8.0	5.0	Small	
	Metformin	−0.28***	−0.45 to −0.11	11	856	9.0	4.0	Small	

Outcomes	Intervention	SMD	95% CI	N. trials	N. participants	AMSTAR	AMSTAR Plus Content	Effect size	Between-group p
	Aripiprazole augmentation	−0.17**	−0.30 to −0.04	9	631	9.5	3.5	Negligible	
	GLP-1 RAs	−0.15*	−0.31 to −0.02	3	166	9.0	1.0	Negligible	
	Dietary interventions	−0.15	−0.30 to 0.00	7	611	8.5	3.5	Non-significant	
Total cholesterol reduction									0.02
	Metformin	−0.51***	−0.81 to −0.20	8	628	9.0	6.0	Medium	
	Lifestyle interventions	−0.35**	−0.54 to −0.16	7	590	8.0	5.0	Small	
	Aripiprazole augmentation	−0.32***	−0.47 to −0.17	10	692	9.3	3.5	Small	
	Topiramate	−0.75	−1.57 to 0.07	3	187	10.0	3.0	Non-significant	
	Dietary interventions	−0.13	−0.29 to 0.03	7	621	8.5	3.5	Non-significant	
HDL-cholesterol elevation									0.007
	Metformin	0.45*	0.00 to 0.90	7	542	9.0	6.0	Small	
	Lifestyle interventions	0.28	−0.16 to 0.72	8	627	8.0	5.0	Non-significant	
	GLP-1 RAs	−0.04	−0.19 to 0.11	3	166	9.0	1.0	Non-significant	
	Topiramate	−0.07	−0.57 to 0.43	4	247	10.0	3.0	Non-significant	
	Dietary interventions	−0.09	−0.24 to 0.06	7	547	8.5	3.5	Non-significant	
	Aripiprazole augmentation	−0.27	−0.44 to 0.01	8	544	9.3	3.5	Non-significant	
LDL-cholesterol reduction									<0.001
	Topiramate	−0.80***	−1.06 to −0.53	4	247	10.0	3.0	Large	
	Lifestyle interventions	−0.36**	−0.60 to −0.12	5	590	8.0	5.0	Small	
	GLP-1 RAs	−0.17*	−0.32 to −0.02	3	162	9.0	1.0	Negligible	
	Metformin	−0.11	−0.31 to 0.09	5	433	9.0	6.0	Non-significant	
	Aripiprazole augmentation	−0.01	−0.18 to 0.15	8	540	9.3	3.5	Non-significant	
Functional exercise capacity	Exercise interventions	1.81**	0.59 to 3.03	1	13	8.0	2.0	Large	

*p<0.05, **p<0.01, ***p<0.001

SMD – standardized mean difference, GLP-1 RAs – glucagon-like peptide-1 receptor agonists, AMSTAR – A Measurement Tool to Assess Systematic Reviews mean scores, HbA1c – hemoglobin A1c, HOMA-IR – homeostatic model assessment of insulin resistance, HDL – high-density lipoprotein, LDL – low-density lipoprotein

Pharmacological interventions

Altogether, 14 meta-analyses investigated pharmacological interventions for body weight (82 trials, N=4,691). The mean AMSTAR score was 8.1±1.3 and the mean AMSTAR-Plus Content was 4.0±1.7.

A medium effect size was observed for aripiprazole augmentation (SMD=−0.73, 95% CI: −0.97 to −0.48, p<0.001; 9 trials, N=813, I^2=68%, Q=6.2), topiramate (SMD=−0.72, 95% CI: −1.56 to −0.33, p<0.001; 15 trials, N=783, I^2=92.7%, Q=13.7), d-fenfluramine (SMD=−0.54, 95% CI: −1.07 to −0.02, p<0.001;

one trial, N=16) and metformin (SMD=−0.53, 95% CI: −0.69 to −0.38, p<0.001; 29 trials, N=1,279, I^2=39.4%, Q=1.6).

A small significant effect was shown by NMDA receptor antagonists (SMD=−0.47, 95% CI: −0.62 to −0.32, p<0.001; 5 trials, N=309, I^2=0%, Q=0.1), GLP-1 RAs (SMD=−0.44, 95% CI: −0.60 to −0.28, p<0.001; 3 trials, N=168, I^2=0%, Q=0.1) and amantadine (SMD=−0.30, 95% CI: −0.57 to −0.03, p=0.03; 3 trials, N=205, I^2=0%, Q=0). Nizatidine showed a negligible effect (SMD=−0.12, 95% CI: −0.24 to 0.00, p=0.02; 4 trials, N=357, I^2=0%, Q=0.4).

No significant weight loss compared to the control condition was observed for fluoxetine (SMD=0.14, 95% CI: −0.09

to 0.36, p=0.22; 2 trials, N=60, I^2=0%, Q=0), dextroamphetamine (SMD=0.11, 95% CI: –0.33 to 0.56, p=0.60; one trial, N=20), ranitidine (SMD=–0.24, 95% CI: –0.67 to 0.20, p=0.05; 4 trials, N=260), famotidine (SMD=–0.02, 95% CI: –0.48 to 0.43, p=0.91; one trial, N=14), the combination of metformin with sibutramine (SMD=–0.24, 95% CI: –0.62 to 0.13, p=0.19; one trial, N=28), orlistat (SMD=–0.21, 95% CI: –0.46 to 0.04, p=0.09; one trial, N=63) and rosiglitazone (SMD=0.14, 95% CI: –0.21 to 0.52, p=0.19; one trial, N=29). Switching from olanzapine to quetiapine or aripiprazole fell also short of statistical significance (SMD=–0.11, 95% CI: –0.23 to 0.03, p=0.06; 2 trials, N=287).

Combined pharmacological and non-pharmacological interventions

The combination of metformin with a lifestyle intervention was explored in one meta-analysis and demonstrated a small effect (SMD=–0.44, 95% CI: –0.69 to –0.19, p<0.001; 3 trials, N=122, I^2=0, Q=0).

Body mass index

Non-pharmacological interventions

Four meta-analyses investigated non-pharmacological interventions for body mass index (42 trials, N=2,157). The mean AMSTAR score was 9.7±0.8 and the mean AMSTAR-Plus Content was 2.2±1.2.

A small effect was observed for group lifestyle counseling (SMD=–0.28, 95% CI: –0.54 to 0.00, p=0.04; 4 trials, N=202, I^2=0%, Q=0), individual lifestyle counseling (SMD=–0.49, 95% CI: –0.77 to –0.22, p<0.001; 4 trials, N=202, I^2=0%, Q=0), and cognitive behavioral therapy focusing on promoting healthy lifestyles (SMD=–0.34, 95% CI: –0.67 to –0.07, p=0.02; 6 trials, N=308, I^2=0%, Q=0.2).

No significant reduction in body mass index compared to the control condition was observed for exercise interventions (SMD=–0.25, 95% CI: –0.56 to 0.06, p=0.11; 8 trials, N=231, I^2=0%, Q=0.4).

Pharmacological interventions

Six meta-analyses investigated pharmacological interventions for body mass index (81 trials, N=4,533). The mean AMSTAR score was 8.1±1.3 and the mean AMSTAR-Plus Content was 4.0±1.9.

Topiramate (SMD=–0.56, 95% CI: –1.54 to –0.22, p<0.001; 11 trials, N=449, I^2=0%, Q=0) had a medium reducing effect, while GLP-1 RAs demonstrated a small effect (SMD=–0.41, 95% CI: –0.57 to –0.26, p<0.001; 3 trials, N=168, I^2=0%, Q=0).

No reduction of body mass index was observed with metformin (SMD=–0.41, 95% CI: –0.93 to 0.10, p=0.10; 23 trials, N=1,228, I^2=90%, Q=20.0), ranitidine (SMD=–0.23, 95% CI: –0.44 to 0.00, p=0.55; 5 trials, N=312, I^2=0%, Q=0), and switch-

ing from olanzapine to quetiapine (SMD=–0.12, 95% CI: –0.29 to 0.05, p=0.16; one trial, N=129).

Waist circumference

Non-pharmacological interventions

Three meta-analyses investigated non-pharmacological interventions for waist circumference reduction (24 trials, N=1,709). The mean AMSTAR score was 9.3±0.5 and the mean AMSTAR-Plus Content was 4.0±0.8.

A small waist circumference reduction effect compared to care as usual was observed for dietary interventions (SMD=–0.39, 95% CI: –0.56 to –0.22, p<0.001; 11 trials, N=858, I^2=0%, Q=0) and multidisciplinary lifestyle/behavioral interventions (SMD=–0.37, 95% CI: –0.60 to -0.13, p=0.002; 10 trials, N=705, I^2=0%, Q=0).

Pharmacological interventions

Seven meta-analyses investigated pharmacological interventions for waist circumference reduction (32 trials, N=1,755). The mean AMSTAR score was 9.3±0.7 and the mean AMSTAR-Plus Content was 2.8±1.6.

Compared with the control condition, the most effective intervention was aripiprazole augmentation (SMD=–1.10, 95% CI: –1.42 to –0.79, p=0.001; 3 trials, N=174, I^2=0%, Q=0, i.e., large effect).

Topiramate had a medium effect (SMD=–0.69, 95% CI: –0.93 to –0.45, p<0.05; 8 trials, N=310, I^2=0%, Q=0). GLP-1 RAs had a small effect (SMD=–0.34, 95% CI: –0.50 to –0.18, p<0.001; 3 trials, N=167, I^2=0%, Q=0). No significant waist circumference reduction compared to the placebo control condition was observed for metformin (SMD=–0.01, 95% CI: –0.68 to 0.65, p=0.97; 12 trials, N=721, I^2=82%, Q=17.1).

Waist to hip ratio

Three meta-analyses investigated the effects of pharmacological interventions on the waist to hip ratio (11 trials, N=419). The mean AMSTAR score was 9.3±0.5 and the mean AMSTAR-Plus Content was 3.3±2.0.

A small waist to hip ratio reduction compared to the control condition was observed for topiramate (SMD=–0.69, 95% CI: –0.90 to 0.27, p=0.009; 5 trials, N=123, I^2=0%, Q=0) and metformin (SMD=–0.32, 95% CI: –1.15 to 0.51, p=0.29; 3 trials, N=133, I^2=0%, Q=0). GLP-1 RAs demonstrated no significant effect (SMD=0.03, 95% CI: –0.13 to 0.18, p=0.39; 3 trials, N=163, I^2=0%, Q=0).

Android/gynoid ratio

Based on data from one meta-analysis, GLP-1 RAs did not outperform the control condition concerning the effect on an-

droid/gynoid ratio (SMD=−0.03, 95% CI: −0.20 to 0.13, p=0.46; 3 trials, N=131, I^2=0%, Q=0).

Visceral fat

Based on data from one meta-analysis, GLP-1 RAs had a small effect in reducing visceral fat (SMD=−0.37, 95% CI: −0.46 to −0.06, p=0.02; 3 trials, N=97, I^2=0%, Q=0).

Blood pressure

Non-pharmacological interventions

Four meta-analyses investigated non-pharmacological interventions for blood pressure reduction (23 trials, N=2,095). The mean AMSTAR score was 9.0±0.0 and the mean AMSTAR-Plus Content was 4.5±0.5.

When looking at dietary interventions alone, a small reduction in diastolic blood pressure versus care as usual was observed (SMD=−0.39, 95% CI: −0.56 to −0.22, p<0.01; 6 trials, N=654, I^2=0, Q=0).

Compared to care as usual, no significant reduction in systolic (SMD=−0.22, 95% CI: −0.49 to 0.05, p=0.11; 7 trials, N=615, I^2=0, Q=0) and diastolic blood pressure (SMD=−0.08, 95% CI: −0.57 to 0.41, p=0.74; 3 trials, N=171, I^2=0, Q=0) was observed for multidisciplinary lifestyle/behavioral interventions.

Pharmacological interventions

Two meta-analyses investigated pharmacological interventions for blood pressure (6 trials, N=336). The mean AMSTAR score was 9.5±0.5 and the mean AMSTAR-Plus Content was 1.5±0.5.

Compared to the placebo condition, no significant reduction in systolic and diastolic blood pressure was observed for metformin and GLP-1 RAs.

Glucose

Non-pharmacological interventions

Three meta-analyses investigated non-pharmacological interventions on fasting glucose levels (16 trials, N=1,256). The mean AMSTAR score was 9.3±0.5 and the mean AMSTAR-Plus Content was 4.0±0.8.

Dietary interventions showed a small glucose level reducing effect (SMD=−0.37, 95% CI: −0.69 to −0.05, p=0.03; 6 trials, N=422, I^2=0%, Q=0).

No significant reduction in glucose levels compared to care as usual was observed for multidisciplinary lifestyle/behavioral interventions (SMD=−0.27, 95% CI: −0.59 to 0.05, p=0.10; 8 trials, N=688, I^2=0%, Q=0).

Pharmacological interventions

Seven meta-analyses investigated the effect of pharmacological interventions on fasting glucose levels (54 trials, N=3,617). The mean AMSTAR score was 9.6±0.6 and the mean AMSTAR-Plus Content was 3.1±1.9.

A medium fasting glucose level lowering effect was found for switching olanzapine to quetiapine or aripiprazole (SMD=−0.71, 95% CI: −0.85 to −0.58, p<0.001; 2 trials, N=280), and for metformin (SMD=−0.65, 95% CI: −0.94 to −0.35, p<0.001; 17 trials, N=1281, I^2=0%, Q=0).

The effect was small for aripiprazole augmentation (SMD=−0.34, 95% CI: −0.47 to −0.21, p<0.001; 10 trials, N=710, I^2=0%, Q=0) and GLP-1 RAs (SMD=−0.39, 95% CI: −0.54 to −0.23, p<0.001; 3 trials, N=166, I^2=0%, Q=0).

No significant reduction in glucose levels compared to the placebo condition was observed for topiramate (SMD=−0.43, 95% CI: −1.00 to 0.14, p=0.14; 6 trials, N=369, I^2=0%, Q=0).

Insulin

Non-pharmacological interventions

Two meta-analyses investigated the effect of non-pharmacological interventions on insulin levels (9 trials, N=1,268). The mean AMSTAR score was 9.0±0.0 and the mean AMSTAR-Plus Content was 4.5±0.7.

Multidisciplinary lifestyle/behavioral interventions had a small effect in improving insulin sensitivity (SMD=−0.28, 95% CI: −0.55 to 0.00, p=0.04; 6 trials, N=481, I^2=0%, Q=0). Dietary interventions alone did not outperform the control condition (SMD=−0.19, 95% CI: −0.42 to 0.04, p=0.10; 11 trials, N=787, I^2=0%, Q=0).

Pharmacological interventions

Five meta-analyses investigated the impact of pharmacological interventions on insulin levels (23 trials, N=1,479). The mean AMSTAR score was 8.4±1.2 and the mean AMSTAR-Plus Content was 4.2±2.2.

Rosiglitazone had a small effect (SMD=−0.42, 95% CI: −0.80 to 0.00, p=0.03; one trial, N=29). Metformin did not outperform the control condition (SMD=−0.37, 95% CI: −0.81 to 0.07, p=0.10; 15 trials, N=1007, I^2=79.2%, Q=4.8).

Homeostatic model assessment of insulin resistance

Pharmacological interventions

Five meta-analyses investigated the effect of pharmacological interventions on homeostatic model assessment of insulin resistance (19 trials, N=1,158). The mean AMSTAR score was 8.4±1.2 and the mean AMSTAR-Plus Content was 4.2±2.2.

Metformin (SMD=–0.75; 95% CI: –1.10 to –0.40, p<0.001; 11 trials, N=680, I^2=0%, Q=0, i.e., medium effect) and rosiglitazone (SMD=–0.44; 95% CI: –0.82 to –0.06, p=0.02; one trial, N=29, i.e., small effect) significantly outperformed the control condition, while GLP-1 RAs did not (SMD=–0.08; 95% CI: –0.23 to 0.08, p=0.10; 3 trials, N=163, I^2=0%, Q=0).

Hemoglobin A1c

Two meta-analyses investigated pharmacological interventions on hemoglobin A1c (7 trials, N=549). The mean AMSTAR score was 9.0±0.0 and the mean AMSTAR-Plus Content was 3.5±3.5.

Metformin (SMD=–0.38; 95% CI: –0.69 to –0.07, p=0.016; 4 trials, N=383, I^2=0%, Q=0) and GLP-1 RAs (SMD=–0.38; 95% CI: –0.53 to –0.22, p=0.02; 3 trials, N=166, I^2=0%, Q=0) outperformed the placebo condition and showed a small effect.

Triglycerides

Non-pharmacological interventions

Four meta-analyses investigated the impact of non-pharmacological interventions on triglycerides (22 trials, N=1,671). The mean AMSTAR score was 8.7±1.1 and the mean AMSTAR-Plus Content was 4.2±0.8.

Multidisciplinary lifestyle/behavioral interventions had a small effect compared with care as usual (SMD=–0.37, 95% CI: –0.54 to –0.20, p<0.001; 8 trials, N=659, I^2=40.0%, Q=1.7). Dietary interventions did not outperform care as usual (SMD= –0.15; 95% CI: –0.30 to 0.00, p=0.06; 7 trials, N=611, I^2=0%, Q=0).

Pharmacological interventions

Seven meta-analyses investigated the effect of pharmacological interventions on triglycerides (36 trials, N=2,564). The mean AMSTAR score was 9.1±1.0 and the mean AMSTAR-Plus Content was 3.6±1.9.

The effect compared with control condition was medium for topiramate (SMD=–0.68, 95% CI: –1.23 to –0.13, p=0.016; 5 trials, N=268, I^2=0%, Q=0), small for metformin (SMD=–0.28, 95% CI: –0.45 to –0.11, p<0.001; 11 trials, N=856, I^2=5%, Q=2.1), and negligible for aripiprazole augmentation (SMD=–0.17, 95% CI: –0.30 to –0.04, p=0.009; 9 trials, N=631, I^2=0%, Q=0) and GLP-1 RAs (SMD=–0.15, 95% CI: –0.31 to –0.02, p=0.04; 3 trials, N=166, I^2=0%, Q=0).

Cholesterol

Non-pharmacological interventions

Ten meta-analyses investigated non-pharmacological interventions for cholesterol levels (56 trials, N=4,288). The mean AMSTAR score was 8.5±1.0 and the mean AMSTAR-Plus Content was 4.5±0.7.

Regarding total cholesterol, multidisciplinary lifestyle/behavioral interventions had a small benefit (SMD=–0.35, 95% CI: –0.54 to –0.16, p=0.003; 7 trials, N=590, I^2=0%, Q=0.3), while dietary interventions alone did not outperform care as usual (SMD=–0.13; 95% CI: –0.29 to 0.03, p=0.10; 7 trials, N=621, I^2=0%, Q=0).

Regarding LDL-cholesterol, multidisciplinary lifestyle/behavioral interventions showed a small benefit (SMD=–0.36, 95% CI: –0.60 to –0.12, p=0.003; 5 trials, N=590, I^2=0%, Q=0.2).

No significant effects on HDL-cholesterol elevations were found with lifestyle or dietary interventions.

Pharmacological interventions

Fifteen meta-analyses investigated pharmacological interventions for cholesterol levels (74 trials, N=5,295). The mean AMSTAR score was 9.4±0.8 and the mean AMSTAR-Plus Content was 3.3±1.8.

Regarding total cholesterol, metformin (SMD=–0.51, 95% CI: –0.81 to –0.20, p<0.001; 8 trials, N=628, I^2=0%, Q=0) demonstrated a medium effect, while aripiprazole augmentation had a small effect (SMD=–0.32, 95% CI:–0.47 to –0.17, p<0.001; 10 trials, N=692, I^2=0%, Q=0). No significant reduction compared to the control condition was observed for topiramate (SMD=–0.75, 95% CI: –1.57 to 0.07, p=0.07; 3 trials, N=187, I^2=0%, Q=0).

Regarding LDL-cholesterol, topiramate (SMD=–0.80, 95% CI: –1.06 to –0.53, p<0.001; 4 trials, N=247, I^2=0%, Q=0) and GLP-1 RAs (SMD=–0.17, 95% CI: –0.32 to –0.02, p=0.04; 3 trials, N=162, I^2=0%, Q=0) outperformed the control condition, although for the latter the effect was negligible. No significant reductions compared to the control condition were found for aripiprazole augmentation (SMD=–0.01, 95% CI: –0.18 to 0.15, p=0.88; 8 trials, N=540, I^2=0%, Q=0) and for metformin (SMD=–0.11, 95% CI: –0.31 to 0.09, p=0.29; 5 trials, N=433, I^2=0%, Q=0.2).

Regarding HDL-cholesterol, only metformin had a small effect (SMD=0.45, 95% CI: 0.00 to 0.90, p=0.049; 7 trials, N=542, I^2=0%, Q=0), while aripiprazole augmentation, topiramate and GLP-1 RAs did not differ from the control condition.

Functional exercise capacity

Based on data from one meta-analysis, exercise outperformed the treatment as usual condition (SMD=1.81; 95% CI: 0.59 to 3.03, p=0.004; one trial, N=13, I^2=0%, Q=0, i.e., large effect).

Adverse drug reactions

Compared to placebo, aripiprazole had higher rates of anxiety (number needed to harm, NNH=8, 95% CI: 5 to 20, p< 0.001)[47] and agitation/akathisia (RR=7.59, 95% CI: 1.43 to 40.18,

p=0.02)[53]. Amantadine was associated with higher rates of insomnia (RR=3.83, 95% CI: 1.41 to 10.38, p=0.008, NNH=9)[57] and abdominal discomfort (quantitative data not provided)[60]. GLP-1 RAs were associated with higher rates of nausea (NNH= 3.8, 95% CI: 2.4 to 9.7, p<0.05)[40]. Among H2 antagonists, famotidine and ranitidine were not associated with higher rates of adverse reactions, while nizatidine had higher rates of dry mouth (RR=4.89, p=0.04; NNH=17, p=0.03) and depression (RR=5.00, p=0.03; NNH=17, p=0.02)[52].

Of the six included meta-analyses of metformin, five reported no difference in rates of adverse reactions[41,46,48,54,62], while one reported higher rates of nausea/vomiting (NNH=16, 95% CI: 10 to 50, p=0.01) and diarrhoea (NNH=6, 95% CI: 3 to 25, p= 0.01)[49]. Although there was no difference in rates of dropouts for orlistat, diarrhoea was the main reason for discontinuation of this drug[48].

Sibutramine plus metformin were associated with an increase of psychotic symptoms. Topiramate was associated with a higher rate of paraesthesia (RR=2.31, 95% CI: 1.17 to 4.56, p<0.05)[39]. There were no data for dextroamphetamine, d-fenfluramine and rosiglitazone. Antipsychotic switching (olanzapine to quetiapine) was associated with higher rates of psychiatric adverse events[54].

None of the meta-analyses reported on adverse effects of non-pharmacological interventions.

Meta-regression analyses

Due to limited data, no meta-regression or subgroup analysis could be performed to examine whether duration of treatment or illness, delivery of the intervention by mental health vs. physical health staff, clinical setting, percent of sessions attended or adherence to treatment could explain variance in the outcomes of interventions.

Study level variance in age and gender did not explain the variance in weight, body mass index or triglycerides levels following pharmacological or non-pharmacological interventions.

DISCUSSION

To our knowledge, this meta-review of meta-analyses is the first to systematically and quantitatively compare the pharmacological and non-pharmacological interventions that have been investigated for improving physical health outcomes in people with schizophrenia. Our data shed new light on the areas where there is or there is not evidence to improve physical health in these people, and should help guide clinical practice and indicate where future research priorities should focus.

When looking at non-pharmacological treatments, individual lifestyle counseling showed a large weight reducing effect. For dietary interventions, the weight reducing effect size was medium, and diastolic blood pressure and glucose level lowering effects were small. Exercise demonstrated large weight reducing effects and large effects on functional exercise capacity, although the evidence for the latter was limited to one small study.

The characteristics of the lifestyle interventions were examined to provide guidelines for future clinical practice. One key finding was that individualized lifestyle interventions showed large effects for reducing body weight, while only a small effect was observed for group-based approaches. Apparently, the benefits of an individual strategy, such as personal advice and attention, meeting patient-specific needs, and a tailored action plan, surpasses the benefits of group-based sessions, such as interpersonal learning, imitative behavior, recognition of similarities in other group members, group cohesiveness and peer support[66]. Future research should, however, explore whether a combined approach, encompassing group sessions while addressing patient-specific needs with a tailored action plan, would be most efficacious.

Cognitive behavioral interventions focusing on weight loss and psychoeducation demonstrated, respectively, small and medium weight reducing effects.

Across 17 pharmacological strategies, 12 outperformed the control condition on various physical health outcomes. No beneficial effects were found for fluoxetine, ranitidine, orlistat, dextroamphetamine and famotidine for any physical health outcome.

Topiramate showed a large effect on LDL-cholesterol, and a medium effect on weight, body mass index, waist circumference and triglycerides. Metformin demonstrated a medium effect on weight, total cholesterol, fasting glucose levels, and homeostatic model assessment of insulin resistance; and a small effect on hemoglobin A1c, triglycerides, and HDL-cholesterol.

Switching from olanzapine to quetiapine or aripiprazole showed a medium fasting glucose lowering effect, while the effect of aripiprazole augmentation on this parameter was small. Aripiprazole augmentation also had a large effect on waist circumference and a medium effect on body weight.

A small weight reducing effect was found for NMDA receptor antagonists. GLP-1 RAs showed small effects on waist circumference, glucose and hemoglobin A1c. Rosiglitazone had a small improving effect on homeostatic model assessment of insulin resistance. Finally, negligible effects were observed for aripiprazole augmentation and GLP-1 RAs on triglycerides, and for GLP-1 RAs on LDL-cholesterol.

In summary, based on the SMDs and the overall high methodological quality of the original meta-analyses (but with lower quality of the meta-analyzed content), individual lifestyle counseling and exercise interventions showed the largest weight reducing effect, followed by psychoeducation, aripiprazole augmentation, topiramate, di-fenfluramine and metformin. With regard to waist circumference, aripiprazole augmentation and topiramate demonstrated the best impact, followed by dietary interventions. Dietary interventions were the only to significantly improve (diastolic) blood pressure.

Switching from olanzapine to quetiapine or aripiprazole and metformin demonstrated the best evidence for glucose level reductions, followed by GLP-1 RAs, dietary interventions and aripiprazole augmentation. Hemoglobin A1c was reduced significantly by both metformin and GLP-1 RAs. Homeostatic model assessment of insulin resistance improved significantly with metformin and rosiglitazone.

Reduction of triglycerides levels were the largest with topiramate, followed by multidisciplinary lifestyle/behavioral interventions, metformin, aripiprazole augmentation and GLP-1 RAs. Total cholesterol was reduced by metformin, lifestyle interventions and aripiprazole augmentation, while LDL-cholesterol reductions were significant with topiramate, lifestyle interventions and GLP-1 RAs. HDL-cholesterol only increased significantly with metformin. Finally, only exercise interventions were meta-analyzed as a means to improve exercise capacity, yielding the largest effect size of all interventions in this review for any outcome (SMD=1.81), although this was based on only one trial.

Taken together, our data offer clinicians some perspective on the potential best methods to address specific physical health issues in people with schizophrenia. In summary, for weight reduction, clinicians should consider individual lifestyle counselling as the top non-pharmacological intervention. There is some evidence that exercise interventions can also help reduce body weight, although we could only include four trials. Dietary interventions also showed promise. Regarding pharmacological interventions, clinicians could consider the adjunctive use of topiramate, though this should be balanced against the possible emergence of paresthesia and cognitive adverse effects (the latter insufficiently studied). Findings for metformin were somewhat heterogeneous, as this medication had a medium effect on body weight but no effect on body mass index, although the latter was likely due to the smaller number of studies examining this outcome. Metformin may be associated with nausea and diarrhea. Further research is required to determine the effects of combining these strategies.

With regards to other markers of metabolic health and cardiovascular risk, there is good evidence that clinicians can use metformin for reducing glucose levels, homeostatic model assessment of insulin resistance and total cholesterol, while there is only a small effect for triglycerides, hemoglobin A1c and HDL-cholesterol. For people with schizophrenia on olanzapine, switching to aripiprazole or quetiapine also shows medium glucose level lowering effects. Of note, only dietary interventions were found to significantly improve (diastolic) blood pressure.

Our data should be considered in the light of some limitations. First, although the included meta-analyses were the most updated and/or largest for each specific strategy and outcome, individual studies published since the last search date of included meta-analyses could not be added. Second, because of limited data for participant characteristics and interventional designs, conducting meta-regression analyses was not possible. Third, while the quality of the methods of the meta-analyses was generally good to very good, the content of

meta-analyzed studies often lacked quality. Fourth, based on the AMSTAR-Plus Content scores, publication bias was problematic for about half of the meta-analyses, potentially overestimating the pooled effect sizes. Finally, the preponderance of studies with small sample sizes in which only large effects were statistically significant presents a challenge.

In conclusion, despite the high risk for physical comorbidities in people with schizophrenia, and the scandal of their premature mortality mainly due to these increased physical health risks, the existing evidence for pharmacological and non-pharmacological interventions to prevent and treat these conditions is still limited. Qualitatively excellent and sufficiently large individual randomized clinical trials are therefore essential.

Additionally, the field should move from study-level to patient-level meta-analyses, as this would provide a more personalized picture of treatment effects for individuals, derived from adequately powered moderator, mediator and subgroup analyses. Comparing pharmacological and non-pharmacological interventions in the same trial would also be desirable, and there is a need for large-scale investigations of combination regimes (i.e., using antipsychotic switching and adjunctive prescribing alongside lifestyle interventions), as well as preventive interventions (i.e., those aiming to prevent physical comorbidities, prior to their development).

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Transdiagnostic dimensions of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)

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The validity of the classification of non-affective and affective psychoses as distinct entities has been disputed, but, despite calls for alternative approaches to defining psychosis syndromes, there is a dearth of empirical efforts to identify transdiagnostic phenotypes of psychosis. We aimed to investigate the validity and utility of general and specific symptom dimensions of psychosis cutting across schizophrenia, schizoaffective disorder and bipolar I disorder with psychosis. Multidimensional item-response modeling was conducted on symptom ratings of the Positive and Negative Syndrome Scale, Young Mania Rating Scale, and Montgomery-Åsberg Depression Rating Scale in the multicentre Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, which included 933 patients with a diagnosis of schizophrenia (N=397), schizoaffective disorder (N=224), or bipolar I disorder with psychosis (N=312). A bifactor model with one general symptom dimension, two distinct dimensions of non-affective and affective psychosis, and five specific symptom dimensions of positive, negative, disorganized, manic and depressive symptoms provided the best model fit. There was further evidence on the utility of symptom dimensions for predicting B-SNIP psychosis biotypes with greater accuracy than categorical DSM diagnoses. General, positive, negative and disorganized symptom dimension scores were higher in African American vs. Caucasian patients. Symptom dimensions accurately classified patients into categorical DSM diagnoses. This study provides evidence on the validity and utility of transdiagnostic symptom dimensions of psychosis that transcend traditional diagnostic boundaries of psychotic disorders. Findings further show promising avenues for research at the interface of dimensional psychopathological phenotypes and basic neurobiological dimensions of psychopathology.

Key words: Psychosis, transdiagnostic phenotypes, schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, general symptom dimensions, specific symptom dimensions, biotypes

The validity of categorical classification in psychiatry is disputed, because the clinical and neurobiological boundaries between disorders are dubious[1-17]. Therefore, there have been calls for alternative approaches to psychiatric classification that are empirically and psychometrically informed through the investigation of neural and psychological mechanisms that transcend current syndromes[3,18,19].

Some projects address the shortcomings of classic psychiatric classification, such as the Research Domain Criteria (RDoC) framework, that integrates many levels of information (from genes to self-report) to further our understanding of basic cross-disorder dimensions of functioning[6,7,20,21]. The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)[22,23] addresses the overlap across psychosis syndromes by examining a broad array of endophenotypes. Recently, the Hierarchical Taxonomy of Psychopathology (HiTOP) consortium has emerged as a research effort that quantifies disorders according to several levels of psychopathology, including spectra, syndromes and symptom components, and characterizes them dimensionally[24]. However, to date, evidence on the link between transdiagnostic dimensions of clinical phenotypes and basic brain-based biomarkers is limited.

In psychosis, the overlap of symptoms across diagnostic categories is especially prevalent, which leads to high comorbidity, as seen with schizophrenia, schizoaffective disorder and bipolar disorder[25,26]. While the Kraepelinian dichotomy regarded dementia praecox/schizophrenia and manic depressive illness as distinct diagnostic entities, recent research has challenged this dichotomy[4,5] and places schizophrenia and bipolar disorder on a transdiagnostic psychosis spectrum[4], with schizoaffective disorder as an intermediate diagnostic category[22]. This overlap may be a result of shared genetic and environmental etiological factors[4,27-29]. Findings also show, however, non-shared genetic and environmental risk factors[4,27,29], which supports the heterogeneity of psychotic disorders.

There remains a dearth of empirical efforts to identify a transdiagnostic phenotype of psychosis. The pentagonal model with five dimensions of positive symptoms, negative symptoms, cognitive disorganization, mania, and depression has received support in previous factor-analytic work[30]. However, recent research has demonstrated evidence for a bifactor model, with a general psychosis factor encompassing non-affective and affective symptoms in patients with schizophrenia, schizoaffective and bipolar disorder, as well as five specific psychosis dimensions of positive, negative, disorganized, manic and depressive symptoms[4,5].

This model was found to better fit empirical symptom data than a pentagonal model[4,5] and a model allowing for distinct

non-affective and affective psychosis factors[31]. It provides support for a psychosis spectrum ranging from bipolar disorder to schizoaffective disorder to schizophrenia. Further, in this bifactor model, shared etiological factors may be associated with the general psychosis factor, whereas non-shared etiological factors could contribute to more specific psychosis dimensions[4, 5]. This approach could also hone the diagnostic process by placing patients broadly on the psychosis spectrum and using the specific symptom dimensions to classify them into specific diagnoses[4,5].

While initial support for the diagnostic utility of these dimensions has been found using the operational criteria system[4], such transdiagnostic models and their diagnostic utility need to be further tested with more detailed measures of psychosis, mania and depression, and cross-validated across a large multisite consortium, such as the B-SNIP. This would allow for improved understanding of the utility of these dimensions not only for diagnosis in research and clinical care, but also in relation to basic neurobiological constructs such as the three recently identified B-SNIP psychosis biotypes[32], in an attempt to connect dimensional psychopathological phenotypes with neurobiological mechanisms[12,14,24].

This study aimed to investigate transdiagnostic dimensions of psychosis spectrum disorders cutting across non-affective and affective psychotic symptoms in patients with schizophrenia, schizoaffective disorder and psychotic bipolar I disorder, using widely established measures for assessing psychosis, mania and depression in the B-SNIP consortium.

We aimed to investigate: a) whether there is a general dimension of psychosis spectrum disorders underlying all affective and non-affective psychotic symptoms; b) whether formation of specific symptom dimensions (positive, negative, disorganized, depressive and manic symptoms) and distinct dimensions of affective and non-affective psychosis is justified in addition to a general psychosis dimension; c) associations of socio-demographic and clinical variables with general, affective, non-affective and specific symptom dimensions; and d) the utility of these dimensions for classifying patients into categorical DSM diagnoses of psychotic disorders and the B-SNIP biotypes.

METHODS

Sample and measures

This study used data collected as part of the multisite B-SNIP consortium[22]. Specifically, patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or psychotic bipolar I disorder (ascertained through the Structured Clinical Interview for DSM-IV Axis I Disorders, SCID-I[33]) were recruited from five sites in the US through regional advertising and from inpatient and outpatient clinics. Patients were in a non-acute symptom state, clinically stable, and provided informed consent.

Participants were assessed extensively for their socio-demographic and clinical features (including age, gender, ethnicity

and DSM diagnosis) with a variety of instruments[22,23]. In this study, the responses of three well-established diagnostic instruments were investigated: the Positive and Negative Syndrome Scale (PANSS)[34], which is a 30-item clinical interview that measures the severity of psychotic symptoms on a scale of 1 to 7; the Young Mania Rating Scale (YMRS)[35], a 11-item measure to assess manic symptoms; and the Montgomery-Åsberg Depression Rating Scale (MADRS)[36], a 10-item measure to assess depressive symptoms. Social functioning was measured using the Birchwood Social Functioning Scale (SFS)[37].

Statistical analysis

Multidimensional item response modeling was conducted with the mirt package of the R environment (i.e., the Metropolis-Hastings Robbins-Monro algorithm[38]) for model estimation. Model fit was examined using the log-likelihood (LL), the Akaike information criterion (AIC), the Bayesian information criterion (BIC), and the sample size-adjusted BIC (SABIC)[39]. Better model fit is indicated by lower values than for the comparison model.

Since there is no definite evidence on the factorial structure of the PANSS, we first analyzed symptom ratings on the PANSS only and compared eighteen previously published factor solutions[5]. We then estimated three alternative item response models: a) a unitary (unidimensional) model with one general factor explaining all symptom ratings to reflect a general dimension of the psychosis spectrum (model A); b) a pentagonal (multidimensional) model to reflect specific positive, negative, disorganized, depressive and manic symptom dimensions (model B); and c) a bifactor model with one general factor independent from five uncorrelated (orthogonal) specific factors (model C; corresponding to the bifactor model in our earlier study[5,40]). Since this is a full likelihood method, data was assumed to be missing at random.

Using the best-fitting model for the PANSS identified in this initial step, we next conducted the primary analysis to investigate general and specific symptom dimensions based on all measures for assessing psychosis, mania and depression (i.e., PANSS, YMRS and MADRS) by comparing models A-C, additionally allowing for factor loadings for YMRS and MADRS items on the general factor as well as on specific manic and depressive symptom factors, respectively. To investigate whether formation of distinct dimensions for affective and non-affective psychosis was justified in addition to one general dimension and five specific symptom dimensions, model comparison of the primary analysis further included: d) a bifactor model with one general psychosis dimension, five uncorrelated specific factors (positive, negative, disorganized, depressive and manic symptom dimensions), and two uncorrelated factors to reflect distinct dimensions of affective and non-affective psychosis (model D); and e) a model with five uncorrelated specific factors (positive, negative, disorganized, depressive and manic symptom dimensions) and two

uncorrelated factors (distinct affective and non-affective psychosis dimensions) but without a general factor (model E). To ensure stable model estimation, the prevalence of responses per category per item was set to be at least 10% of the sample. Due to low coverage in the more severe categories, responses were collapsed into three categories for the PANSS, YMRS and MADRS.

The association of socio-demographic characteristics (i.e., age, gender, ethnicity), DSM diagnosis, and social functioning (as independent variables) with factor scores of general and specific psychosis dimensions (as outcome variables) were analyzed using linear regression.

Multinomial receiver operating characteristic (ROC) analysis[41] was conducted in Stata version 14[42] to investigate the extent to which factor scores of general, affective, non-affective and specific dimensions allow for accurate classification of patients into categorical DSM diagnoses of psychotic disorders and the B-SNIP biotypes.

RESULTS

Basic sample characteristics

Basic characteristics of the total B-SNIP sample (N=933 patients) and the B-SNIP sample used for estimating item response models, that included all response vectors with at least one response to items of the PANSS, YMRS and MADRS (N=860), were almost identical (Table 1). The mean age at interview was 36 years, and approximately half were male. The sample primarily consisted of patients with Caucasian or African American ethnicity. The most common diagnosis was schizophrenia, followed by psychotic bipolar I disorder and schizoaffective disorder.

Table 1 Basic sample characteristics of B-SNIP sample

	Total B-SNIP sample (N=933)	Current B-SNIP sample (N=860)
Age (years, mean±SD)	36.2±12.6	36.1±12.6
Gender, N (%)		
Men	471 (50.5)	433 (50.4)
Women	461 (49.4)	427 (49.7)
Ethnicity, N (%)		
Caucasian	530 (56.8)	496 (57.7)
African American	338 (36.2)	306 (35.6)
Other	61 (6.5)	57 (6.6)
DSM diagnosis, N (%)		
Schizophrenia	397 (42.6)	353 (41.1)
Schizoaffective disorder	224 (24.0)	216 (25.1)
Psychotic bipolar I disorder	312 (33.4)	291 (33.8)

B-SNIP – Bipolar-Schizophrenia Network on Intermediate Phenotypes

Dimensionality of psychotic disorders

Initial analysis of symptom ratings on the PANSS indicated that a bifactor model with one general and five specific factors best matched the B-SNIP sample data (AIC=53209.8, BIC=53920.0, SABIC=53443.7). Building on this initial step, we next compared item response models for symptom ratings on all measures for assessing psychosis, mania and depression (i.e., PANSS, YMRS, MADRS). This showed that the bifactor model with general, non-affective, affective and five specific factors (i.e., model D) provided the best model fit, as indicated by the lowest AIC, BIC and SABIC (AIC=65988.4, BIC=67201.4, SABIC=66391.6) compared with alternative models (Table 2).

Findings on the best-fitting model showed that the largest amount of item variance was explained by the general psychosis dimension (ω_H=0.67), followed by negative (ω_S=0.45), depressive (ω_S=0.38) and positive (ω_S=0.30) symptom dimensions (Table 3).

Overall, factor loadings were heterogeneous in magnitude across symptom dimensions. Factor loadings for the general psychosis dimension were moderate to strong for most positive, negative, disorganized, manic and depressive symptom ratings of PANSS and YMRS items, but weaker for MADRS items (Table 4). The non-affective psychosis dimensions showed the strongest factor loadings for negative and disorganized symptom ratings on the PANSS. Factor loadings for the affective psychosis dimension were strongest for MADRS depressive symptom ratings and, to a lesser extent, YMRS manic symptom ratings. Specific positive and negative symptom dimensions demonstrated moderate to strong factor loadings for most items of the PANSS, whereas factor loadings for the specific disorganized symptom dimension were only weak to moderate at most. Factor loadings for specific manic and depressive symptom factors were strongest for YMRS and MADRS, respectively.

Symptom profiles showed that, compared with psychotic bipolar I disorder, factor scores on the general, non-affective, affective, positive, negative, disorganized and depressive symptom dimensions were higher for schizoaffective disorder (all p<0.05) (Table 4). By contrast, factor scores on the specific manic symptom dimension were lower for schizoaffective than psychotic bipolar I disorder (p<0.001). Further, factor scores on the non-affective, positive, negative and disorganized symptom dimensions were higher, and factor scores on the affective and manic symptom dimensions lower, for schizophrenia than for psychotic bipolar I disorder (all p<0.001).

Table 4 further shows that factor scores for the general psychosis dimension were significantly higher for patients with African American than Caucasian ethnicity (p=0.001) and with lower social functioning (p<0.001). Further, factor scores for the non-affective psychosis dimension were lower in women (p<0.001), but higher in younger patients (p=0.001) and patients with lower social functioning (p=0.023). Factor scores for the affective psychosis dimension increased with increasing age (p=0.017) and were higher in female patients (p<0.001) and

Table 2 Model fit statistics for unitary (unidimensional), pentagonal (multidimensional), and bifactor models of psychosis based on PANSS, YMRS and MADRS symptom ratings

	LL	FP	AIC	BIC	SABIC
Unidimensional (unitary) model (Model A)	−35660.2	153	71626.4	72354.2	71868.3
Multidimensional (pentagonal) model with five correlated specific factors (Model B)	−33615.3	163	67556.5	68331.9	67814.3
Bifactor model with one general factor and five specific symptom factors (Model C)	−33253.0	204	66914.1	67884.5	67236.6
Bifactor model with one general factor, two factors for non-affective and affective psychosis, and five specific symptom factors (Model D)	**−32739.2**	**255**	**65988.4**	**67201.4**	**66391.6**
Bifactor model with two factors for non-affective and affective psychosis and five specific symptom factors (model E)	−33372.9	204	67153.7	68124.2	67476.3

PANSS – Positive and Negative Syndrome Scale, YMRS – Young Mania Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, LL – log-likelihood, AIC – Akaike information criterion, BIC – Bayesian information criterion, SABIC – sample size-adjusted Bayesian information criterion. All response vectors with at least one response were analyzed (N=860). Model D provides the best model fit, as indicated by lower BIC, AIC and SABIC compared to other models.

those with lower social functioning (p=0.020). Older patients had higher factor scores on specific positive and disorganized symptom dimensions. Female patients scored lower on the specific positive symptom dimension and higher on the specific depressive symptom dimension (all p<0.05).

Compared with Caucasian patients, patients with African American ethnicity had higher factor scores on the positive, negative and disorganized symptom dimensions and lower scores on the depressive symptom dimension (all p<0.05). Social functioning decreased as scores on positive, negative, disorganized and depressive symptom dimensions increased, whereas social functioning increased with increasing scores on the manic symptom dimension (all p<0.05).

When we examined the utility of symptom dimensions for classifying patients correctly into categorical DSM diagnoses of psychotic disorders using multinomial ROC analysis, this showed that the proportion of patients correctly classified into diagnostic categories based on factor scores of general, non-affective, affective and specific symptom dimensions (M=0.57, 95% CI: 0.53-0.62) was higher compared with classifying patients by chance (M=0.39, 95% CI: 0.33-0.44).

We next examined the utility of symptom dimensions for accurately predicting the B-SNIP psychosis biotypes. Figure 1 (and Table 4) shows high non-affective, positive, negative and disorganized symptom factor scores for Biotype 1; high affective, manic and depressive symptom factor scores for Biotype 3; and high general symptom dimension (and moderate other symptom dimension) factor scores for Biotype 2.

There was evidence that the proportion of patients correctly classified into B-SNIP biotypes based on factor scores of general, non-affective, affective and specific symptom dimensions (M=0.41, 95% CI: 0.35-0.47) was higher than what would be expected by chance (M=0.35, 95% CI: 0.29-0.41). However, this did not hold for categorical DSM diagnoses (DSM diagnoses: M=0.41, 95% CI: 0.36-0.46; random accuracy: M=0.38, 95% CI: 0.31-0.44).

As can be seen in Figure 2, findings on ROC curves further indicated that patients were classified into B-SNIP biotypes with greater accuracy based on symptom dimensions (AUC=0.87) than DSM diagnoses (AUC=0.68).

DISCUSSION

Main findings

This study provides evidence of a transdiagnostic dimension underlying affective and non-affective psychotic symptoms in patients with psychotic disorder in the B-SNIP consortium. There was further evidence to suggest that formation of distinct dimensions of non-affective and affective psychosis as well as specific psychosis dimensions of positive symptoms, negative symptoms, disorganization, mania and depression is justified.

Transdiagnostic, non-affective, affective and specific symptom dimensions were differentially associated with age, gender, ethnicity and social functioning, and classified patients correctly into categorical DSM diagnoses. Finally, there was evidence on the utility of symptom dimensions for predicting the B-SNIP biotypes with greater accuracy than DSM diagnoses.

Methodological considerations

In the current study, we examined the dimensionality of psychotic disorders in a large sample of patients with schizophrenia, schizoaffective and bipolar I disorder with psychosis. This sample allowed for multidimensional item response modeling to identify variance driven by a transdiagnostic psychosis dimension independent from variance due to non-affective, affective and specific symptom dimensions based on extensively studied measures of psychosis, mania and depression (i.e., the PANSS, YMRS and MADRS).

While further sub-dimensions of mania, depression and other specific symptom dimensions (positive, negative and disorganized symptoms) may have been considered, the focus of the current study was on transdiagnostic, affective/non-affective psychosis and specific symptom dimensions, but not subcomponents of these (e.g., avolition as a subcomponent of the negative symptom dimension; euphoria as a subcompo-

Table 3 Factor loadings in bifactor model with general, non-affective, affective, and five specific symptom factors based on PANSS, YMRS, and MADRS symptom ratings

Items	General	Non-affective	Affective	Positive symptoms	Negative symptoms	Disorganization	Mania	Depression
PANSS								
Delusions	0.55	0.22		0.75				
Hallucinatory behaviour	0.45	0.20		0.48				
Grandiosity	0.54	-0.00		0.20				
Suspiciousness	0.63	0.04		0.32				
Unusual thought content	0.55	0.34		0.53				
Lack of judgment and insight	0.48	0.32		0.15				
Blunted affect	0.09	0.69			0.44			
Emotional withdrawal	0.42	0.28			0.73			
Poor rapport	0.38	0.59			0.40			
Passive social withdrawal	0.30	0.16			0.80			
Lack of spontaneity	0.28	0.69			0.39			
Motor retardation	0.27	0.66			0.38			
Disturbance of volition	0.55	0.30			0.35			
Active social avoidance	0.50	0.02			0.71			
Conceptual disorganization	0.58	0.27				0.44		
Difficulty in abstract thinking	0.24	0.32				0.06		
Stereotyped thinking	0.61	0.40				0.46		
Mannerisms and posturing	0.55	0.50				0.20		
Disorientation	0.57	0.22				-0.11		
Poor attention	0.67	0.27				0.15		
Preoccupation	0.68	0.23				0.34		
Excitement	0.70		0.14				0.32	
Hostility	0.74		0.16				0.09	
Uncooperativeness	0.72		-0.07				0.07	
Poor impulse control	0.76		0.10				0.05	
Somatic concern	0.46		0.16					0.14
Anxiety	0.52		0.38					0.39
Guilt feelings	0.33		0.21					0.26
Tension	0.64		0.22					0.17
Depression	0.40		0.30					0.68

Table 3 Factor loadings in bifactor model with general, non-affective, affective, and five specific symptom factors based on PANSS, YMRS, and MADRS symptom ratings (*Continued*)

Items	General	Non-affective	Affective	Positive symptoms	Negative symptoms	Disorganization	Mania	Depression
YMRS								
Elevated mood	0.31		0.11				0.81	
Increased motor activity-energy	0.28		0.17				0.79	
Sexual interest	0.24		0.15				0.52	
Sleep	0.16		0.88				0.22	
Irritability	0.48		0.44				0.16	
Speech (rate and amount)	0.38		0.22				0.73	
Language-thought disorder	0.51		0.19				0.47	
Content	0.55		0.10				0.35	
Disruptive-aggressive behavior	0.63		0.22				0.27	
Appearance	0.26		0.07				0.16	
Insight	0.38		–0.11				0.12	
MADRS								
Apparent sadness	0.29		0.29					0.74
Reported sadness	0.27		0.36					0.81
Inner tension	0.39		0.52					0.38
Reduced sleep	0.12		0.96					–0.03
Reduced appetite	0.23		0.57					0.26
Concentration difficulties	0.31		0.43					0.37
Lassitude	0.24		0.36					0.56
Inability to feel	0.30		0.39					0.55
Pessimistic thoughts	0.27		0.41					0.60
Suicidal thoughts	0.30		0.39					0.63
ω_H/ω_S	0.67	0.23	0.25	0.30	0.45	0.09	0.20	0.38

PANSS – Positive and Negative Syndrome Scale, YMRS – Young Mania Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, ω_H/ω_S – proportion of item variance explained by general, non-affective and affective factors (ω_H) and specific factors (ω_S)

Table 4 Factor scores of general, non-affective, affective and specific symptom dimensions by socio-demographic and clinical variables

	General	Non-affective	Affective	Positive symptoms	Negative symptoms	Disorganization	Mania	Depression
	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p	B (95% CI), p
Age	-0.00 (-0.01 to 0.00), 0.167	-0.01 (-0.01 to 0.00), 0.001	0.01 (0.00 to 0.01), 0.017	0.01 (0.00 to 0.01), 0.010	0.00 (-0.00 to 0.01), 0.282	0.01 (0.01 to 0.01), <0.001	0.00 (-0.00 to 0.01), 0.401	-0.00 (-0.01 to 0.00), 0.356
Gender								
Women vs. men	0.09 (-0.04 to 0.22), 0.156	-0.33 (-0.44 to -0.22), <0.001	0.26 (0.15 to 0.38), <0.001	-0.16 (-0.27 to -0.05), 0.006	-0.02 (-0.14 to 0.09), 0.683	-0.07 (-0.17 to 0.03), 0.179	-0.02 (-0.13 to 0.09), 0.684	0.22 (0.10 to 0.34), 0.001
Ethnicity								
African American vs. Caucasian	0.22 (0.09 to 0.35), 0.001	0.05 (-0.08 to 0.17), 0.456	-0.04 (-0.17 to 0.08), 0.487	0.23 (0.11 to 0.35), <0.001	0.16 (0.03 to 0.29), 0.013	0.20 (0.09 to 0.30), <0.001	0.00 (-0.11 to 0.12), 0.977	-0.16 (-0.30 to -0.03), 0.017
Other vs. Caucasian	0.02 (-0.24 to 0.28), 0.855	0.00 (-0.24 to 0.24), 0.976	0.02 (-0.22 to 0.26), 0.858	0.22 (-0.02 to 0.45), 0.071	0.12 (-0.12 to 0.37), 0.325	0.06 (-0.14 to 0.27), 0.554	-0.10 (-0.33 to 0.13), 0.377	0.09 (-0.17 to 0.35), 0.489
Social functioning	-0.01 (-0.01 to -0.00), <0.001	-0.00 (-0.01 to -0.00), 0.023	-0.00 (-0.01 to -0.00), 0.020	-0.01 (-0.01 to -0.01), <0.001	-0.01 (-0.02 to -0.01), <0.001	-0.01 (-0.01 to -0.00), <0.001	0.01 (0.01 to 0.01), <0.001	-0.01 (-0.01 to -0.00), <0.001
DSM diagnosis								
Schizoaffective vs. bipolar disorder	0.34 (0.17 to 0.50), <0.001	0.27 (0.13 to 0.41), <0.001	0.15 (0.01 to 0.30), 0.042	0.87 (0.74 to 1.00), <0.001	0.58 (0.43 to 0.73), <0.001	0.46 (0.33 to 0.58), <0.001	-0.30 (-0.48 to -0.15), <0.001	0.29 (0.13 to 0.45), <0.001
Schizophrenia vs. bipolar disorder	0.06 (-0.09 to 0.21), 0.417	0.70 (0.58 to 0.83), <0.001	-0.40 (-0.54 to -0.28), <0.001	0.75 (0.63 to 0.87), <0.001	0.55 (0.42 to 0.68), <0.001	0.53 (0.42 to 0.64), <0.001	-0.24 (-0.37 to -0.12), <0.001	-0.08 (-0.22 to 0.06), 0.286
B-SNIP biotypes								
Biotype 2 vs. biotype 1	0.16 (-0.01 to 0.34), 0.070	-0.13 (-0.29 to 0.04), 0.132	0.19 (0.03 to 0.35), 0.022	-0.09 (-0.25 to 0.07), 0.283	-0.05 (-0.22 to 0.12), 0.574	-0.16 (-0.30 to -0.01), 0.033	-0.01 (-0.16 to 0.15), 0.924	0.11 (-0.06 to 0.29), <0.001
Biotype 3 vs. biotype 1	0.03 (-0.14 to 0.20), 0.712	-0.37 (-0.53 to -0.22), <0.001	0.12 (-0.03 to 0.28), 0.117	-0.26 (-0.42 to -0.11), 0.001	-0.21 (-0.37 to -0.05), 0.010	-0.30 (-0.44 to -0.16), <0.001	0.02 (-0.12 to 0.17), 0.751	0.13 (-0.04 to 0.29), 0.129

B-SNIP – Bipolar-Schizophrenia Network on Intermediate Phenotypes
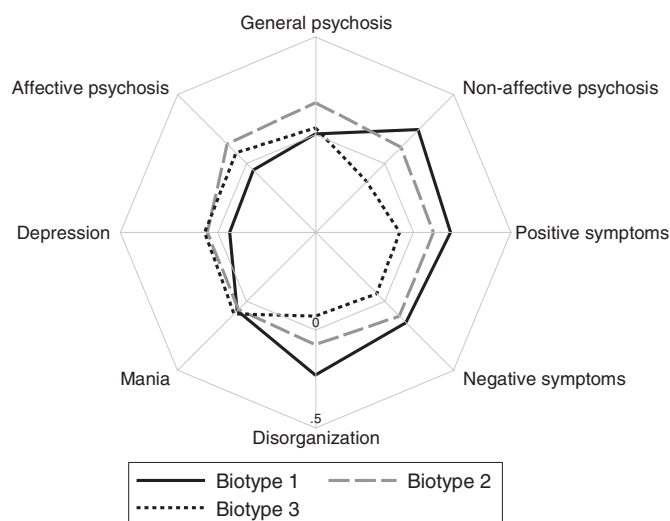
Figure 1 Symptom profiles by the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) biotypes

nent of mania; or anhedonia as a subcomponent of depression). Models to account for these subcomponents would have been difficult to estimate even with the sample size obtained in this study, given the high number of items required and free parameters to be estimated in such models. Further, a more stringent measurement design (e.g., a multitrait-multimethod design) would have been required to disentangle measurement from substantive conceptual variance.

The use of YMRS and MADRS as more detailed measures of mania and depression, however, did allow us to capture a broader spectrum of variance than would have been the case when using the PANSS alone, and hence provided a better reflection of these specific symptom dimensions. They now need to be investigated further to disentangle method and substantive conceptual variance, using comprehensive measures of psychopathology in large samples of psychotic disorders, including psychotic depression.

## Comparison with previous research

Evidence on a transdiagnostic dimension underlying affective and non-affective psychotic symptoms in the current sample of clinically stable patients is consistent with our earlier findings on such a dimension in patients with early and enduring psychosis[4,5]. Reverberating the results of numerous previous studies[30], including our own[4,5], we identified five specific symptom dimensions of positive symptoms, negative symptoms, disorganization, mania and depression.

Our findings move beyond those from previous research in providing evidence of distinct non-affective and affective psychosis dimensions in addition to transdiagnostic and specific symptom dimensions. These were primarily characterized by negative and disorganized symptom ratings (for the non-affective dimension) and depressive and manic symptom ratings (for the affective dimension).

According to the recently proposed hierarchical taxonomy of psychopathology[24], the broad transdiagnostic psychosis dimension may best be interpreted at the level of psychopathological super-spectra or higher-order dimensions, whereas specific symptom dimensions may be classified at lower levels as symptom components, and non-affective and affective psychosis dimensions as psychopathological spectra or syndromes[24].

While the latter may resemble the previously reported thought disorder and internalizing dimensions[2], the extent to which the transdiagnostic psychosis dimension overlaps with, or is independent from, a general psychopathology factor[43] remains to be established. As the evidence base on the dimensionality of psychotic disorders continues to emerge and strengthen, the need for transdiagnostic investigations of psychotic and non-psychotic disorders becomes more pressing to examine important spectra or syndromes across disorders.

Notably, our finding of higher factor scores on the positive, negative and disorganized symptom dimensions and lower scores on the depressive symptom dimension in patients with African American ethnicity compared with Caucasian patients is in line with earlier studies reporting higher positive[44,45], negative[45]
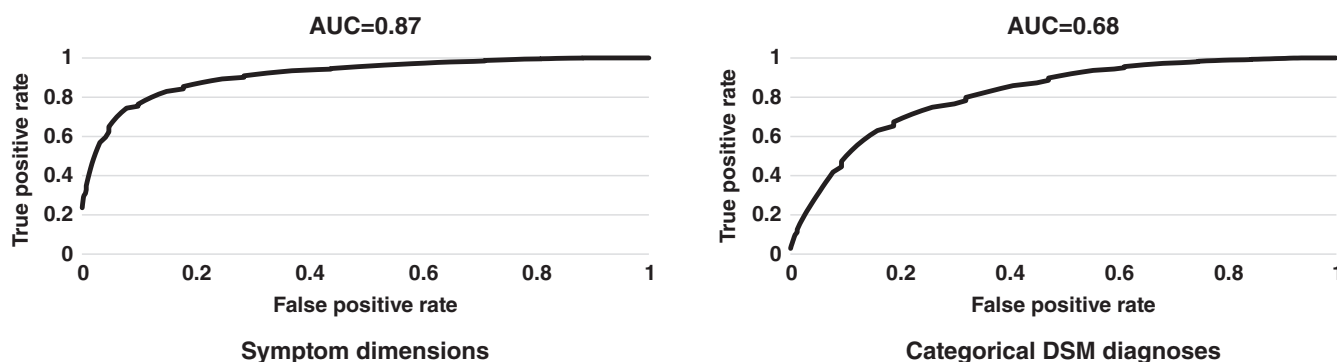
Figure 2 Multinomial receiver operating characteristic (ROC) curves of transdiagnostic symptom dimensions and categorical DSM diagnoses used in the prediction of Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) biotypes (discontinuities due to rounding of the estimated density functions)

and disorganized[44] symptom scores, as well as lower depressive symptom scores[44], in patients with Black African compared with White Dutch and White British ethnicity in the Netherlands[45] and the UK[44], respectively. Our findings additionally showed that factor scores on the transdiagnostic psychosis dimension were higher for African American than Caucasian patients. Overall, the associations between transdiagnostic, non-affective, affective and specific symptom dimensions on the one hand, and age, gender, ethnicity and social functioning on the other, were broadly consistent with the clinical and social epidemiology of psychosis and, therefore, in support of their concurrent validity[17,46-49].

These dimensions, however, need not only be valid but also useful[14]. In order to elucidate the utility of the symptom dimensions we identified here, we investigated their accuracy for classifying patients into categorical DSM diagnoses and the B-SNIP psychosis biotypes. Overall, strong diagnostic utility of the transdiagnostic, non-affective, affective and specific symptom dimensions for allocating patients to DSM diagnoses was demonstrated with the PANSS, YMRS and MADRS, which are all established clinical symptom measures that can be used in both research and routine care. Since our findings on symptom profiles by DSM diagnoses were consistent with operational definitions of current classification systems, these may provide a basis for a psychometrically-informed approach for more accurate classification of patients into these diagnoses.

When we examined the utility of symptom dimensions in relation to the recently identified B-SNIP biotypes[32], this showed that patients were classified into these biotypes with greater accuracy based on symptom dimensions than categorical DSM diagnoses. Findings further showed more pronounced non-affective (Biotype 1), affective (Biotype 3) and transdiagnostic (Biotype 2) dimensional symptom profiles for individual B-SNIP biotypes (Figure 1).

More generally, these findings show how dimensional psychopathological phenotypes can be characterized by connecting them to basic neurobiological constructs and, vice versa, offer valid dimensional psychopathological phenotypes to research into basic neurobiological dimensions of psychopathology such as RDoC[12,20,21,24]. In other words, joining hands rather than viewing phenomenological and neurobiological approaches as separate or competing endeavors may be the way forward.

CONCLUSIONS

Our findings provide new evidence on the dimensionality of psychosis spectrum disorders and, specifically, suggest that a transdiagnostic psychosis dimension, distinct non-affective and affective psychosis dimensions and five specific symptom dimensions best account for symptom data collected using widely established measures in patients with schizophrenia, schizoaffective and bipolar I disorder with psychosis. There was also strong evidence on the utility of these dimensions in relation to categorical DSM diagnoses and B-SNIP psychosis biotypes. This should inform use of dimensional approaches in current diagnostic classification systems.

Findings further show promising avenues for research at the interface of dimensional psychopathological phenotypes and other transdiagnostic approaches such as RDoC focusing on basic neurobiological dimensions of psychopathology[1-17,20,21]. This needs to be extended to transdiagnostic investigations of shared and non-shared genetic and socio-environmental factors of symptom dimensions of psychotic and non-psychotic disorders to examine overlap (and independence) of important spectra or syndromes and more fully map and model the dimensionality of mental disorders as a basis for (more) valid diagnostic classification systems.

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Estimating the risk of PTSD in recent trauma survivors: results of the International Consortium to Predict PTSD (ICPP)

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A timely determination of the risk of post-traumatic stress disorder (PTSD) is a prerequisite for efficient service delivery and prevention. We provide a risk estimate tool allowing a calculation of individuals' PTSD likelihood from early predictors. Members of the International Consortium to Predict PTSD (ICPP) shared individual participants' item-level data from ten longitudinal studies of civilian trauma survivors admitted to acute care centers in six countries. Eligible participants (N=2,473) completed an initial clinical assessment within 60 days of trauma exposure, and at least one follow-up assessment 4-15 months later. The Clinician-Administered PTSD Scale for DSM-IV (CAPS) evaluated PTSD symptom severity and diagnostic status at each assessment. Participants' education, prior lifetime trauma exposure, marital status and socio-economic status were assessed and harmonized across studies. The study's main outcome was the likelihood of a follow-up PTSD given early predictors. The prevalence of follow-up PTSD was 11.8% (9.2% for male participants and 16.4% for females). A logistic model using early PTSD symptom severity (initial CAPS total score) as a predictor produced remarkably accurate estimates of follow-up PTSD (predicted vs. raw probabilities: r=0.976). Adding respondents' female gender, lower education, and exposure to prior interpersonal trauma to the model yielded higher PTSD likelihood estimates, with similar model accuracy (predicted vs. raw probabilities: r=0.941). The current model could be adjusted for other traumatic circumstances and accommodate risk factors not captured by the ICPP (e.g., biological, social). In line with their use in general medicine, risk estimate models can inform clinical choices in psychiatry. It is hoped that quantifying individuals' PTSD risk will be a first step towards systematic prevention of the disorder.

Key words: Post-traumatic stress disorder, prediction, risk assessment tool, trauma survivors, clinician-administered PTSD scale for DSM-IV (CAPS), female gender, lower education, exposure to prior interpersonal trauma, prevention

Post-traumatic stress disorder (PTSD) is the most frequent psychopathological consequence of traumatic events[1,2]. Chronic PTSD is tenacious, debilitating and frequently intractable[3-9]. Early PTSD symptoms are sensitive but non-specific predictors of chronic PTSD[10]. They subside in over 70% of those expressing them[11-13], whilst few initially asymptomatic survivors develop delayed-onset PTSD[14].

Early cognitive behavioral interventions significantly reduce the prevalence of PTSD, and their effect is stable[8,15,16]. These interventions, however, are resource-demanding, and unnecessary for low-risk survivors, whose symptoms subside spontaneously[15,17]. Thus, an accurate individual estimate of survivors' risk for chronic PTSD is a prerequisite for efficient prevention and service planning[18].

Previous studies have had difficulty producing such estimates, due to the multiplicity, complexity and distributional variation of PTSD risk indicators. Additionally, most studies have attempted to predict cases (i.e., who will develop PTSD) rather than produce PTSD likelihood estimates for every participant (i.e., how likely is a person to develop PTSD)[19,20].

Longitudinal studies have nonetheless reported numerous group-level PTSD risk indicators[21,22], such as female gender[23,24], age[23], education[25], ethnicity[26], lifetime exposure to traumatic events[27], and marital status[24]. Several symptom-based case predictions have been developed, consistently performing better than chance[28-31], but unable to build a reliable, personalized risk estimator[32]. Meta-analyses[21,22] and systematic reviews[21,22,33,34] have similarly endorsed group-level risk indicators without a clear path to clinical implementation[34].

Trauma admissions to acute care centers and emergency departments (EDs) offer a first point of contact with numerous survivors at risk. EDs evaluate in the US over 39 million individuals yearly for treatment of traumatic injury[35-39]. Worldwide, road traffic accidents, a mainstay cause of ED admissions, cause an estimated 1.25 million deaths and over 20 million non-fatal injuries yearly[40].

The prevalence of PTSD after ED admissions resembles that seen in survivors who do not require or receive ED care – e.g., 52% incidence of new PTSD among women survivors of interpersonal violence admitted to EDs vs. 51-76% among women surveyed in shelters, domestic-violence clinics and therapy groups[41,42]. The 18-month prevalence of PTSD among drivers admitted to general hospitals after injury-producing car crashes (11%) is somewhat higher than that of car drivers not seen in EDs (7%)[43].

Quantifying individuals' PTSD risk following acute care trauma admission could provide an empirical foundation for mitigating and preventing a major public health issue. Towards that goal, members of the International Consortium to Predict PTSD (ICPP) shared item-level data from ten longitudinal, acute care based studies of the early development of PTSD, performed in the US, Australia, Japan, Israel, Switzerland, and The Netherlands. The data were harmonized, pooled into a single individual participant-level dataset (IPD) and submitted to data analysis.

An analysis of IPD, or mega-analysis, offers a sensible approach to aggregating data across studies[44,45]. Unlike systematic reviews and meta-analyses, mega-analyses do not rely on the original studies' data analytic approaches and reporting perspectives and enable direct estimates of parameters of interest (i.e., predictors, outcomes). This allows data source heterogeneity and subgroup variations to be examined directly, and makes it possible to interrogate the combined data in ways not considered, or impossible, in the component studies, due to their sample sizes or limited population diversity[46,47].

In line with current medical risk assessment practices (e.g., in oncology[48-50], surgery or cardiology[51-54]), we used the ICPP IPD to develop a prediction function that estimates the probability of PTSD given a set of early, observable risk indicators. Following replicated demonstrations of their predictive yield in classification models[55-62], we positioned PTSD symptoms as a key predictor, subsequently enriching the predictive models by including other previously documented and clinically-obtainable risk indicators available in the ICPP dataset (e.g., gender, trauma type, lifetime trauma history).

METHODS

Studies, participants and variables

Using a previously described literature search strategy[63], the ICPP IPD consisted of thirteen longitudinal acute-care based studies of recent trauma survivors conducted in six countries. Investigators obtained informed consent using procedures approved by their local institutional review boards. Item-level data from studies were shared, harmonized (see below) and combined into a pooled dataset. All ICPP studies used the DSM-IV PTSD template to infer PTSD diagnosis and symptom severity. Included in this report are the ten studies[15,64-72] that used the repeatedly validated Clinician-Administered PTSD Scale for DSM-IV (CAPS)[73,74].

Study participants were included if they had an initial CAPS interview within 60 days of the traumatic event, and at least one follow-up CAPS assessment 4 to 15 months (122 to 456 days) after trauma exposure. These criteria were met by 2,473 participants (Table 1). To maximize the utility of prediction, we used the earliest observation for individuals with two early (<60 days) assessments, and the latest observation for those with multiple assessments during follow-up.

PTSD severity and diagnosis

The CAPS quantifies the frequency and severity of each of the seventeen DSM-IV PTSD symptom criteria[73] by assigning to each symptom a 0-4 incremental frequency score and a 0-4 intensity score. A continuous measure of PTSD severity is obtained by adding all individual symptom scores (CAPS total score). A diagnosis of PTSD is determined using DSM-IV PTSD diagnostic criteria of at least one re-experiencing (Criterion B), three avoidance/numbing (Criterion C), and two hyperarousal (Criterion D) symptoms[73]. Following recommendations, a PTSD symptom was deemed "present" if its frequency score was 1 or more, and its intensity score was 2 or more[74,75].

Information on DSM-IV Criterion E (duration of at least one month) and F (clinically significant distress or impairment) were collected in four out of the ten studies. A sensitivity analysis within these studies found very high concordance between diagnoses determined by meeting DSM-IV symptom criteria alone (i.e., criteria B through D) and those obtained using both the symptom criteria and the E and F criteria (sensitivity 0.92, specificity 1.00, Cohen's kappa=0.95). We consequently assumed PTSD diagnosis as present, across studies, based on meeting DSM-IV PTSD symptom criteria alone.

Risk indicators

The study's primary risk indicator was PTSD severity at the initial assessment ($CAPS_0$, range 0-136), with age, gender, ethnicity, educational attainment, lifetime history of trauma exposure, and current trauma type considered as additional predictors.

Differences in data collection and instruments across studies required harmonization of four risk indicators. Educational attainment, which varied by participating countries' schooling systems, was recoded into a binary variable of less than secondary education versus completion of at least secondary education. Recoding participants' lifetime exposure to traumatic events followed a previous demonstration of a strong association between interpersonal trauma and PTSD[76] and included: a) exposure to at least one instance of interpersonal violence (e.g., physical or sexual violence, war or terror), b) in the absence of the former, exposure to at least one instance of non-interpersonal trauma (e.g., road traffic accidents), and c) no trauma exposure. Traumatic events leading to current acute care admission were categorized as motor vehicle accidents, other non-interpersonal events, and interpersonal violence (e.g., assaults).

Data completeness and handling missing observations

$CAPS_0$ data were available for all 2,473 participants. Data on age, gender, and current trauma were available for >99% of the sample. Marital status was missing in 4.5%, education in 6.2%, ethnicity in 12.3%, and prior trauma in 16.8% of the sample.

Table 1 Key participant characteristics in contributing studies and in the total sample

	Hepp et al[64]	Shalev et al[65]	Jenewein et al[67]	Irish et al[68]	Bryant et al[69]	Shalev et al[70]	Shalev et al[15]	Matsuoka et al[71]	Mouthaan et al[72]	Frijling et al[66]	Total sample
Country	SUI	ISR	SUI	US	AUS	ISR	ISR	JPN	NLD	NLD	
Eligible participants (N)	109	27	255	143	825	103	529	92	348	42	2,473
Age (mean±SD)	38.0±13.1	28.4±10.5	41.3±12.9	39.1±15.4	38.7±13.6	31.9±11.7	37.2±12.0	38.8±16.1	44.5±15.7	36.9±14.0	39.0±13.9
Gender (% male)	74	59	67	53	72	60	51	66	61	50	63
High school education (%)	85	NA	83	93	68	90	81	83	78	64	77
Trauma type (%)											
Motor vehicle accident	60	85	31	100	65	82	82	100	65	69	69
Other non-interpersonal	40	7	69	0	29	5	6	0	32	21	25
Interpersonal	0	7	0	0	6	11	12	0	3	10	6
Prior trauma (%)											
None	NA	7	NA	48	27	42	33	45	41	50	29
Non-interpersonal	NA	67	NA	42	61	38	32	28	46	50	40
Interpersonal	NA	22	NA	7	12	19	27	27	13	0	14
Baseline CAPS score (mean±SD)	21.6±15.3	33.8±31.5	13.3±13.0	24.8±22.6	16.9±15.6	25.9±24.7	57.1±24.9	20.0±17.4	20.7±18.5	38.5±19.4	27.4±25.1
Endpoint PTSD (%)	3.7	25.9	4.3	9.1	9.9	19.4	23.6	8.7	5.7	2.4	11.8

CAPS – Clinician-Administered PTSD Scale for DSM-IV, PTSD – post-traumatic stress disorder, SUI – Switzerland, ISR – Israel, US – United States, AUS – Australia, JPN – Japan, NLD – The Netherlands, NA – not available

Table 2 Comparison of participants with complete and incomplete data

Variable	Complete (N=1,682)	Incomplete (N=791)	p
Age (mean±SD)	37.5±14.1	39.0±13.6	0.347
$CAPS_0$ (mean±SD)	21.0±26.0	14.0±22.3	<0.001
Gender, N (%)			
Male	1,028 (66)	533 (34)	<0.001
Female	654 (72)	251 (28)	
Ethnicity, N (%)			
White	1,502 (76)	481 (24)	<0.001
Non-White	180 (97)	5 (3)	
Education, N (%)			
At least secondary education	1,389 (73)	505 (27)	0.057
Less than secondary education	293 (69)	133 (31)	
Marital status, N (%)			
Married/living with a partner	860 (74)	304 (26)	0.005
Single/not living with a partner	822 (69)	375 (31)	
Trauma type, N (%)			
Motor vehicle accident	1,285 (75)	421 (25)	<0.001
Other non-interpersonal	291 (47)	329 (53)	
Interpersonal	106 (77)	31 (23)	
Prior trauma, N (%)			
None	298 (86)	49 (14)	<0.001
Non-interpersonal	626 (87)	93 (13)	
Interpersonal	758 (76)	233 (24)	
Endpoint PTSD, N (%)			
No	1,474 (68)	708 (32)	0.178
Yes	208 (71)	83 (29)	

PTSD – post-traumatic stress disorder, $CAPS_0$ – baseline score on Clinician-Administered PTSD Scale for DSM-IV

Participants missing at least one variable (N=791; 32%) differed from those with complete data (N=1,682) with respect to several risk indicators (Table 2). To address these missing observations, we present analyses in which missing predictors were handled by multiple imputation using chained equations (MICE) performed on the IPD[77]. Ten imputed datasets were created after twenty iterations and the results were pooled using Rubin's method[78]. For completeness, we also computed the results using individuals who had complete data (i.e., without imputation). The results did not differ substantially from those obtained after imputation and are available upon request.

Data analyses

Differences in frequency and severity of risk predictors between participants with and without endpoint PTSD were assessed using Mann–Whitney tests for continuous risk predictors and χ^2 tests for categorical risk predictors. The number of participants endorsing each $CAPS_0$ severity score (smoothed for five-points intervals) was visualized using a histogram, separately for all participants and for those with PTSD at the study's endpoint.

The relatively large sample size in the ICPP dataset enabled us to obtain simple raw estimates of the probability of downstream PTSD for each $CAPS_0$ score. The estimator used was the fraction of PTSD cases among all individuals with a given $CAPS_0$ score, smoothed with a window of five adjacent points.

Logistic regression models were obtained using $CAPS_0$ as the only predictor ($CAPS_0$ model), $CAPS_0$ plus all risk predictors (full model), and $CAPS_0$ plus significant predictors only (significant predictors model). The models' fits were evaluated using the Brier score[79], Efron's R^2, model's predicted-to-raw ratio, and the area under the receiver operating characteristic curve (AUC).

The Brier score[79] measures the accuracy of probabilistic predictions. It expresses the mean standard error of the squared difference between the estimated probabilities and the true PTSD classification. Its range is 0 to 1. A Brier score of zero represents a perfect model and scores of 0.25 or greater signal a non-informative model. Efron's R^2 is the correlation between the predicted probabilities and the smoothed probabilities.

Two options were considered for selecting the regression model's intercept: a fixed effects intercept, where a common intercept is estimated after pooling or "stacking" the data together, and a random effects intercept, where the intercept is allowed to vary by study[44]. Random effects (or stratified approaches) have not been recommended when the prevalence of an outcome varies substantially between studies[44], as is the case with the ICPP studies. Alternatively, it could be hypothesized that heterogeneity in endpoint PTSD prevalence across ICPP studies reflected heterogeneity in the distribution of $CAPS_0$ severity across studies, which was due to variability in studies' sampling routine. Under this hypothesis, ICPP studies could be seen as representing different samplings from a common parent population of acute care trauma admissions.

To evaluate the two models, we compared the predictive fits of the fixed effects and the random effects logistic regressions with $CAPS_0$ as the only predictor, using a bootstrap approach where participants were randomly sampled with replacement, models were obtained, and then predicted probabilities from both models were estimated among the left-out participants. For each approach, the ratio of expected PTSD diagnoses and actual PTSD diagnoses (expected/observed or E/O), the calibration slope $\beta_{overall}$ (the slope from a logistic regression of the predicted probabilities on endpoint PTSD), and the Brier score were obtained. An E/O far from 1 indicates whether the model's intercept, which determines the predicted prevalence of PTSD, is too high or too low, while the calibration slope reflects heterogeneity of the predictor-outcome associations or over-fitting of the data[44]. This process was repeated 100 times with statistics averaged across iterations. A finding of poorer results in the

fixed effects model compared to the random effects model would indicate that the studies were too heterogeneous to be analyzed together after accounting for differences in the distribution of $CAPS_0$.

Differences in the predicted probability of PTSD given different risk factors were estimated by drawing 1,000 posterior simulations of each model's β coefficients, predicting endpoint PTSD at each value of $CAPS_0$ with different risk profiles (e.g., male versus female gender), and evaluating the differences in the predicted probabilities across baseline $CAPS_0$ scores[80].

The selected time window for determining endpoint PTSD status (122-456 days; 4-15 months) maximized the number of ICPP studies included in each time interval. To evaluate whether the substantial width of that time window affected the

results, and to additionally produce an estimate of prolonged PTSD likelihood, we repeated the logistic regressions using participants whose PTSD status was obtained 9 to15 months (273-456 days) after the traumatic events.

RESULTS

Participants' characteristics, risk predictors, and $CAPS_0$ scores

Participants' average age at studies' onset was 39.0±13.9 years. There were fewer female participants (37%) in the sample than males. Motor vehicle accidents (69%) were the most common in-

Table 3 Sample variables stratified by endpoint post-traumatic stress disorder (PTSD) status

Variable	No endpoint PTSD	Endpoint PTSD	Total sample	p
N (%)	2,182 (88)	291 (12)	2,473	
Age (mean±SD)	38.0±14.2	39.0±11.8	39.0±13.9	0.366
$CAPS_0$ (mean±SD)	23.1±21.4	59.6±27.8	27.4±25.1	<0.001
Gender, N (%)				
Male	1,418 (91)	143 (9)	1,561	<0.001
Female	757 (84)	148 (16)	905	
Missing			7 (0.3)	
Ethnicity, N (%)				
White	1,742 (88)	241 (12)	1,983	0.592
Non-White	165 (89)	20 (11)	185	
Missing			305 (12.3)	
Education, N (%)				
At least secondary education	1,698 (90)	196 (10)	1,894	0.051
Less than secondary education	368 (86)	58 (14)	426	
Missing			153 (6.2)	
Marital status, N (%)				
Married/living with a partner	1,035 (89)	129 (11)	1,164	0.780
Single/not living with a partner	1,060 (89)	137 (11)	1,197	
Missing			112 (4.5)	
Current trauma type, N (%)				
Motor vehicle accident	1,485 (87)	221 (13)	1,706	<0.001
Other non-interpersonal	588 (95)	32 (5)	620	
Interpersonal	100 (73)	37 (27)	137	
Missing			10 (0.4)	
Prior trauma, N (%)				
None	308 (89)	39 (11)	347	0.061
Non-interpersonal	641 (89)	78 (11)	719	
Interpersonal	848 (86)	143 (14)	991	
Missing			416 (16.8)	

Comparisons (p values) are between participants with vs. without endpoint PTSD
$CAPS_0$ – baseline score on Clinician-Administered PTSD Scale for DSM-IV

dex trauma, followed by other types of non-interpersonal trauma (25%) and interpersonal trauma (6%). The median time to the initial assessment was 15±16.7 days (range 1-60). The median time to the endpoint assessment was 333±103.1 days (range 122-456).

The prevalence of endpoint PTSD was 11.8% (N=291). Endpoint PTSD was significantly more frequent among female participants (16.4%, compared to 9.2% in males, p<0.001) and among participants who suffered interpersonal trauma compared to a motor vehicle accident or other traumatic events (respectively, 27%, 5% and 13%, p<0.001). No significant differences were observed by ethnicity, marital status, or age (see Table 3).

The histogram in Figure 1 displays the number of participants who endorsed each $CAPS_0$ score, smoothed for a five points interval. As can be seen, the total number of participants declines progressively with increasing $CAPS_0$ scores. The $CAPS_0$ scores of participants with endpoint PTSD, however, span across the instrument's severity range, such that the proportion of those with endpoint PTSD increases with increasing $CAPS_0$ severity.

Prediction of endpoint PTSD

The results from fixed effect models using $CAPS_0$ alone ($CAPS_0$ model), $CAPS_0$ plus all available predictors (full model), and $CAPS_0$ plus significant predictors only (significant predictors model) are presented in Table 4.

The $CAPS_0$ model (plotted in Figure 2 along with its 95% confidence interval) fits well (Efron's R^2=0.230, Brier score=0.080, AUC=0.847), with a very high correlation between the model's predicted probability and the smoothed estimate of conditional probability (r=0.976). Logistic regression using the full model showed that female gender (β=0.309, SE=0.151, p=0.041), having less than a secondary education (β=0.486, SE=0.188, p=0.009), and prior interpersonal trauma (β=0.662, SE=0.238, p=0.006) contributed significantly to the PTSD outcome.

With the inclusion of all risk indicators (full model) or that of significantly contributing factors (significant predictors model), accuracy remained high (respectively, smoothed probability correlation=0.941, Efron's R^2=0.246, Brier score=0.078, AUC=0.855; and smoothed probability correlation=0.946, Efron's R^2=0.246, Brier score=0.078, AUC=0.851). Thus, the addition of female gender, lifetime exposure to interpersonal violence, and less than a secondary education to the $CAPS_0$ model increased PTSD likelihood whilst keeping the $CAPS_0$ model's accuracy.

In the bootstrap analysis comparing the fixed effects logistic model with a random effects model using only $CAPS_0$ as a predictor, the E/O ratio and $\beta_{overall}$ from the fixed effects model (1.01 and 1.00, respectively) were closer to 1.00 than the random effects model (1.14 and 0.75, respectively), and the Brier score was lower on average for the fixed effects model (0.081, SD=0.01) than the random effects model (0.084, SD=0.01). Overall, the fixed effects model seems to estimate the likely number of participants with PTSD at follow-up more accurately, with less heterogeneity or over-fitting, than the random effects model, thereby supporting the pooling of participating studies.

After accounting for the $CAPS_0$ effect, female participants were found to have a maximum of 5% (95% CI: −2% to 12%) higher risk for endpoint PTSD compared to male participants. Moreover, participants with all significant risk factors (i.e.,
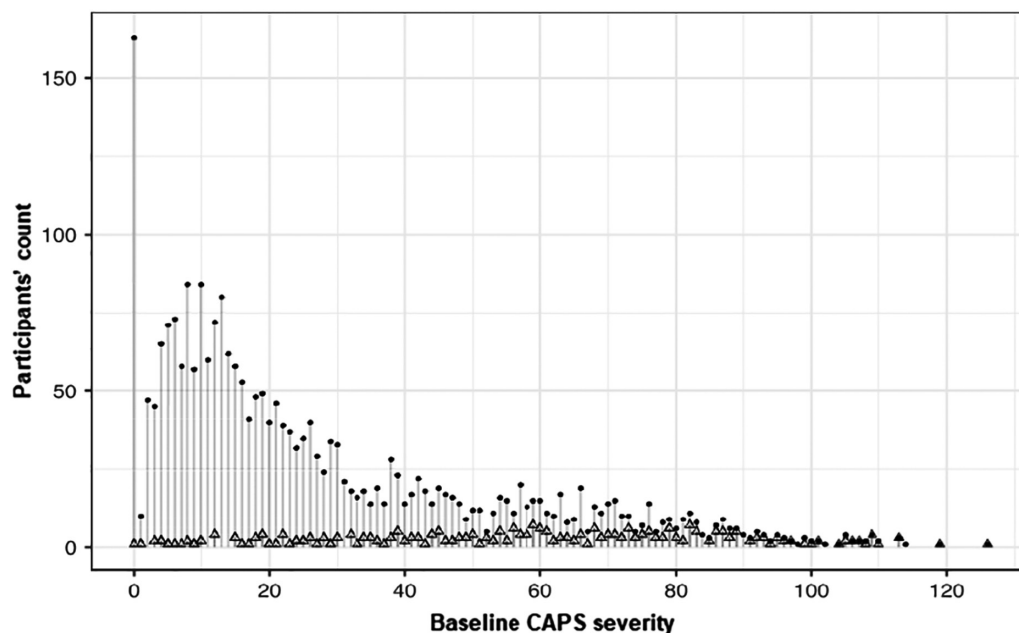
Figure 1 Histogram of participants' baseline PTSD symptoms severity scores ($CAPS_0$ total scores). Dots represent individual participants; overlayed triangles those who subsequently developed PTSD. PTSD – post-traumatic stress disorder, $CAPS_0$ – baseline score on Clinician-Administered PTSD Scale for DSM-IV.

**Table 4** Coefficients (with SE) and fit statistics from the $CAPS_0$, significant predictors and full models

Model parameters	$CAPS_0$ model	Significant predictors model	Full model
Intercept	–3.981*** (0.149)	–4.628*** (0.27)	–4.659*** (0.377)
$CAPS_0$	0.05*** (0.003)	0.051*** (0.003)	0.05*** (0.003)
Female	-	0.307* (0.149)	0.309* (0.151)
Age	-	-	0 (0.006)
Less than secondary education	-	0.483** (0.186)	0.486** (0.188)
Non-White	-	-	0.42 (0.281)
Single	-	-	0.051 (0.164)
Current traumatic event			
Interpersonal	-	-	0.286 (0.255)
Other	-	-	–0.201 (0.222)
Lifetime trauma exposure			
Non-interpersonal	-	0.113 (0.249)	0.128 (0.249)
Interpersonal	-	0.656** (0.237)	0.662** (0.238)
Efron's R^2	0.23	0.246	0.246
Smoothed probability correlation	0.976	0.946	0.941
Brier score	0.08	0.078	0.078
AUC	0.847	0.851	0.855

*p<0.05, **p<0.01, ***p<0.001

$CAPS_0$ – baseline score on Clinician-Administered PTSD Scale for DSM-IV, AUC – area under receiver operating characteristic curve

female gender, less than secondary education, and exposure to prior interpersonal trauma) had a 34% (95% CI: 20-48%) higher risk of PTSD compared to participants without any significant risk factors (i.e., male with secondary education and no prior interpersonal trauma). Estimated probabilities and 95% confidence intervals for endpoint PTSD based on each combination of the significant predictors are provided in Table 5.
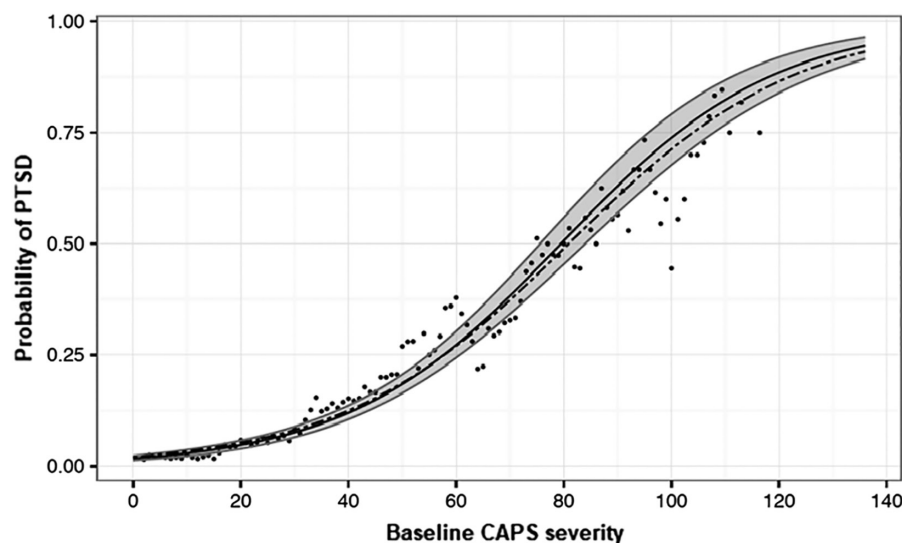
Figure 2 Predicted probabilities of endpoint PTSD conditional on initial ($CAPS_0$) severity scores. The dots represent the raw conditional probability of PTSD at follow-up given the $CAPS_0$ score, smoothed with a kernel of width 5. The solid black line represents the logistic model predicted probability given the $CAPS_0$ score. The gray area is the 95% confidence interval for the prediction model. The dashed line represents the prediction function derived from participants with follow-up observations later than 9 months. PTSD – post-traumatic stress disorder, $CAPS_0$ – baseline score on Clinician-Administered PTSD Scale for DSM-IV.

Table 5 Estimated probabilities (with 95% CIs) of endpoint PTSD diagnosis by incremental values of CAPS$_0$ scores

CAPS$_0$ total score	Probability of PTSD (CAPS$_0$ alone)	Probability of PTSD by gender (CAPS$_0$ plus gender)		Probability of PTSD by gender (CAPS$_0$, plus less than secondary education, and prior interpersonal trauma)	
		Males	Females	Males	Females
0	0.018 (0.014-0.024)	0.017 (0.013-0.023)	0.021 (0.015-0.029)	0.030 (0.020-0.043)	0.041 (0.025-0.061)
5	0.024 (0.018-0.030)	0.022 (0.017-0.029)	0.027 (0.020-0.037)	0.038 (0.026-0.054)	0.052 (0.033-0.076)
10	0.03- (0.024-0.038)	0.028 (0.021-0.036)	0.034 (0.025-0.046)	0.049 (0.034-0.068)	0.065 (0.042-0.095)
15	0.038 (0.031-0.047)	0.035 (0.028-0.045)	0.043 (0.033-0.056)	0.062 (0.044-0.085)	0.083 (0.054-0.119)
20	0.048 (0.040-0.059)	0.045 (0.036-0.056)	0.055 (0.042-0.070)	0.079 (0.056-0.106)	0.104 (0.070-0.147)
25	0.061 (0.051-0.073)	0.057 (0.046-0.069)	0.069 (0.054-0.086)	0.099 (0.071-0.132)	0.130 (0.089-0.181)
30	0.077 (0.066-0.090)	0.071 (0.059-0.086)	0.086 (0.069-0.106)	0.124 (0.091-0.163)	0.161 (0.113-0.220)
35	0.097 (0.084-0.112)	0.090 (0.075-0.106)	0.108 (0.088-0.130)	0.154 (0.114-0.201)	0.198 (0.142-0.265)
40	0.121 (0.106-0.138)	0.112 (0.094-0.132)	0.134 (0.111-0.161)	0.190 (0.143-0.245)	0.241 (0.177-0.317)
45	0.150 (0.133-0.169)	0.139 (0.117-0.162)	0.165 (0.139-0.195)	0.232 (0.177-0.296)	0.290 (0.218-0.375)
50	0.185 (0.165-0.207)	0.171 (0.145-0.199)	0.202 (0.172-0.235)	0.280 (0.217-0.352)	0.345 (0.264-0.436)
55	0.226 (0.201-0.251)	0.208 (0.176-0.241)	0.244 (0.209-0.284)	0.334 (0.262-0.413)	0.404 (0.315-0.500)
60	0.272 (0.243-0.302)	0.252 (0.213-0.292)	0.293 (0.253-0.337)	0.392 (0.312-0.477)	0.466 (0.372-0.564)
65	0.324 (0.289-0.360)	0.301 (0.256-0.349)	0.346 (0.300-0.393)	0.453 (0.367-0.543)	0.528 (0.431-0.626)
70	0.381 (0.340-0.423)	0.355 (0.302-0.410)	0.404 (0.352-0.455)	0.516 (0.425-0.608)	0.590 (0.492-0.685)
75	0.442 (0.394-0.488)	0.413 (0.353-0.475)	0.464 (0.406-0.519)	0.579 (0.484-0.670)	0.649 (0.553-0.739)
80	0.504 (0.450-0.555)	0.474 (0.409-0.540)	0.525 (0.463-0.582)	0.638 (0.544-0.726)	0.704 (0.612-0.787)
85	0.566 (0.507-0.621)	0.535 (0.465-0.604)	0.586 (0.519-0.644)	0.694 (0.602-0.776)	0.754 (0.668-0.829)
90	0.625 (0.564-0.682)	0.595 (0.524-0.665)	0.644 (0.576-0.702)	0.745 (0.657-0.819)	0.797 (0.720-0.864)
95	0.682 (0.619-0.738)	0.653 (0.579-0.722)	0.698 (0.631-0.752)	0.790 (0.708-0.855)	0.835 (0.765-0.893)
100	0.733 (0.671-0.787)	0.706 (0.632-0.772)	0.747 (0.682-0.798)	0.828 (0.754-0.886)	0.867 (0.805-0.916)
105	0.778 (0.719-0.830)	0.754 (0.682-0.816)	0.790 (0.729-0.838)	0.861 (0.795-0.911)	0.893 (0.840-0.934)
110	0.818 (0.763-0.864)	0.796 (0.730-0.853)	0.828 (0.769-0.871)	0.888 (0.830-0.931)	0.915 (0.869-0.949)
115	0.852 (0.801-0.893)	0.833 (0.773-0.883)	0.860 (0.807-0.899)	0.911 (0.861-0.946)	0.932 (0.894-0.961)
120	0.881 (0.835-0.917)	0.864 (0.809-0.909)	0.887 (0.839-0.921)	0.929 (0.887-0.959)	0.947 (0.915-0.970)
125	0.904 (0.864-0.935)	0.890 (0.840-0.929)	0.909 (0.867-0.938)	0.944 (0.908-0.968)	0.958 (0.931-0.977)
130	0.924 (0.888-0.950)	0.912 (0.868-0.945)	0.927 (0.890-0.952)	0.956 (0.926-0.976)	0.967 (0.945-0.982)
135	0.939 (0.909-0.962)	0.929 (0.892-0.957)	0.942 (0.910-0.963)	0.965 (0.940-0.981)	0.974 (0.956-0.986)

PTSD – post-traumatic stress disorder, CAPS$_0$ – baseline score on Clinician-Administered PTSD Scale for DSM-IV. For the full array of risk indicator combinations, see https://wvdmei.shinyapps.io/PTSD_Risk_Lookup/.

Using data from participants whose last follow-up assessment fell between 9 and 15 months from the traumatic event (N=1,359) to fit a CAPS$_0$-only logistic regression yielded similar prediction probabilities (see dotted line in Figure 2), with similar model accuracy (Efron's R^2=0.195, Brier score=0.071, AUC=0.822).

DISCUSSION

The results of this study demonstrate that the probability of meeting PTSD diagnostic criteria 4 to 15 months after acute care admission is reliably modeled by a logistic function of initial PTSD symptom severity. Added to this model, female gender, having less than secondary education, and prior interpersonal trauma were associated with higher likelihood of endpoint PTSD. Other previously documented risk factors, such as age, marital status, and current trauma type, did not improve the prediction over the model that had CAPS$_0$ score as the only predictor. Importantly, the limited margin of error of the resulting risk estimate enables its clinical use to assess PTSD likelihood for each combination of the significant risk indicators.

The limited incremental effect of several known risk factors was an unexpected finding, suggesting that the contribution of

these factors to PTSD likelihood is mediated by their effect on early symptom severity. In line with this view, a previous comparison of PTSD following terror attacks with PTSD following motor vehicle accidents from the same ED has shown that the higher prevalence of 4-month PTSD following terror attacks (38% vs. 19%) was entirely accounted for by survivors' early responses, that included one-week PTSD symptoms, ED heart rate and peri-traumatic dissociation[61].

Our results extend previous findings of an association between high initial PTSD symptoms and being diagnosed with PTSD[55-62] by highlighting the added informational value of likelihood estimates relative to predictive classification. The uniform distribution of PTSD participants initial $CAPS_0$ scores illustrates a barrier to classification models: trauma survivors who ultimately developed PTSD had their initial symptom severity distributed across the entire range of $CAPS_0$ total scores, thereby defying the use of a threshold separating future cases from non-cases. Predicting who will develop PTSD, as much as predicting who among heavy smokers will develop lung cancer, is a difficult task, frequently replaced by likelihood estimates. Classification models have significantly informed our understanding of disorders' etiology and pathogenesis[81-86]. Likelihood estimates, however, may be better suited for quantifying individual risk. As in other areas of medicine[48-54], quantifying risk ultimately informs clinical action.

How can our results inform clinical action? Consider, for example, three female survivors with a $CAPS_0$ score of, respectively, 20, 40, 60; less than secondary education, and lifetime exposure to interpersonal violence. These individuals will have, respectively, 10.4% (95% CI: 7.0-14.7), 24.1% (95% CI: 17.7-31.7) and 46.6% (95% CI: 37.2-56.4) likelihood of chronic PTSD. Male survivors with the same initial scores and no additional risk factors will have, respectively, 2.7% (95% CI: 1.8-4.0), 7.1% (95% CI: 4.8-10.1) and 17.3% (95% CI: 12.2-23.4) likelihood of chronic PTSD. Individuals endorsing the highest $CAPS_0$ score, in both genders, might be seen as requiring clinical attention, e.g., an early intervention. The lower scores may justify a "watchful wait" with additional assessments.

A strength of this study follows from the use of data on a large number of participants from culturally and geographically diverse settings. Each included investigation utilized a longitudinal design, assessed PTSD symptoms shortly after index trauma, and based its appraisal of symptoms and diagnostic status on the repeatedly validated CAPS instrument.

In interpreting our findings, one should nonetheless consider some limitations. First, the time frame to determine PTSD status in our main analyses was 4-15 months, thus very wide. However, when the data were restricted to participants re-interviewed more than 9 months after the trauma, the resulting logistic prediction model remained essentially unchanged. Our prediction is nonetheless calibrated for the wider and earlier time bracket and centered on 333.0±103.1 days (less than a year) from trauma exposure.

Second, several risk predictors were harmonized due to the variety of instruments used by site investigators, which resulted in a loss of granularity. While those harmonized variables (less than secondary education, lifetime interpersonal trauma) have contributed to PTSD probability estimates, results involving recoded variables may miss important predictors' information. Simplified predictors, however, might be easier to obtain in clinical practice and are widely used in predictive models in other areas of medicine (e.g., "smoking yes/no" and "diabetes yes/no" in the Framingham 10 years cardiovascular disease risk score).

Third, the ICPP data display considerable heterogeneity among contributing studies, which, as discussed above, raised methodological concerns about the best approach to pooling the data. We found that the fixed effects model was more accurate than the data source dependent random effects model and thus justified pooling from different studies. We also believe that a fixed effects model is more applicable to new environments, because a global slope and intercept were estimated across studies. Our choice, however, is neither beyond critique nor without significance: large multi-source data compilations are currently evaluated in genetic, genomic and imaging research[87], all of which have to contend with data source heterogeneity resembling the ICPP effort. Our theoretical premise that ICPP studies were differentially sampling subsets of an underlying population of reference (i.e., acute care trauma admissions) should be corroborated by testing the resulting risk assessment tool in newly admitted acute care trauma survivors.

The use of the CAPS structured clinical interview may add some burden on service delivery, and that interview is not properly a screening instrument. Moreover, several PTSD (i.e., CAPS) symptoms (e.g., insomnia, avoidance, inability to recall important aspects of the traumatic event) may not be present during ED admission. The early CAPS, nonetheless, is a robust risk indicator. Future work should explore earlier and simpler screening alternatives, or establish stepwise "screening and prediction" models, starting upon ED admission and predicting the likelihood of expressing high levels of early PTSD symptoms.

Finally, our model was developed using acute care trauma admissions, and as such its implementation in other traumatic circumstances (e.g., prolonged adversities such as wars, captivity and relocation) may require adjustments. Notwithstanding the precise risk estimates for other traumatic circumstances, we believe that early symptom severity has been convincingly shown here to be a major predictor of PTSD risk, and that, as such, its evaluation among individual survivors provides a valid warning and a call for action.

These limitations do not take away from the robustness of our likelihood estimates and their ability to support a personal risk assessment in individual survivors. Similar risk estimate tools are used in other medical domains to support clinical decisions (e.g., for determining breast[48] or lung[49,50] cancer likelihood given risk indicators). The risk estimates provided in this work can be similarly used to trigger action (either watchful follow-up or early intervention) according to local resources and the desirability of prevention.

Quantifying individual risk is a step forward in planning services and interventions, better targeting high-risk individuals,

and ultimately decreasing the burden of PTSD following acute care admission.

APPENDIX

ACKNOWLEDGEMENTS

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The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: time for change?

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The content and organization of mental health care have been heavily influenced by the view that mental difficulties come as diagnosable disorders that can be treated by specialist practitioners who apply evidence-based practice (EBP) guidelines of symptom reduction at the group level. However, the EBP symptom-reduction model is under pressure, as it may be disconnected from what patients need, ignores evidence of the trans-syndromal nature of mental difficulties, overestimates the contribution of the technical aspects of treatment compared to the relational and ritual components of care, and underestimates the lack of EBP group-to-individual generalizability. A growing body of knowledge indicates that mental illnesses are seldom "cured" and are better framed as vulnerabilities. Important gains in well-being can be achieved when individuals learn to live with mental vulnerabilities through a slow process of strengthening resilience in the social and existential domains. In this paper, we examine what a mental health service would look like if the above factors were taken into account. The mental health service of the 21st century may be best conceived of as a small-scale healing community fostering connectedness and strengthening resilience in learning to live with mental vulnerability, complemented by a limited number of regional facilities. Peer support, organized at the level of a recovery college, may form the backbone of the community. Treatments should be aimed at trans-syndromal symptom reduction, tailored to serve the higher-order process of existential recovery and social participation, and applied by professionals who have been trained to collaborate, embrace idiography and maximize effects mediated by therapeutic relationship and the healing effects of ritualized care interactions. Finally, integration with a public mental health system of e-communities providing information, peer and citizen support and a range of user-rated self-management tools may help bridge the gap between the high prevalence of common mental disorder and the relatively low capacity of any mental health service.

Mental suffering has been the topic of intense academic research, covering areas of epidemiology, neurobiology, therapeutics and health services organization, and giving rise to evidence-based practice (EBP) guidelines to achieve symptom reduction that can be used for specific diagnosable mental disorders.

Evidence-based medicine, in the sense of trying to find out what is or is not likely to work for a particular patient, based on what is known, makes eminent sense. However, the way in which it is (mis)understood and applied may give rise to numerous side effects and limitations, including "cookbook" practice, lack of relevance of EBP outcomes for patients, and lack of group-to-individual generalizability[1-3].

The area of mental disorders, and changes therein over time, may be particularly difficult to capture in the conventional medical paradigm of diagnosis and treatment-induced symptom reduction at the group level. Nevertheless, according to the group-level symptom-reduction principle as applied in mental health care, mental suffering comes in the form of universally diagnosable mental disorders which are of bio-psycho-social origin and can be classified on the basis of symptoms.

Treatment guidelines are constructed on the basis of meta-analytic evidence of measurable group-level symptom reduction, the by far most frequently researched mental health treatment outcome[4]. The professionals who populate mental health services have been trained in, first, diagnosing a mental disorder in those who seek help for symptoms and, second, providing treatment as prescribed by EBP guidelines.

As different disorders have different symptoms, the diagnosis-EBP concept as organizing principle of language and activities in mental health service systems has contributed to diagnostic stratification and specialization of institutions, professionals and researchers. Both patients and professionals perceive a need for specialized treatments for specific problems as the primary reference for quality. Consumers know it takes time to search the Internet to find a professional who is adequately specialized in, for example, autism, bipolar disorder, obsessive–compulsive disorder, attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder or borderline personality disorder.

The diagnosis-EBP symptom-reduction model has also impacted health survey technology, which has seen the systematic application of symptom-based diagnostic criteria for mental disorder to the general population, resulting in high rates of disorders like major depression and anxiety disorders, landing them in the top causes of the global burden of disease.

The total estimated global disease burden of mental illness accounts for 21.2% of years lived with disability (YLDs) and 7.1% of disability-adjusted life-years (DALYs)[5], which some have argued may represent a substantial underestimation[6]. Given the limited capacity of the mental health system, data from the population surveys indicating that yearly prevalence

rates of mental disorder are around 20% result in the perception of much morbidity remaining untreated.

Mental health awareness campaigns, attuned to the diagnosis-EBP model, have contributed to growing public awareness of the existence of diagnosable mental disorders and the importance of access to care. Western countries have seen a growing demand for treatments, as evidenced by marked increases in the consumption of psychotropic medications such as antidepressants[7], particularly in young people[8], growing use of easy-access manualized non-pharmacological therapy symptom reduction centres[9], and increasing rates of involuntary admissions in European countries[10].

Within the diagnosis-EBP symptom-reduction perspective, the task of mental health services is to "deliver" specialized treatments that should be made available to those who need them, regardless of whether the setting is "inpatient", "outpatient", or "community" treatment.

Countries traditionally differ widely in what mental health services do and how they are organized[11]. It is assumed that better mental health services are more "evidence-based"[12], and that "routine outcome monitoring" of symptom reduction can be used to assess the quality of the mental health service. However, organizing services around diagnostic specialities providing evidence-based symptom reduction implies that the diagnosis-EBP group-level symptom-reduction principle is valid, relevant and useful, and that group-level findings can be translated to individuals[3]. It also suggests that symptom reduction is a useful construct as a primary focus in the training of professionals and the organization and evaluation of services.

However, "evidence-based" at the group level may not naturally result in patient-centred care at the idiographic level[13] and has been developed around the discourse of diseases and symptoms, rather than resilience and possibilities[14]. The question arises to what degree the training of professionals and the planning and evaluation of mental health services should also be guided by other factors.

In this paper, we discuss a number of issues that are relevant in this regard. First, we consider factors that are relevant to the validity of the diagnosis-EBP symptom-reduction principle in mental health care, such as the trans-syndromal nature of psychopathology and the fact that much of the treatment effect observed in EBP is, in fact, reducible to contextual components that are insufficiently acknowledged and embedded in the service and in the training of mental health professionals.

Second, we discuss to what degree organizing services around higher-order social, existential and somatic outcome domains may potentially be more relevant to users than the traditional focus on evidence-based, group-level symptom reduction. Third, we point out that, while the high prevalence rates of mental disorder indicate the need for a coherent public mental health approach, this has not materialized[15].

In the final part, we discuss the consequences of these issues for the planning, organization and implementation of mental health services, and make suggestions for change. Although most of the discussion is based on practice as developed in high-income countries, we believe that some of the core issues are relevant to mental health services worldwide.

THE ADVENT OF TRANS-SYNDROMAL FORMULATIONS OF PSYCHOPATHOLOGY AND BEYOND

The likelihood ratios for etiology, symptoms, treatment response and prognosis, occasioned by traditional diagnostic categories, are too low to be considered "useful" as required by EBP[16-18]. Mental difficulties represent highly variable clusters of trans-syndromal symptom dimensions that defy detailed diagnostic reduction. The use of 10-15 broad and overlapping "umbrella" syndromes may be sufficient for daily practice[19].

If this is the best "evidence" of classification of psychopathology, should clinicians in mental health services work in diagnostic specialization clinics or "care pathways", or should they bring their expertise to impact on trans-syndromal psychopathology, regardless of formal diagnosis?

The perceived value of diagnostic specialization is driven, in part, by the possibility of delineation of homogenous groups in terms of psychopathology, treatment response and prognosis. However, patients with a diagnosis of major depression are heterogeneous in terms of symptoms, treatment response and prognosis, and show high levels of overlap with patients with other diagnoses in terms of symptoms, treatment response and prognosis.

Explicit exclusion criteria in diagnostic systems create a higher-order factor of what diagnostic categories are *not*[20], resulting in a myriad of categories that may be separately diagnosable but at the same time remain strongly correlated with each other, resulting in confusingly high "comorbidity" rates and poor reliability in clinical practice. This *status quo* often leaves patients as well as referring general practitioners (GPs) confused.

A patient-centred trans-syndromal framework that flexibly combines categorical, dimensional and network approaches may better serve the purpose of maximizing usefulness for different aspects of clinical practice. However, current diagnostic specialization in research and clinical practice has given rise to a cultural and structural balkanization[21] that cannot be readily dismantled, because the professional identity of clinicians tends to fuse with these specializations. Changing the *status quo*, i.e. bringing practice more in line with available scientific evidence, may thus result in an identity crisis and resistance to what may be seen as a non-professional sham.

In order to constructively deal with this issue, the DSM-5 project attempted to introduce the notion of trans-syndromal dimensions across the different chapters, which would have opened the way to a new form of trans-syndromal clinical practice and research. Unfortunately, the project proved too complex and only resulted in some trans-syndromal dimensions being included in one of the appendixes. These, however, were not truly trans-syndromal, in the sense of cutting across chapters, as all were about within-chapter dimensional variation[22].

In contrast, the US National Institute of Mental Health (NIMH) formulated a range of trans-syndromal dimensions of behaviour and functioning, with the specific aim to link dimensional variation to biology in research, but these were not meant for use in clinical practice (Research Domain Criteria, RDoC project)[23].

The trans-syndromal approach thus remains an attractive option to bridge the cultural and structural silos that have been built around correlated diagnostic categories, but requires more work. It may be productive to develop a trans-syndromal framework of mental suffering that not only revolves around symptoms, but also focuses on aspects of behaviour, functioning, psychological traits, somatic factors, social factors and environmental exposures, depending on clinical diagnostic relevance and user preference. This may be productively combined with a limited number of "umbrella" diagnostic categories at the level of the broad syndrome (e.g., psychosis spectrum syndrome)[19].

SERVICE AND RELATIONAL EFFECTS AS "INVISIBLE" COMPONENTS OF TREATMENT

Just as there is methodological and statistical doubt as to what degree even a well-established psychotherapy like cognitive-behavioral therapy (CBT) is at all effective, doubt has been voiced as to what degree medications like antidepressants have real effects[24-29].

While recent meta-analytic work suggests that antidepressants may have a small effect on symptoms in the short term[30], important factors – like bias due to withdrawal symptoms in the placebo group and differential expectations due to the lack of use of active placebo in the comparison with side effect-rich antidepressants – remain unaddressed. In fact, one of the factors underlying the weak effects of psychotherapy and antidepressants as compared to placebo is the issue of expectations, which evidence suggests may be one of the key elements driving change in states of mental ill-health[31,32].

As effect sizes of psychotherapy are small, at least in analyses that take into account the many sources of bias and factors impacting quality[26], the likelihood of meaningful differences between different types of psychotherapy logically must be similarly small, likely remaining below the threshold of statistical resolution and clinical relevance. This may explain why, despite much research and debate, there is no meta-analytic evidence that well-researched psychological treatments for common disorders like depression, anxiety, post-traumatic stress disorder and borderline personality disorder show clear and clinically relevant differences from each other in effect size, regardless of the level of complexity or underlying anthropological rationale. Instead, meta-analyses reveal the same (small) effects across different treatment approaches[33-36].

Similarly, there is therapeutic equivalence between different classes of antidepressant medications[37] and, although many guidelines suggest that clozapine may be more effective than other antipsychotics in treatment resistant psychotic disorder, the evidence on which this is based is not strong[38]. However, clozapine may be more effective than other antipsychotics in different outcome areas, which have been researched insufficiently but may stand out clinically.

Where it has been examined, equivalence also applies across pharmacological and non-pharmacological approaches, for example in depression[39]. Thus, while some specific differences between treatments may exist in low-prevalence subareas of mental health, for example in anorexia nervosa[40] and obsessive-compulsive disorder[39], findings more often point to equivalence within and between pharmacological and non-pharmacological treatment approaches for common mental disorders[41].

Findings of equivalence of small effects across pharmacological and non-pharmacological treatments may be, first, suggestive of underlying heterogeneity, in the sense of some people responding only to treatment A and others only to treatment B, and all research populations representing a mix of these two and other types. Although this may be relevant, for example in the case of genetic variation underlying differences in response to pharmacological treatment, no reliable markers of such heterogeneity in response have been identified, despite much research. Also, in psychotherapy research, leaving out critical theoretic components of the therapy does not impact effect size[42,43].

A stronger, although not mutually exclusive, case can be made for a second explanation of apparent equivalence, i.e., that it is not only the specific treatment itself (the "what"), but also generic aspects of treatments (the "how") which impacts outcome. In favor of the latter is evidence of small but significant "clinician" random effects, meaning that, under the overall small effect of specific treatments, reside differences between the particular patient-clinician mix, some being more conducive to change than others, not just in psychotherapy research[44] but also, in the rare instances where it has been examined, in pharmacological research[45].

Thus, if the "how" of treatment contributes to improvement, what is it? Research suggests that two aspects of the context of treatment may be important: a general background service-level effect and a patient-clinician relational effect at the level of the therapeutic ritual. These service-level and patient-clinician level contextual effects are discussed below.

Service-level contextual effects

Meta-analyses have shown that the placebo response in trials of pharmacological treatments such as antidepressants[46], antipsychotics[47,48] and pain medications[49] has risen over time. One of the factors that may contribute to the rise in placebo response is the change in trial context and design[50]. If the standard care context amounts to relative "neglect" by poorly developed services, placebo effects will approach natural course, and be lower compared to placebo effects in the context of well-developed supportive services, confounding comparisons between time periods and countries[51]. Thus, the early trials are more likely to reflect the comparison between natural course

and active treatment, whereas later trials reflect a more "mature" comparison between placebo in the context of general supportive treatment and the specific psychotropic agent.

The same contextual issue regarding the role of standard care may impact trends in psychotherapy research over time, given meta-analytic evidence that the efficacy of psychotherapeutic treatments like CBT[52] has become progressively smaller over time. This is likely related to early trials more often including a "waitlist" comparison – amounting to a comparison with natural course – whereas later trials more often included a more active comparison treatment. As a result, a temporal effect will emerge in meta-analyses, given evidence from CBT psychotherapy trials that comparison with waiting-list conditions yields a substantially higher effect size than against care as usual or pill placebo[25].

These temporal effects are important, as they appear to suggest that having interactions with an active mental health service brings about improvement in the same way as specific treatments do. It may be productive to further study this issue, as an optimized "general service effect" can impact many patients at the same time in a very cost-effective fashion.

Patient-clinician level contextual effects

In conditions such as depression, effects do not appear to differ between treatment approaches, whereas they do vary as a function of the specific patient-clinician mix. This observation has inspired an ongoing debate on the degree to which so-called "common factors" contribute to the observed phenomenon of equivalence of treatments[31]. Common factors have to do with non-specific relational and ritual elements in the encounter between patient and clinician, such as offering an explanatory model, proposing a theory for change, raising expectations, and inspiring patient engagement, all within the context of a productive therapeutic relationship characterized by empathy, an active and caring attitude, and the capacity to motivate, collaborate and facilitate emotional expression.

The existence for most mental health problems of a 30-40% "placebo" effect, in the sense of being offered some kind of therapeutic ritual, and the fact that specific evidence-based treatments only create a small additional effect, is an argument in favor of the existence of common factors.

Evidence for common factors comes from research, including some fascinating examples of experimental studies[53,54], showing the effect of expectations[32,54], the impact of therapeutic relationship[55], and therapist effects[44]. Other support comes from meta-analyses showing that: a) in depression, having the same number of psychotherapy sessions over a shorter period of time is more effective, suggesting an effect of the intensity of human contact[56]; b) leaving out critical theoretic components of psychotherapy does not impact effect size[42,43] (although adding components may yield a small increase)[43]; c) comparisons between active treatments and structurally inequivalent placebos produce larger effects than comparisons between active treatments and structurally equivalent placebos[57].

Furthermore, in depression, the rise in placebo response over time has been accompanied by a similar rise in antidepressant response[46]. This suggests that, at least for depression, the "placebo" response is additive and part of the therapeutic response, in contrast with other areas of medicine, such as oncology, where placebo response constitutes a negligible part of the therapeutic effect (see Figure 1).

Meta-analyses of depression trials of antidepressants and transcranial magnetic stimulation also found a positive correlation between the rate of placebo response and active treatment response in trials[58,59]. These data are compatible with the notion that the response to active treatment in depression is "added" to the placebo response or that the placebo response is an integral component of the treatment response. In other words, common factors that are part of the general therapeutic ritual may form the basis on which antidepressant treatment can build.

This proposition is supported by research showing that a "relationally warm" treatment works better than a "cold" treatment[53] and by studies documenting that pharmacological and non-pharmacological approaches reinforce each other in the sense of their combined effect being additive, at least in depression and anxiety disorders[60]. In one trial, a simple focus on positive affect monitoring and feedback on the course of
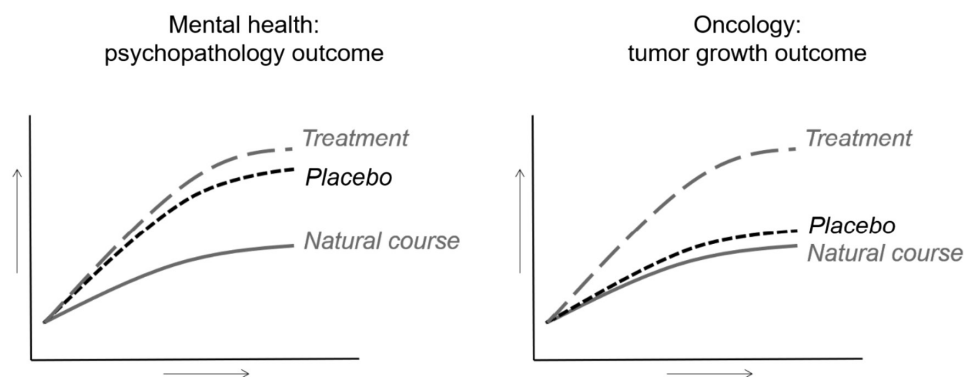
Figure 1 Contrasting placebo components of therapeutic effect (vertical) over time (horizontal) in psychiatry and oncology

positive emotions was sufficient to make the antidepressant treatment effective[61].

THE RELATIVE DISCONNECT OF DIAGNOSIS-EBP SYMPTOM-REDUCTION INTERVENTIONS

The delivery of evidence-based treatments focusing on symptom reduction should ideally serve the higher-order goal of social participation and existential integration ("recovery"). However, diagnosis-EBP symptom-reduction interventions, if they are available at all, are typically delivered by professionals who work in relative dissociation from the existential, social and medical needs of the patient[62,63]. For example, a patient may receive a course of CBT for hearing voices, be prescribed antipsychotic medication by a psychiatrist, see a social worker for help with housing and benefits, and visit his general practitioner to receive medication for diabetes. In daily life, however, he may struggle with social isolation, lack of meaning, feelings of hopelessness and massive weight gain.

The different professionals involved in his care may know of each other's existence, but have different schedules and work across different departments and bureaucracies, making it difficult to integrate their efforts. Most importantly, existential needs such as loneliness, meaninglessness and hopelessness are not addressed. While different countries and regions have different levels of integration of care, anecdotal evidence suggests that the situation as depicted here is not rare[62,63]. Below, we discuss the issue of integration with social, existential and medical needs in more detail.

Integration with user knowledge and a focus on existential values

The diagnosis-EBP symptom-reduction perspective was developed in the context of a bio-psycho-social model of mental health difficulties. Several novel developments, however, suggest that the bio-psycho-social model requires extension with an existential component, thus reinventing itself as a bio-psycho-socio-existential framework in which the existential component is central.

First, the concept of "health" as absence of disease is risky, as it may result in "too much medicine, too little care"[64]. This traditional concept, therefore, is increasingly supplanted by the notion that health is about the ability to adjust to and manage medical, social and mental challenges in order to pursue life goals that are meaningful to the person[65]. In other words, restoration of health is not the goal, but rather the means to enable the patient to find and pursue meaningful goals.

Accordingly, patient existential values are becoming central in the practice of a novel "era 3" of evidence-informed (interventions support higher-order social and existential outcomes) rather than evidence-based (symptom reduction constitutes the core goal) medicine[66,67]. In this scenario, doctors naturally focus on existential values, practicing shared decision making in the sense of adjusting interventions to the existential needs of the patient[68,69].

Of course, similar developments have been occurring in mental health care, where users over the last 40 years have become increasingly vocal in asking for more sensitivity on the part of professionals for the existential domain of personal recovery, in the sense of helping people to overcome and adjust to the often extreme experience of mental vulnerability and find meaningful goals to live a fulfilling life, beyond the diagnosis[70].

Values associated with the existential recovery perspective are connectedness, empowerment, identity, meaning, hope and optimism[71,72], all reflecting the work of reinventing and reintegrating oneself and one's life after experiencing the existential crisis that comes with mental illness.

While the diagnosis-EBP symptom-reduction perspective is not incompatible with these existential notions, there are clear challenges in bringing the medical "symptom reduction" and the existential "meaningful life" perspectives together in one service[73,74]. Although research suggests that it is possible to achieve growth in the existential domain in patients attending a psychiatric service[75], the level of organizational readiness of traditional psychiatric services may be a rate-limiting factor in bringing the two perspectives together[76,77].

The diagnosis-EBP model and the existential domain are complementary from a treatment perspective, as the former has its focus on the psychometric outcome of symptom reduction and the latter on the personal process of resilience. Working on resilience means a focus on things like being connected to other people, narrative development, positive emotions, sense of purpose, material resources and acceptance, requiring novel service initiatives such as a "recovery college", structural peer support, "housing first", "individual placement and support", and "open dialog", which can be difficult to implement in traditional mental health services[78-83].

Integration of mental, medical, substance use and social care

Perhaps the most persistent unresolved need for people with complex mental health difficulties is the lack of alignment between social care and medical care on the one hand, and mental health care and, if organized separately, addiction services on the other[84].

People with severe mental health difficulties are more likely to experience a complex social situation characterized by poverty, social isolation, exclusion, unemployment, stigma and housing needs, and more likely to die prematurely, smoke, develop obesity, diabetes, addictions and other chronic conditions. Meeting these needs is difficult, as they require life style changes for which care is allocated to different services. Optimal management involves collaboration between complex bureaucracies managing separate budgets[85], giving rise to a range of barriers[86]. The available evidence suggests that the simple

integration of budgets may not be enough to impact outcomes[87] and that the area of mental health care can learn from other health areas where such integration has been attempted[88,89].

For example, integration of social and mental health care can focus on the creation of recovery-oriented social enterprises as a key component of the integrated service[90]. A user-driven recovery college may be set up as a social enterprise using social care funding, thus in effect paying users to help other users achieve recovery outcomes.

Successful integration of social, existential, mental, substance use and somatic care needs to take into account the different echelons of clinical, service-level and public health approaches[91]. Another factor is scale. It has been suggested that the scale on which integration is attempted is critical, as integration may be best served by focusing on local networks in a relatively small area as a model for organizing mental health services[92]. Working together in local networks has the advantage of having first-name-basis interactions, creating opportunities for flexible needs-based consultation and joint projects in the area.

A small-scale area may be around 15,000 population with five-ten GP practices, allowing for collaboration in an "enhanced primary care" model of mental health services[93,94].

THE PUBLIC HEALTH PERSPECTIVE

The yearly prevalence of diagnosable mental suffering is around 20%, whilst mental health services have the capacity to treat 4-6% of the population in a given year. These figures indicate that there is considerable scope for public mental health, in the sense of freely accessible sources of information, self-management and peer support e-communities.

A public mental health problem cannot be tackled by pushing the diagnosis-EBP symptom-reduction system to absurd limits, as evidenced by concern about overprescription of antidepressants[95] and ADHD medication[96], and increasing rates of involuntary admissions in European countries[10].

Although much has been written about the need for a well-developed system of public mental health alongside the traditional one-on-one mental health care system, countries have been slow to implement any of this[15,97].

Nevertheless, in many countries, there is a growing informal network of online, self-help e-communities for people with a variety of mental health problems, for example, eating disorders, obsessive-compulsive disorder, psychosis and post-traumatic stress disorder. Although some of these have millions of visitors each year, and many increasingly offer forms of e-health and m-health solutions that can be used for self-management, they lack stable funding, even though it is increasingly recognized that they form the backbone of an informal public mental health system which interacts with the traditional mental health care system[98].

A minor shift in funding from one-on-one care in the traditional diagnosis-EBP symptom-reduction mental health care system towards a public mental health network of complementary e-communities offering information, self-help and peer support, including a community-rated market of e-health and m-health tools that people help each other using, would bring a welcome balance.

E-communities are not diagnosis-specific, but vary in their initial presentation so as to offer people choice in seeking help for what is most compatible with their experience. They can not only help people who are not in contact with services, but also offer self-help and help in navigating the mental health service system for people already in care[99].

CONSEQUENCES FOR MENTAL HEALTH SERVICES

While the specialist diagnosis-EBP symptom-reduction principle is dominant or even normative in the way mental health services are organized and evaluated, the question arises to what degree it is relevant to patients. While this model has been productive, there is evidence that it is less than optimally connected to patient primary needs in the social and existential domains.

The expectation that the most vulnerable individuals would naturally reconnect with these domains, when their symptoms resolve, should not be taken for granted. In contrast with common mental health problems, the circularity (reversal of cause and effect) of symptoms, participation and existential domains is the core of the new "severe mental illness" definition developed by a large consensus group in the Netherlands[100].

The multitude of randomized controlled trials may have served as trees through which the wood of the larger question, i.e. what patients actually require, could not be seen. In addition, while the diagnosis-EBP symptom-reduction model is framed in terms of technical skills and specialized knowledge, the evidence also indicates that a good case can be made for the relational and healing components of ritualized interactions mediating clinical improvement.

Thus, the larger question may be how an effort can be organized to make mental health services more relevant to those who need them, and more in line with a critical analysis of scientific and experiential knowledge. This would require taking a fresh look at both content and organization of services, based on the current level of knowledge (see Table 1).

If one were to design a mental health service from scratch, taking into account these developments, it is likely that the new service would bear only moderate resemblance to the current system of diagnosis-EBP symptom-reduction based specialist services. It has been suggested that the concept of recovery may serve as the organizing and integrating principle for the novel mental health service[101].

If integration and connectedness are important values, it may be more logical to create the mental health service on a relatively small scale (covering around 15,000 population), so as to have an authentic "look and feel" of a local healing community fostering connectedness and strengthening resilience

Table 1 Factors in the design of a mental health service

- Mental difficulties represent highly variable clusters of trans-syndromal symptom dimensions that defy detailed diagnostic reduction. Use of 10-15 broad syndromes may be sufficient for daily practice.

- The model of "specialist" care in diagnostic silos may be less useful than a model of applying professional skills in a trans-syndromal fashion.

- User knowledge describes the prime importance of working on the process of strengthening resilience in the social (e.g., connectedness, social resources) and the existential (e.g., meaning, identity, sense of purpose) domain, rather than symptom reduction *per se*.

- The context of the mental health service contributes to clinical change, in the form of a "general service effect", suggesting the importance of setting and design.

- Critical analysis of professional knowledge indicates that specialist "evidence-based practice" effects may be overly attributed to the technical (the "what") rather than the relational/ritual components (the "how") of treatment.

- The importance of the "how" of treatment suggests the need for enhanced research and training on the set of skills and principles mediating relational/ritual effects.

- The scale of the mental health service is important in relation to the need for integration with social, medical and addiction care at the clinical, service and public health levels.

- Development of traditional mental health services needs to go hand in hand with the development of a public mental health system, the backbone of which may be formed by a number of complementary e-communities.

in learning to live with mental vulnerability. Peer support, for example, organized at the level of a recovery college, may form the backbone of the community.

The primary process of narrative development and finding and realizing meaningful goals should be supported by treatments aimed at trans-syndromal symptom reduction, specifically tailored to strengthen the primary process of recovery and participation, and applied by professionals who have been trained to embrace idiography and to maximize effects mediated by therapeutic relationship and aspects of the care ritual.

Education would be organized as person-centered, self-directed, practice-based and inter-professional interaction between clients, students of different professions, and different mental health professionals, to ensure adequate development of attitudes, knowledge and skills in collaborating, communicating and relating to each other[102]. Crisis intervention may be organized using a combination of peer-supported open dialog and local shelters, increasing the community capacity for social holding.

Some aspects of mental health services would continue to require a regional organization level: for example, high intensive care units, medium security units, and child/youth transition psychiatric services, including "headspace"-type public mental health approaches[103].

Importantly, the local healing community should be integrated with local social care (housing, work, education), focusing on recovery-oriented local social enterprises, working with "enhanced" local GP practices in order to integrate medical care.

The mental health service, organized as local healing community and associated regional components, should be able to cater for around 4-6% of the population and have strong links with a public mental health system of complementary e-communities with capacity for up to 20% of the population, integrated with a user-quality rated public health "market" of e-health and m-health tools for "blended" self-management approaches.

It is clear that the scale and complexity of the proposed change is such that it cannot be evaluated in a randomized controlled trial. We have, therefore, suggested that it may be more productive to engage in a form of action-research and create a number of pilot projects along the lines described above and learn along the way[104]. A number of these pilot projects are currently underway, in the Netherlands and undoubtedly in many other countries.

A more ambitious attempt at evaluation would be to study pilot areas in a quasi-experimental design, with even perhaps randomization at the county or neighborhood level. While this would require considerable funding, it could be argued that it involves the most pressing, yet perhaps most neglected, area of mental health research to date.

After decades of funding of large scale efforts to delineate the biological mechanisms of mental illness and to conduct randomized clinical trials of symptom reduction strategies, that are not independent of legitimization issues of the academic professions of psychiatry and psychology, the time may have come to coordinate a large-scale effort around the content and design of (public) mental health services, taking into account both professional and user knowledge.

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Towards a consensus around standards for smartphone apps and digital mental health

Mental disorders impact one in four people worldwide, yet access to care is challenging for those who suffer from them[1]. Mental health apps offer the potential to overcome access barriers for the nearly three billion people projected to own a smartphone by 2020.

Although there are over 10,000 mental health apps commercially available, there are few resources available to help end users (patients, clinicians and health care organizations) to evaluate the quality and suitability of these products. Thus, there is an urgent need for an agreement about appropriate standards, principles and practices in research and evaluation of these tools.

We represent leaders in mHealth research, industry and health care systems from around the globe, and we seek here to promote consensus on implementing these standards and principles for the evaluation of mental health apps. At a minimum, standards should include consideration of: a) data safety and privacy, b) effectiveness, c) user experience/adherence, d) data integration. Our consensus on the challenges and recommendations in each of these areas is presented below.

Data safety and privacy. Given the climate today regarding the misuse of online data such as email and social media, mental health apps must ensure that data storage, use and sharing practices fulfill health care standards for handling patient health information data[2]. Like with all sensitive health data, smartphones-based sensor data such as global positioning system (GPS), voice, keyboard usage, photos, video and overall phone usage behavior are features that many mental health apps collect, posing significant privacy challenges[2,3].

Our recommendations are: a) agreed upon standards for data storage, use and sharing are needed; b) data storage, use and sharing policies must be made transparent to users of the app; c) if data are shared with external partners (e.g., researchers), the partner's storage, use and sharing plans must be shared with the end user; d) the end user must have the option to "opt out" of sharing his/her information; e) any language regarding data storage, use and sharing must be written at a maximum of a 6th grade reading level; f) technical security reviews and data audits are necessary to guarantee that apps follow the standards they set out and ensure that new vulnerabilities are quickly identified.

App effectiveness. Most mental health apps that are sold as therapeutic tools have not undergone rigorous evaluation, but instead claim that they are evidence based because they are informed by evidence based treatments[4]. Even when apps do have an evidence base, changes in technology may mean that app updates need to be re-evaluated for their efficacy. Small cosmetic changes, platform changes and aspect changes do not likely require a retest of an intervention, as long as the therapeutic principle that has been evaluated remains intact.

Particularly where the aim is to increase reach, engagement and adherence rather than efficacy, A/B testing may be most appropriate. However, significant changes, such as adding a new therapeutic principle or substantial changes to that principle, must demonstrate efficacy through the same evaluation pathways as novel therapeutics.

Our recommendations are: a) newly adapted therapeutic principles, which should be identified and defined, must undergo controlled clinical trials to determine their efficacy and effectiveness; b) small changes to an app with an evidence base need not undergo another clinical trial, but any major change requires a re-evaluation of app effectiveness; c) a nosology for mental health apps[5] and guidelines to match the necessary level of evidence for each app's use cases and risks[6] should be developed.

User experience/adherence. Many patient end users stop using a health app two weeks after download[7]. Clinician end user adherence is influenced by familiarity with technology and app match to the clinician's therapeutic expertise. Lack of adherence is likely a function of app usability, as the input of clinician and patient end users is often missing when a mental health app is designed, resulting in apps that do not align with the preferences and goals of the intended users[6].

Our recommendations are: a) user-centered/user experience (UX) design methods should be employed when creating an app; this includes involving the intended end user in the development, and conducting as-is workflow analysis to ensure that the app is useful and usable, and that it fits into the fabric of the person's life, not producing unnecessary burden to the end user; b) when usability is evaluated, developers should report use statistics to all end users; c) standards concerning best practice in user design research for mental health apps should be articulated.

Data integration. Apps should allow appropriate electronic health record (EHR) integration and sharing of health information with clinicians. One challenge is that EHRs have non-uniform data integration requirements and not all support use of application programming interface (API) for data exchange. In the US, there is a strong move towards allowing patients access to their electronic health record information via SMART Health IT (https://apps.smarthealthit.org/), an open, standards-based technology platform that enables innovators to create apps that run across platforms. However, there are few agreed upon internal data standards to facilitate this level of interoperability.

Our recommendations are: a) mental health apps that are intended to be used in conjunction with health care systems should employ methods to ensure interoperability with electronic health records; b) mental health apps will need to document the processes they use to ensure the secure exchange of information between platforms; c) internal data standards for

interoperability are needed, much like those outlined in http://www.openmhealth.org/.

As mHealth transitions towards medical care in the mental health field, now is the critical moment for researchers, clinicians, service-users, policy makers and funders to guide that transition and ensure that these tools meet rigorous standards, as is required of any novel therapeutic.

Movement in this direction is taking place. In the US, the Food and Drug Administration has announced that it is moving away from evaluating individual apps, and focusing its regulatory efforts on the app makers. Additionally, US professional groups like the American Psychiatric Association and the American Medical Association are creating app evaluation frameworks[8]. In the UK, the National Health Service has recently re-opened the App Library in beta phase, providing recommendations for apps across a range of conditions including mental health, and the British Standards Institute has published standards for health app development. In the European Union, the National Institute of Health and Care Excellence (NICE) is actively developing standards for apps and other technology based behavioral change interventions.

We thus make a final recommendation that these organizations, and others, come together to set universal standards for mental health app quality control, and that those standards include at a minimum the review of data security, app effectiveness, usability, and data integration.

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AVATAR therapy: a promising new approach for persistent distressing voices

AVATAR therapy was invented and first described by J. Leff and colleagues[1]. The therapy involves a three-way conversation between therapist, patient and a digital simulation ("avatar") of one of his/her hallucinated voices. The avatar comprises a visual representation of the agent that the patient believes is responsible for the voice and uses a speech transformation software to change the therapist's voice into a close match of the vocal characteristics (e.g., tone and pitch) of the voice that the patient has chosen for the therapy.

Therapy takes place over 6-8 short sessions of approximately 45 min, of which around 15 min are spent in dialog with the avatar, and the rest reviewing the experiences of the previous week, planning the session and reviewing the experience after the dialog is complete. The therapist, sitting in a room remotely from the patient, speaks either as him/herself or in his/her transformed voice as the avatar. The patient sits in front of a monitor on which the avatar appears. Starting with verbatim copies of what the patient reports hearing from his voices, the therapist adjusts what the avatar says according to the unfolding dialog, in which the patient is encouraged to confront the avatar and, through the dialog, to get to a point where it is no longer intimidating and may even become encouraging and supportive.

The origins of the approach lie in dialogic therapies[2-4] and is based on the observation that voices are best understood not simply as misattributions of internal thoughts, but represent hallucinated social entities that have personal relevance, meaning and purpose[5,6]. Thus, the content of therapy is based on a formulation that takes account of the person's beliefs about the identity, power and malevolence of the voices. It includes consideration of whether the voice is of someone he/she knows and whether what it says echoes earlier difficulties in relationships, as for example experiences of being bullied, shamed or humiliated.

The therapy proceeds in two broad phases[7]. The first three sessions focus on assertively standing up to the avatar and rejecting its onslaught. The content of the second phase (sessions 4 through 6) is more variable, as it is based on a formulation of what needs to change in the relationship and what might persuade the avatar to take a more conciliatory and accepting view of the person. Strategies to improve self-esteem have turned out to be a key target, both as an end in themselves and in the understanding of the origin and maintenance of the voice.

There have now been two pilot studies comparing AVATAR therapy to a waiting list control[1,8] and one powered controlled

trial comparing AVATAR therapy to a supportive counseling intervention[9]. All have shown benefit over the control condition in terms of reduced frequency and severity of voices at 12 weeks (all voices, not only the one selected to create the avatar).

The larger trial[9] also showed that the early benefit was sustained at 24 weeks, although the comparison supportive counseling group also improved, so that the residual difference between the two arms was not statistically significant at that point. It is worth emphasizing, however, that it was the improvement in the control condition that accounted for this apparent loss of effect and not a dissipation of effect of AVATAR over the longer follow-up[9].

The results of these studies are extremely encouraging and have generated a huge worldwide interest among therapists, patients and their families. Together, they suggest a significant advance in the treatment of psychosis. There is, however, still some way to go before the therapy is available beyond the research setting. Some steps towards this are mundane, albeit time consuming, such as ensuring that the software has the necessary regulatory approvals for use outside of research and distilling the experience of the research into manuals and training programmes. Both are currently underway.

Another mundane consideration is the technological platform required to deliver the therapy. In principle this is not a significant challenge, as the specialized software runs on standard desktop and laptop computers with a Microsoft operating system, and there is no requirement of more elaborate or expensive immersive virtual reality equipment. However, the approach requires the use of two rooms, which can be a challenge to find in a busy outpatient clinic, and the host health care organization has to consent for the therapy computers to be connected using their ethernet or wireless facilities, with local protocols in place to manage confidentiality and what they wish to be recorded from therapy sessions.

Beyond these practical considerations is the availability of clinical staff with the level of expertise required to safely deliver therapy. There is no doubt that the therapy is challenging, both for patients and the therapist and, although there were no adverse events attributed to the therapy in the trials, it is obvious that AVATAR interventions may frighten and harm, deliberately or inadvertently.

The therapists in the three studies were all experienced clinicians, some with specific psychological therapy skills for psychosis. On the other hand, in our trial, substantial improvements occurred as early as the third session, raising the possibility that, for some people, the straightforward exposure and assertiveness component was sufficient. If this can be substantiated in future work, and rapid responders can be identified in advance, it would enable the therapy to be delivered by a much wider workforce, with, of course, appropriate training and supervision.

A further consideration is the timing of the therapy within the wider envelope of care for psychosis. To date, the therapy has been delivered as a "stand alone" treatment with a focus entirely on the hallucinated voices. Participants were only included if they agreed to remain on their routinely prescribed medication and were not receiving a psychological therapy other than those provided by the research. In clinical practice, it might be more appropriate to consider AVATAR therapy as one component of a wider psychological intervention. For example, in many cases voices were accompanied by persecutory beliefs and consequent social difficulties. It struck us clinically that, for these participants, the timing and impact of AVATAR therapy would have been better if delivered as a component of a therapy plan that also addressed these wider problems.

Moreover, the focus to date has been on people suffering from treatment resistant auditory hallucinations in the context of long-standing illness. It is not clear whether the intervention would be as effective in younger people experiencing their first episode of illness. Here, the personification of the voices is often less fixed or elaborated, possibly making the evolution of a coherent dialog more difficult to attain.

Finally, while the benefits seen in all three studies to date are a reasonable basis for wider dissemination, there is no doubt that further research is also needed. Larger multicentre replications are necessary before organizations such as the National Institute for Health and Care Excellence (NICE) will include AVATAR therapy in their recommendations, and other studies will be needed to clarify the subgroup of patients who can benefit from the simpler first phase treatment alone. Studies using new virtual reality headsets may replace the need for two rooms and perhaps open the way to deal with more than one voice at a time.

To conclude, while there is much to be done to take the existing research to routine care, there is every reason to be optimistic. The technology is relatively inexpensive and enough is known to provide training. The immediate practical obstacles are likely to be resolved shortly, and preparation for dissemination is underway. In the longer run, it seems likely that AVATAR therapy will be provided as one component of wider psychological therapy for psychosis, possibly alongside other digitally-enhanced approaches for paranoia and cognitive impairment.

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Parental divorce or separation and children's mental health

An increasing number of children across the world experience family instability due to divorce/separation and the consequences of non-marital childbearing/cohabitation[1].

Alternatives to stable marriage are most common in Western countries (including Australia and New Zealand) and less common but growing in industrializing Asia. Cohabitation, which is more unstable than marriage, is especially common in Northern and Western Europe, necessarily lowering rates of divorce but not of single-parent households.

The US has been a "leader" in family change with an early (rising in the late 1960s) and high increase in divorce, followed by an explosion in non-marital birth with or without cohabitation. Divorce increased in most other Western nations a decade or two later; industrializing Asia appears to be in the midst of change. Today, only about 60% of US children live with their married, biological parents, a low second only to Latvia.

Some call family instability a major public health problem for children; others see divorce/separation as relatively innocuous, even a positive change, especially for women in unhappy marriages or children exposed to high conflict.

Research has documented that parental divorce/separation is associated with an increased risk for child and adolescent adjustment problems, including academic difficulties (e.g., lower grades and school dropout), disruptive behaviors (e.g., conduct and substance use problems), and depressed mood[2].

Offspring of divorced/separated parents are also more likely to engage in risky sexual behavior, live in poverty, and experience their own family instability. Risk typically increases by a factor between 1.5 and 2.

Still, most children whose parents divorce are resilient and exhibit no obvious psychological problems. It is important to recognize, however, that even resilient young people from divorced families often report painful feelings or encounters, such as worrying about events like graduations or weddings when both parents will be present[3].

Many associated risk factors – for example, lower income and parent conflict – are linked with non-random selection into family stability and/or are consequences of family break-up. To help rule out potential confounds, researchers have used a variety of methods, including measuring covariates and employing designs, such as children-of-twin studies, that account for unmeasured environmental and genetic factors that could influence both generations[2,4]. Controls for such confounds reduce but do not eliminate the risk tied to parental divorce, consistent with causal inference.

A wealth of research also points to factors mediating the association, including less effective parenting, interparental conflict, economic struggles, and limited contact with one parent, typically the father (listed in decreasing order of the magnitude of their relation with children's mental health)[5]. Marital instability presents not a single risk factor, but a cascade of sequelae for children.

Individual, family, ethnic and cultural factors moderate the risks associated with changes in children's family life, underscoring the importance of recognizing family diversity. In the US, for example, parental separation is associated with more socioemotional problems among white children than black or Hispanic children[2]. Acceptance of alternatives to marriage and extended family support contribute to such ethnic variation.

Understanding family change and its consequences is critical to health care professionals across numerous settings. Physicians treating children may observe warning signs, be asked to help children cope with family transitions, or face parental disputes about a child's well-being or needed treatment. Schools encounter similar opportunities and difficulties.

Children and adult offspring of separated parents are overrepresented in the mental health system. Most mental health interventions target the known mediators of risk, such as parenting problems or family conflict. Structured interventions offering parenting support and education have been shown to reduce children's psychological problems[6]. Unfortunately, few mental health interventions for divorcing families have been carefully studied.

Separation/divorce also raises legal concerns bearing on the well-being and custody of children. The "best interests of children" is the prevailing custody standard, and "best" typically is interpreted in psychological terms (as opposed to, for example, economic ones). Mental health professionals and others may become involved, willingly or unwillingly, as expert witnesses in custody contests. Alternatively, some professionals promote or offer alternative dispute resolution, such as mediation.

Mediators are neutral third parties who help parents living apart to resolve disputes themselves. In addition to dispute settlement, mediation potentially benefits children by lowering conflict, improving parenting, and encouraging both parents to remain an active presence in their children's lives. One randomized trial with a 12-year follow-up demonstrated that mediation produced all of these outcomes relative to litigation[5,7]. Another randomized study found that carefully involving children in the process improved the success of mediation[7].

While initial results are promising, mediation and many other legal and mental health interventions demand rigorous study, as well-intentioned services may have no effect or may even be harmful for some individuals, while wasting limited resources[8].

Mental health professionals also can play a critical role in advising parents, and perhaps in the development of law and policy. One controversial issue is how strongly, and under what circumstances, to promote joint physical custody, sharing 25-50% parenting time[9]. Joint legal custody, which involves legally sharing important decisions, including elective medical care, is becoming ubiquitous. It has increased in the US and in many Western countries, but still typically comprises a minority of separated families (from 15 to 50% across countries)[9].

Fathers groups are currently advocating for a universal 50/50 shared time presumption.

While such agreements may benefit numerous families, many experts, including ourselves, worry that such a presumption may offer the "right" solution for the wrong group of parents: the 10% or fewer who contest custody in court[5]. Other concerns we share include avoiding extensive time away from attachment figures among very young children, avoiding placing excessive travel demands on children in order to share parenting time across long distances, whether shared time needs to be precisely 50/50, and if some child mental health problems (e.g., autism spectrum) or personality (e.g., high conscientiousness) make shared custody less likely to work[5].

There is, therefore, a critical need for studies on interventions, including policy changes, that consider the risks, role of resiliency, and heterogeneity in the consequences associated with family instability.

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Resilience from a developmental systems perspective

Interest in human resilience is surging in the context of natural disasters, war, political conflict, and increasing awareness regarding possible consequences of adversity in childhood for health and well-being in adulthood[1,2]. Although resilience science is not new, current research is more multidisciplinary, multilevel and developmental than ever before, reflecting a developmental systems perspective with profound implications for defining and investigating resilience, as well as for translating evidence into practice[3].

Resilience science emerged from research on etiology of mental disorders[1]. Investigators studying children at risk for psychopathology observed striking variation in outcome, as many individuals with risk factors for mental health problems (e.g., maltreatment, poverty) nonetheless developed well. Resilience research aims to understand this variation in order to inform interventions that mitigate risk and promote positive development.

Models of resilience shifted with the infusion of dynamic systems theory into developmental science[4]. As a living system, a human individual develops through myriad interactions at many levels, from genetic and neurobiological to social and cultural[5,6]. Adaptive systems develop within the person (e.g., immune system, stress-regulation system, self-regulation system) as the individual, embedded in larger systems, adapts simultaneously to external contexts. All these dynamic interactions shape development, yielding diverse pathways of adaptive function[3].

The capacity of a developing child to respond to challenges and adversities depends on the operation of many systems, varying from neurobiological stress-regulation systems to families, schools, community safety and health care systems, and numerous other sociocultural and ecological systems. Resilience reflects resources and processes that can be applied to restore equilibrium, counter challenges, or transform the organism.

Definitions of resilience evolved to reflect insights on developing systems. Currently, resilience can be defined broadly as "the capacity of a system to adapt successfully to disturbances that threaten the viability, function, or development of the system"[1]. This definition can be applied to diverse systems, including individuals, families, businesses, communities, economies, or ecosystems. It has the advantage of scalability across system levels, which is increasingly crucial for integrating concepts and knowledge about human resilience across disciplines and levels of analysis.

As this definition suggests, the resilience of an individual depends on resilience of interconnected systems. Systems interdependence is salient in major disasters, when multiple systems are overwhelmed at the same time, and also in family-level crises, when disturbances in the mental health of a caregiver can disrupt the quality of care or lead to child maltreatment[7]. It is important to remember that resilience of an individual is not limited to the capacity that person can muster alone. Indeed, much of human resilience is embedded in relationships and social support[8].

Accumulating evidence on resilience has identified a number of factors that could explain why some individuals fare so much better than others. Some factors are common, associated with positive adjustment during or following different adverse experiences, although they vary in form and relevance across development and context. Such factors may well reflect adaptive systems preserved by human evolution, biological and sociocultural, because they enhance survival[1]. Common protective factors include effective caregiving and other supportive relationships, problem-solving and self-regulation skills, self-efficacy and optimism, and beliefs that life has meaning[3]. Identified early in resilience studies, common factors were

corroborated repeatedly in basic studies with diverse populations and in intervention trials designed to promote resilience[3]. Other protective factors appear to be relatively unique to a particular culture or context, such as specific forgiveness rituals or spiritual practices.

Initial resilience research focused on psychosocial factors that might mitigate risk or promote better adaptation. With advances in measurement at other levels of analysis, resilience science expanded rapidly to include the neurobiology of resilience, genetic processes, cultural influences, and the cascading spread of risk and protection across systems, levels and generations[3]. Advances in the study of epigenetic change raised interesting considerations about biological embedding of experience, via gene methylation and related processes, which may explain effects of trauma and caregiving quality on brain development and lifelong health[9]. One of the most provocative questions posed by recent theories of biological sensitivity to experience, and the related concept of differential susceptibility, is whether children who adapt poorly to adverse experiences may also be more responsive to positive experiences, such as interventions tailored to foster mental health and competence among sensitive individuals[3].

Resilience research has had a transformative effect on multiple disciplines concerned with promoting mental health and well-being, shifting intervention frameworks away from deficit models toward more comprehensive approaches that include promotive and protective factors as well as risks and vulnerabilities, focusing on health as well as illness[1]. Examples range from strength-based school counseling to global humanitarian efforts moving beyond child survival to thriving[3]. A meta-analysis of resilience-oriented school interventions found reductions in mental health symptoms (depression, anxiety), particularly for cognitive-behavioral strategies[10].

Current directions in resilience science hold exciting promise for elucidating how adaptive capacity develops and operates to mitigate risk or promote resilience, guiding intervention models, targets and timing. Strategies could focus on preventing trauma, lowering stress, inoculating against stress through calibrated exposures, reducing vulnerability, boosting resources, restoring and mobilizing powerful adaptive systems, or generating positive cascades across system levels or generations. Timely targeted interventions could range from preventing maternal perinatal stress to boosting social relationships in late adulthood. It is conceivable that key adaptive systems adversely affected by early trauma, such as neurobiological stress-regulation systems, can be "reprogrammed" later in development to improve adaptive function[9].

Developmentally-informed research on resilience has the potential to elucidate processes across systems and levels that would inform efforts to promote mental health, prevent psychopathology, and facilitate recovery. Developmental studies may identify windows of opportunity when there is greater plasticity and leverage for change, so that interventions can be effectively tailored and timed for efficacy, adapted to individual, developmental and situational differences. Policy makers and non-governmental organizations are already evaluating synergistic effects of integrating their services across system levels (vertical), sectors (horizontal) and generations. As knowledge expands, resilience theory can be tested and refined through randomized trials that target malleable processes with strategic timing to leverage opportunities for change.

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Using biobehavioral technologies to effectively advance research on negative symptoms

Negative symptoms have been a core component of schizophrenia since the pre-neuroleptic era and are related to particularly poor clinical outcomes (e.g., in terms of recovery, quality of life, subjective well-being). They are often one of the first markers of illness risk, emerging in the premorbid and prodromal phases, and in many patients remain stable throughout the first episode and chronic phases of illness[1]. Unfortunately, the mechanisms underlying these symptoms are poorly understood, and currently available treatments are unsatisfactory and palliative at best[2].

To date, our understanding of negative symptoms is almost entirely dependent on psychometrically-supported clinical rating scales. Within the last few decades, a literature has emerged using "biobehavioral" technologies to measure negative symptoms from objective vocal, language, facial, decision making, gestural, electrophysiological, neurobiological, and reaction time measures.

While clinical ratings reveal abnormalities on the scale of three to seven standard deviations in patients versus non-psychiatric controls[1,3], group differences in biobehavioral measures tapping their underlying constructs are much smaller, if not altogether absent. For example, despite dramatic clinically-rated patient abnormalities in alogia, blunted affect, anhedonia, and avolition[1,3,4], studies of computerized speech analysis, hedonic experience, and motivation often find negligible or small effect size abnormalities[5,6].

Moreover, biobehavioral measures often show surprisingly modest and negligible correlations with conceptually overlapping negative symptom ratings[6,7], or similarly sized correlations to a wide array of non-negative symptom ratings[8]. Though statistical significance may be reported in isolated studies for specific biobehavioral features, findings often do not replicate across studies, and the magnitude of effects are generally well below levels suggestive of acceptable convergent validity[3].

In light of this surprisingly low convergence between clinical ratings and biobehavioral technologies, it is tempting to champion one of the two as being superior for measuring negative symptoms. Clinical ratings tend to be consistent across trained raters (i.e., reliability) and are associated with a wide range of important clinical variables (i.e., validity). On the other hand, biobehavioral technologies show near perfect reliability (assuming static recording conditions), and are instrumental to modern biometrics for measuring human functions that potentially underlie negative symptoms. So how can clinical ratings and biobehavioral technologies both be "reliable" and "valid" for measuring negative symptoms, yet show such surprisingly modest convergence?

Clinical ratings and biobehavioral technologies are fundamentally different in how they scale negative symptoms. Clinical ratings reflect the integration of an impressive number of complicated data streams over dynamic conditions. Using clinical rating scales, for example, a clinician is able to derive a gross ordinal value (e.g., "mild") regarding blunted affect from a highly complex "spectrum" of vocal, verbal, facial and gestural data that fluctuate over time, questions and a changing environment.

Unfortunately, an individual negative symptom rating cannot be systematically "downscaled" for quantification. For example, deconstructing clinically-rated blunted affect proves impossible in terms of which exact psychomotor channel was abnormal, when it was abnormal, or what factors may have mitigated the abnormality. In contrast, biobehavioral technologies afford the opportunity to precisely quantify continuous streams of highly specific speech, facial and gestural data, and to isolate, upscale, downscale and integrate them in a myriad of ways.

Unfortunately, it is unclear how to best do this. Which of the thousands of potential features computed from, for example, vocal analysis should be used, and how should they be weighted when they do not converge? Should computerized facial analysis reflect aggregate statistics during an entire interview, only when patients are speaking, during key temporal epochs, or following specific questions? In short, clinical ratings provide a view of the forest at the expense of being able to see the trees, whereas biobehavioral technologies afford the opposite.

Ideally, there would be a way to measure negative symptoms by marrying "low-resolution" but "ecologically-valid" ratings with "high-resolution" but "dizzyingly-complex" biobehavioral data. Within computational psychiatry more generally, an emerging "big data" literature now exists modeling various clinical diagnoses and ratings using biobehavioral features. Within these studies, models are typically built and optimized using a single biobehavioral channel without regard to other biobehavioral channels or to temporal, contextual or other dynamic factors.

While impressive accuracy rates are being reported, the models produced from this literature have yet to progress beyond "proof of concept" and seem particularly ill-equipped for modeling negative symptoms. This is because clinician ratings are typically derived from multiple behavioral domains, and it is difficult to evaluate even one of these domains without considering context. For example, a patient's failure to activate his/her zygomaticus major muscle, language production, or reward systems can only be interpreted as abnormal when context is taken into account. After all, non-patients are not actively smiling, talking or experiencing joy the vast majority of their day. Further complicating this issue is the reality that the behaviors underlying negative symptoms vary dramatically across and within people as a function of neurodevelopmental and cultural factors. In this manner, norms regarding smiling, talking and experiencing joy are very difficult to derive.

So, how can biobehavioral-based modeling of negative symptoms progress? Technology and software systems have pro-

gressed so that they are affordable, reliable, highly sensitive, and unobtrusive, with a high potential for large-scale international data collection across a broad range of behavioral domains. This allows for biobehavioral data collection that extends well beyond the relatively artificial confines of the clinic or research laboratory. For this, ecological momentary and ambulatory assessment methods, such as geolocation, passive vocal recording, activity tracking, and social media analysis, can complement existing measurement approaches.

Efforts to validate these technologies for understanding negative symptoms are currently underway. However, integrating and understanding these data within a network that can handle temporally and contextually dynamic data is a complex computational obstacle. Relatively simplistic "connectionist" and dynamic algorithms are being developed for many important human functions, and there is a growing field of understanding "networks of networks" to model complex interactions (e.g., "network medicine")[9].

In sum, existing clinical rating measures offer a level of precision that has not promoted advances in understanding underlying mechanisms and developing targeted treatments of negative symptoms. This reflects a "scalability" problem that can potentially be solved by modeling clinical ratings with multidimensional biobehavioral data streams.

Developing biobehavioral models can help pinpoint neurobiological and environmental mechanisms, modify them in real time using biobehavioral feedback, and develop, test and individualize targeted psychosocial and pharmacological agents to ameliorate their severity, and ideally, develop treatments.

Accurate modeling of negative symptoms is a complex endeavor, and an exciting computational opportunity that may advance multidisciplinary sciences and bring together researchers, patients and their support teams from around the world.

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Testing a neurophenomenological model of basic self disturbance in early psychosis

The construct of basic (core, minimal) self disturbance has emerged in recent years as a possible key phenotypic marker of the schizophrenia spectrum[1].

Two nested concepts can be identified as constituting this aspect of selfhood: sense of ownership/mineness (I perceive my body, perceptions and thoughts as my own) and sense of agency (I experience myself as the source of my actions and their consequences). These are generally implicit or "given" aspects of a normal sense of basic self and facilitate (and are in turn consolidated by) interactions with others/the world. Fragility or instability of the basic self can manifest in a variety of anomalous subjective experiences, which can intensify and crystallize over time into episodes of positive and negative psychotic symptoms[2].

A considerable body of research has accumulated over the last 15 years indicating that basic self disturbance is a trait vulnerability feature that (though overlapping in some respects with non-schizophrenic dissociative conditions) has considerable specificity to schizophrenia spectrum disorders and is present in the prodromal phase of these disorders[3]. Indeed, disturbed "self-experience" is included in the criteria for schizophrenia of the beta version of the ICD-11.

Taking basic self disturbance as a phenomenological starting point allows researchers to examine correlates and contributing factors, cross-sectionally and longitudinally. Some progress is now beginning to be made in this respect. Sestito et al[4] found that facial reactions in response to negative emotional stimuli, recorded using electromyography, specifically and strongly correlated with basic self disturbance in schizophrenia spectrum patients. Martin et al's[5] findings in schizophrenia indicated a relationship between compromised extraction of temporally predictive information assessed in experimental tasks and basic self disturbance. Given the complexity and foundational nature of the basic self disturbance construct, multiple neural mechanisms are likely to be associated with this constellation of anomalous subjective phenomena.

Nelson et al[6] introduced a theoretical model proposing that the neurocognitive constructs of source monitoring deficits and aberrant salience, both of which have been found to be prominent in schizophrenia spectrum disorders and related to psychosis risk, may be of particular relevance to basic self disturbance in schizophrenia. Source monitoring deficits refer to difficulties in making attributions about the origins of phenomenal experience – e.g., whether an experience was real or imagined, or whether its origin was self- or other-generated. Aberrant salience refers to the reduced ability to suppress attention to irrelevant or familiar information or environmen-

tal stimuli (in other words, *excessive* attention to information that is irrelevant or highly familiar), leading to an unusual salience of stimuli. There is strong face validity that the phenomenological disturbances which might arise from (and in turn consolidate) these neurocognitive disturbances accord with many of the experiential alterations associated with basic self disturbance[6] (e.g., diminished "ownership" of mental content, confusion of self-other boundaries, hyper-reflexivity).

We tested this model empirically in 50 ultra-high risk for psychosis subjects, 39 first-episode psychosis patients and 34 healthy controls. Participants were assessed with a variety of clinical measures, including the Examination of Anomalous Self-Experience (EASE)[7], and neurocognitive and neurophysiological measures of source monitoring deficits (Action Memory Task, Word Recognition Test, Temporal Binding Task, Auditory Button-Press Task) and aberrant salience (Salience Attribution Test, Babble Task, Auditory Oddball Paradigm).

Linear regression indicated that source monitoring (composite score across neurocognitive and neurophysiological measures), with study group as an interaction term, explained 39.8% of the variance in EASE scores (R^2=.41, $F_{(3,85)}$=14.78, $p<0.001$). Source monitoring significantly predicted EASE scores (β=.80, $p<0.001$), and there was a significant source monitoring by study group interaction effect (β=.29, $p<0.05$).

In order to determine the specificity of the relationship between source monitoring deficits and EASE scores, a series of regressions with other clinical scales as dependent variables were performed. Although source monitoring was found to significantly predict variance in scores on each of these clinical measures, the variance explained was not as substantial as for the EASE scale: 25% for Brief Psychiatric Rating Scale (BPRS) scores (R^2=.25, $F_{(3,85)}$=9.01, $p<0.01$); 19% for BPRS positive symptoms (R^2=.19, $F_{(3,85)}$=6.69, $p<0.01$); 26% for Comprehensive Assessment of At Risk Mental States (CAARMS) positive symptoms (R^2=.26, $F_{(3,85)}$=9.45, $p<0.01$); 14% for Scale for the Assessment of Negative Symptoms (SANS) scores (R^2=.14, $F_{(3,85)}$=4.71, $p<0.01$).

The same analysis was performed with the aberrant salience composite score. This score explained only 6% of the variance in EASE scores (R^2=.06, $F_{(3,85)}$=1.44, $p=0.93$). However, exploratory analyses indicated moderate relationships between aberrant salience, particularly the Babble task[8], and general psychopathology (BPRS score in first-episode psychosis patients, r=.44, $p<0.05$), particularly with positive psychotic symptoms (BPRS positive symptoms in first-episode psychosis patients, r=.53,

$p<0.01$; CAARMS positive symptoms in ultra-high risk subjects, r=.44, $p<0.01$).

This is the first empirical test of a neurophenomenological model[6] organized around the construct of basic self disturbance. Partial support for the model emerged: there was a significant relationship between basic self disturbance and source monitoring deficits, while no relationship was found with aberrant salience, which was moderately related to general psychopathology, particularly positive psychotic symptoms (and is therefore possibly more a state-based feature of the illness).

The model may need to be expanded from source monitoring deficits to encompass other constructs that recent theoretical and empirical work suggests may be relevant, such as disturbed temporal processing, intermodal/multisensory integration, and hierarchical predictive processing. These are overlapping constructs and it is yet to be determined if one or several of these constructs have causal or explanatory primacy with regard to basic self disturbance.

The current data and other related recent research show an emerging picture of neurocognitive and neurophysiological correlates of core phenomenological aspects of schizophrenia spectrum disorders beyond surface-level episodic psychotic symptoms. Pursuing this approach offers the possibility of integrating levels of research around central features of the schizophrenia spectrum and of "mutual enlightenment" between these different levels of enquiry.

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Improving access to evidence-based interventions for young adolescents: Early Adolescent Skills for Emotions (EASE)

About half of all mental disorders emerge by 14 years of age[1]. In adolescents, depression is the main cause of disability, anxiety is ranked seventh, and suicide is the third leading cause of

death[1]. An estimated 10-20% of adolescents worldwide suffer from mental disorders[2], which are associated with health and social problems, such as poor academic attainment, substance

misuse, and economic difficulties[3]. Consequently, adolescence is a critical period in which to intervene.

Adolescents living in low- and middle-income countries (LMICs) may be especially at risk of mental disorders when they are exposed to adversity, such as extreme poverty and violence[4]. While advances have been made, access to evidence-based psychological treatments for adolescents in LMICs is rare[4].

There is a growing literature on effectiveness of psychosocial interventions for youth in LMICs. A recent systematic review and meta-analysis of individual participant data from 3,143 children affected by conflict recruited to eleven randomized controlled trials found that focused psychosocial interventions can be effective in reducing post-traumatic stress disorder (PTSD) symptoms and in increasing hope, coping and social support, and reducing functional impairment[5].

The World Health Organization (WHO) is seeking to strengthen the quantity and quality of mental health services. As part of the Mental Health Gap Action Programme (mhGAP), the WHO is developing and testing the effectiveness of brief, transdiagnostic psychological interventions, including those for young adolescents, that can be implemented by trained and supervised non-specialists in multiple settings, including health, protection and education[6,7].

Building on ongoing work to develop and test potentially scalable psychological interventions for adults[8], the WHO has developed a group intervention for young adolescents (about 10 to 14-year-olds) exhibiting internalizing problems (e.g., symptoms of depression or anxiety). The intervention is called Early Adolescent Skills for Emotions (EASE).

Central to the development of EASE was the capacity to address comorbid emotional problems in one intervention and promote scale-up in LMICs with the use of briefly trained non-specialists. The formative process to develop EASE included a narrative review, the identification of empirically-supported strategies that were most commonly used in effective interventions according to the PracticeWise[9] database, and extensive expert consultation (a concept note on the development of EASE is available upon request).

EASE aims to mitigate symptoms of internalizing disorders, such as depression and anxiety, by the provision of four core empirically-supported strategies delivered face-to-face over seven group sessions with adolescents, and three group sessions with their caregivers.

Strategies with young adolescents are introduced in order of complexity, thus each session reviews and rehearses previously introduced strategies, with practice between sessions encouraged. Sessions are designed to last 90 min. They include pictures, stories and activities to encourage youth engagement.

The first session aims to build rapport with participants and develop group cohesion. Psychoeducation is presented, informing participants about adversity and emotional distress. Participants are also taught how to appropriately identify their own emotions ("Understanding My Feelings") which is seen as fundamental to basic emotional regulation. Session 2 addresses

problems of physical arousal associated with stress, anxiety and anger, and introduces slow breathing ("Calming My Body") to promote arousal reduction.

Participants are encouraged to engage in meaningful activities to improve their mood in sessions 3 and 4 ("Changing my Actions"). Based on behavioral activation, this strategy aims to address symptoms of inactivity and help engage adolescents in more meaningful activities.

Sessions 5 and 6 promote independent problem solving skills via a simplified problem solving technique called "Managing my Problems". Embedded within this strategy are questions to prompt participants to seek social support. Finally, session 7 focuses on relapse prevention and helps participants prepare to use the strategies independently in the future.

Given difficulties with engagement of employed or overburdened caregivers, and in the context of a brief intervention, only three two-hour group caregiver sessions are included. They aim to build on existing strengths and promote adaptive parenting practices to improve the caregiver-child relationship and enhance confidence when responding to adolescent distress.

In the first session, caregivers are provided with psychoeducation and skills to better equip them to respond and provide comfort to their child when they are overwhelmed by feelings of distress. Emotion identification, active listening and slow breathing are taught and practiced. The second session focuses on positive parenting strategies including praise, boosting their child's confidence and the discontinuation of physical discipline. Finally, caregiver self-care (e.g., sleep, nutrition, stress reduction strategies) is covered in session 3. This session aims to enhance caregiver's capacity to cope with challenges related to the environment and to parenting an adolescent experiencing significant distress. Education about relapse prevention is also provided in this final session. Practice and application of strategies is encouraged between sessions. In addition, across all sessions, caregivers are informed of the strategies being taught in the adolescent sessions.

Beyond the caregiver and youth sessions, facilitators are trained to monitor and identify indicators of threats to adolescents' wellbeing in the home environment and to make referrals as indicated.

The capacity to effectively implement and scale up this intervention in LMICs is critical. Adopting a responsibly implemented (e.g., including ongoing supervision and support) task-sharing approach by employing non-specialists makes EASE more affordable and scalable. Facilitators of this intervention are expected to have at least high-school education, but are not required to have previous mental health experience. They will complete eight to ten days of training in basic mental health education, counseling and group management skills and the EASE intervention, and receive weekly supervision. Similar task-sharing approaches have been employed in studies demonstrating effectiveness in adults[10].

Access to effective psychological interventions for adolescents is essential to promote healthy development into adulthood. EASE is a brief, transdiagnostic intervention that aims to mitigate symptoms of emotional distress in young adolescents. If proven

effective, it can potentially be scaled-up in many settings. The effectiveness of EASE is currently being tested through randomized controlled trials in Lebanon, Jordan, Pakistan and Tanzania.

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Lack of evidence for the efficacy of psychotherapies for PTSD and depression in child and adolescent refugees

Post-traumatic stress disorder (PTSD) and depression are known to be prevalent among young refugees and internally displaced individuals. The need for effective interventions for this population is becoming increasingly evident in view of the large number of recent and current armed conflicts.

We conducted a systematic review and meta-analysis of randomized controlled trials on the efficacy of psychological interventions for PTSD and depression in child and adolescent refugees and internally displaced individuals. The aims and methods of the meta-analysis were registered with the PROSPERO database (CRD42017071384).

We searched the databases PsycINFO, MEDLINE, and PILOTS up to February 2018. The following search terms in keywords, titles and abstracts were used: PTSD, depression, refugee (or related terms such as asylum seeker or displaced person), and treatment (or related terms such as intervention or psychotherapy). Additionally, reference lists of identified publications and systematic reviews were examined.

The inclusion criteria were: a) trial conducted with child or adolescent refugees or internally displaced individuals; b) participants randomly assigned to treatment conditions; c) at least ten participants completing an active psychological treatment for PTSD or depression or both. No restrictions were made upon intervention format, publication type, or publication language. If studies did not provide sufficient data for performing the meta-analysis, the authors were contacted by e-mail to retrieve these data.

We coded and extracted relevant study, intervention and participant characteristics, such as number of participants, comparison group(s), type of outcome measure used, outcome scores, and number of sessions. Furthermore, we rated the quality of the included trials by applying nine criteria used in similar meta-analyses[1]. To conduct the analyses, the control group mean was subtracted from the treatment group mean at post-treatment or follow-up, and divided by the pooled standard deviation. Subsequently, to obtain the effect size Hedges's g, the outcome was multiplied by a sample size correction factor and the random effects model was applied. Analyses were completed with Comprehensive Meta-Analysis Version 3. Given that less than ten trials met our inclusion criteria, no test of publication bias could be conducted.

After screening 1,716 potential hits, eight trials met our criteria[2-9]. All publications were written in English, seven were published in peer-reviewed journals and one was a doctoral thesis[7]. Seven of the trials were conducted with internally displaced individuals, whereas two were conducted with refugees[6,8]. In three trials, treatment was performed in group format[2,5,9]. Four trials assessed both PTSD and depression[4,5,7,9], one focused on depression only[2], and three focused on PTSD only[3,6,8].

Experimental conditions consisted of trauma-focused cognitive behavior therapy that included narrative exposure therapy[3,4,6-8], interpersonal therapy[2], classroom-based intervention[9], and writing for recovery[5]. Active treatments were compared to waitlist in four trials. In two trials, the experimental condition was compared to an inactive control condition in addition to the waitlist. In three trials, two active conditions were compared to each other.

The number of participants per condition varied from 11 to 248, with a mean of 78.7±61.9. The mean age of participants was 13.1±1.9, and 49.9% of them were female. Two and three trails, respectively, used structured clinical interviews to assess PTSD or depression; the remaining trials applied self-reports. The number of sessions ranged from 6 to 16.

Active treatments for PTSD yielded non-significant aggregated effect sizes at post-treatment (k=7; g=0.02; 95% CI: −0.13 to 0.15) and at follow-up (k=5; g=0.24; 95% CI: −0.13 to 0.62) when compared to control conditions. Only one trial produced a significant effect of the experimental condition over the control condition[6].

Active treatments for depression also produced non-significant aggregated effect sizes at post-treatment (k=6; g=−0.01; 95% CI: −0.55 to 0.52) and at follow-up (k=3; g=0.02; 95% CI: −0.16 to 0.19) when compared to control conditions. Only one trial showed a large effect for depression[3].

Three trials that reported on functional impairment led to a small effect size at post-treatment (k=3; g=0.31; 95% CI: 0.08-0.54) and at follow-up (k=3; g=0.32; 95% CI: 0.01-0.64) when active treatments were compared to control conditions.

The assessment of quality of the included publications indicated that six trials (75%) were rated with an average score of 2, indicating good quality.

This meta-analysis demonstrates that there is a limited number of clinical trials on the efficacy of psychotherapies for PTSD and depression among child and adolescent refugees and internally displaced individuals. The results of existing trials do not provide support for the efficacy of psychological interventions in this population.

Given the urgent public health issues raised by escalating levels of violence and civil conflict around the globe, it is essential for government and non-government agencies to have the most reliable evidence to shape policy and practice. Accordingly, we urgently need to develop and test effective interventions for mental health problems in young refugees and internally displaced individuals.

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The trait-state distinction between schizotypy and clinical high risk: results from a one-year follow-up

Psychoses are severe, yet heterogeneous psychiatric conditions of multifactorial etiology. Both a clinical high-risk (CHR) condition and trait anhedonia (as part of the schizotypy construct) have recently been reported in an umbrella review published in this journal[1] as promising clinical risk factors for early detection of psychosis.

These results reflect the two main lines of phenomenological research in the field of early detection of psychosis prior to its first episode[2]: the clinical high-risk approach[3] and the schizotypy approach[4,5]. With few exceptions[2,6], these two approaches were so far examined for their psychosis predictive value independent of each other, as well as by different means in different populations: schizotypy by means of self-report scales in mostly non-clinical samples, and CHR criteria by means of clinical interviews in mostly clinical samples[2].

Schizotypy is regarded as a latent trait or personality organization, frequently assessed by the Wisconsin Schizotypy Scales (WSS)[2,7] (physical anhedonia, social anhedonia, perceptual aberration and magical ideation). The latter two scales were reported to load on the same factor as attenuated and transient positive symptoms as well as perceptive basic symptoms[8], that, next to cognitive basic symptoms, are commonly used to define a symptomatic CHR state[3].

Supporting the assumption of the trait character of schizotypy, results from non-clinical samples showed relatively good stability of the WSS scores across short time periods[9]. In contrast, and supporting their conceptualization as state factors, CHR criteria and symptoms are rarely stable over time in clinical samples[10]. Yet, it is so far unknown whether CHR symptoms influence the report on WSS, especially with regard to the partly overlapping (attenuated) positive symptoms and the positive WSS[2,6], in clinical samples.

To shed first light on this question, we examined the temporal stability as well as the interrelation of potential temporal changes of WSS and CHR symptoms over one year in 29 patients recruited at the Bern Early Detection and Intervention Centre for Mental Crises. At baseline, patients were 18±5 years of age on average (range: 9-27 years) and 41% were male. One patient (3%) already had a psychotic disorder, 22 (76%) fulfilled CHR criteria, and six (21%) received diagnoses unrelated to the psychotic spectrum.

The Schizophrenia Proneness Instruments were used to assess the 14 basic symptoms included in the two basic symptom criteria[3]. The Structured Interview for Psychosis-Risk Syndromes was used to assess the five positive symptoms included in the symptomatic UHR criteria[3]. Schizotypy was assessed by the WSS. As required by the local ethics committee, patients and, if minors, their legal guardians gave informed consent for their anonymized clinical data to be used in scientific analyses and publications.

Using SPSS 24, differences between baseline and follow-up (delta) of the mostly normally distributed sum scores were

analyzed through dependent t-tests with bootstrapping to test for effects of potential outliers and reliability of results. These revealed significant temporal differences in basic symptoms (mean delta=3.45, t(28)=2.38, p=0.024) and positive symptoms sum scores (mean delta=2.00, t(28)=2.48, p=0.021). In contrast, differences in WSS scores remained non-significant: physical anhedonia (mean delta=1.55, t(28)=1.79, p=0.106), social anhedonia (mean delta=1.35, t(28)=1.68, p=0.107), magical ideation (mean delta=0.28, t(28)=0.40, p=0.691), and perceptual aberration (mean delta=0.62, t(28)=0.92, p=0.360).

Furthermore, examining Pearson's correlations between the scales difference scores, we found a significant strong correlation only between magical ideation and perceptual aberration (r=0.506, p=0.005), and trend-level moderate correlations between physical anhedonia and both magical ideation (r=0.337, p=0.091) and perceptual aberration (r=0.319, p=0.073), as well as between the two CHR symptoms difference scores (r=0.328, p=0.083). Difference scores of WSS and CHR symptoms never correlated (r=0.012 to 0.306; p=0.969 to 0.106). In linear regression analyses, WSS difference scores were not predictive of CHR symptom difference scores, which, in turn, did not predict WSS difference scores.

Our results strengthen the distinction between CHR symptoms and schizotypy in terms of independent state and trait factors and, thus, the notion that CHR symptoms occur on top of a heightened schizotypy, as suggested by the model by Debbané et al[2]. Furthermore, their independence support notions that the prediction of psychosis might be improved by their combination[6]. To this aim, physical anhedonia and social anhedonia, that constitute the negative schizotypy dimension, might be especially promising candidates.

Negative schizotypy might be able to detect those people most likely to progress to a severe mental disorder among those at an already increased risk to experience psychotic or psychotic-like symptoms – detected by CHR criteria. This might explain why both anhedonia scales showed greater, though still non-significant, variation over time.

Future studies on larger samples with longer follow-up and more assessment times are needed to explore the reliability of our findings, the potential specific relationships between trait and state factors, the potential patterns related to conversion to psychosis, and, ultimately, the role of these likely important risk factors of psychoses in their aetiology[1].

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Borderline personality disorder or a disorder within the schizophrenia spectrum? A psychopathological study

Borderline personality disorder (BPD) is one of the most frequently used diagnoses in European and American psychiatry. Nonetheless, the borderline diagnosis is nosologically unclear, especially with respect to its differentiation from the schizophrenia spectrum disorders.

When entering the DSM-III, BPD was separated from schizotypal personality disorder (SPD), formerly often denoted as borderline schizophrenia. In a detailed historical, conceptual and empirical review[1], we have argued that the division of the borderline group into BPD and SPD was not entirely justified, and that the BPD category today is overinclusive and both clinically and conceptually difficult to differentiate from the schizophrenia spectrum disorders. In a separate study[2], we have pointed out that the BPD criteria of "identity disturbance" and "chronic feelings of emptiness" refer to multi-layered phenomena which in their basic aspects of structural change of experience were both originally ascribed to the schizophrenia spectrum[3].

Informed by these studies, we conducted an empirical study of 30 patients (28 females, mean age 30.0±8.0 years) who had received a main clinical diagnosis of BPD at three university-affiliated outpatient clinics specifically dedicated to the treatment of BPD in the capital region of Denmark. Among these patients, 56.7% had previously been hospitalized and 70.0% had previously received a non-BPD diagnosis, mostly affective or anxiety/stress related disorders, in line with a recent Danish register study of 10,876 patients[4].

The patients underwent a careful psychiatric evaluation by a senior clinical psychologist and researcher. Interviews were conducted in a semi-structured and conversational manner ac-

cording to standard phenomenological principles and involved a composite instrument used for several psychopathological studies at our department[5]. In addition, we specifically rated all BPD and SPD criteria according to both DSM-5 and ICD-10. All interviews except one were videorecorded and reviewed, and narrative summaries were made of all of them.

Research diagnoses were made according to DSM-5 and ICD-10 at a consensus meeting between MZ and JP. In cases of uncertainty about crucial psychopathological phenomena, MZ and JP jointly evaluated extracts of video recordings or made a joint extra interview with the patient. A random sample of five interview summaries was independently diagnosed by an external senior psychiatrist, who agreed with the consensus diagnoses.

The study found that the vast majority of patients in fact met the criteria for a schizophrenia spectrum disorder (66.7% according to DSM-5 and 76.7% according to ICD-10), i.e. schizophrenia (20.0% according to both DSM-5 and ICD-10) or SPD. Among the non-schizophrenia patients, 40.0% had "quasi-psychotic episodes" (SPD criterion in ICD-10). Five patients had psychotic symptoms that were more articulated than at a "quasi-psychotic" level, yet still failing to meet the criteria for schizophrenia.

The most frequent diagnostic criteria were the SPD "inappropriate/constricted affect" and "unusual perceptual experiences", whereas the least frequent were the BPD "impulsivity" and "intense and unstable relationships". The BPD criteria of "identity disturbance" and "chronic feelings of emptiness" were significantly correlated with the total score of self-disorders as measured by the Examination of Anomalous Self-Experience (EASE)[6].

Patients with schizophrenia and SPD had significantly (p<0.01) higher levels of self-disorders than the non-spectrum group (17.5±6.0 vs. 6.8±5.4 in DSM-5; 16.9±6.0 vs. 4.1±2.6 in ICD-10), and these levels are very similar to findings in other studies[5]. There were no significant differences in total EASE score between the schizophrenia and SPD group according to both diagnostic systems.

We believe that this state of pronounced diagnostic confusion may in part be an unintended result of the "operational revolution" and its introduction of polythetic criteria which are defined by short layman statements open to multiple interpretations and semantic-historical drifts.

The pre-DSM-III borderline concept evolved from several sources[1].

One source was the clinical and psychotherapeutic notion of sub-psychotic cases of schizophrenia originally described as latent, pseudoneurotic or borderline schizophrenia or "Hoch-Polatin syndrome"[7]. This Gestalt comprised subtle Bleulerian fundamental symptoms such as disorders of expressivity and affectivity, formal thought disorder, ambivalence, experiential ego disorders, and a variety of psychosis-near disintegrative features.

Another source came from psychotherapeutic practice describing extroverted, dramatic patients with intense but fluctuating interpersonal relationships, shifting between idealization and devaluation, and problematic to manage in a psychotherapeutic setting.

Finally, Kernberg's[8] structural-dynamic concept of borderline personality organization influenced the development of BPD criteria (e.g., identity diffusion and a specific pattern of defense mechanisms such as splitting). However, Kernberg's concept was a transdiagnostic dimension applicable to such different categories as schizoid (and presumably schizotypal), paranoid, hypomanic, narcissistic and antisocial personalities and different psychosis-near disorders.

Since 1980, the founding prototypes and the original psychopathological insights that imbued the creation of the polythetic criteria have gone into oblivion. The polythetic criteria have resulted in an a-contextual emphasis on single emblematic elements (e.g., self-mutilation) and a general decline in psychopathological knowledge. This has contributed to the contemporary diagnostic confusion. For instance, impulsivity as a personality trait (i.e., manifest in different situations across the span of life) may be confused with disorganized behaviour or impulsions appearing within the schizophrenia spectrum.

Today, near-psychotic symptoms appear as DSM-5 criteria in both BPD and SPD. This makes the differentiation of BPD from the schizophrenia spectrum heavily dependent on the detection and registration of the schizophrenic fundamental symptoms. Unfortunately, clinicians and researchers no longer pay careful attention to those features, and their expressive nature make them impossible to be assessed through self-report questionnaires and structured interviews.

Since DSM-III, psychiatric diagnoses have become reified and considered as "natural kinds", and only research based on the diagnostic criteria of the most recent edition of DSM is usually considered for publication[9]. Instead, we perhaps ought to re-instantiate theoretical and empirical psychopathology at the core of scientific psychiatry.

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Prevention of depression will only succeed when it is structurally embedded and targets big determinants

About 150 million people worldwide are affected with major depressive disorder (further depression) at any moment, and one in every five women and one in every eight men experience an episode of major depression over the course of their life.

Although, since the 1970s, more and more people in Western countries have received mental health care, most notably pharmacotherapy, epidemiological data do not indicate a drop in the population prevalence of depression[1]. It is clear that the effectiveness of current therapies relative to placebo is modest, and substantial treatment quality gaps still exist[1]. However, even with optimal treatment delivery, other approaches are necessary to address the public health burden of depression and other common mental disorders.

Prevention is a largely neglected option, but has its own complexities. Recent meta-analyses of randomized controlled trials of preventive interventions that seek to reduce the incidence of depression consistently report small to occasionally moderate effectiveness, with numbers needed to treat (NNT) around 22[2,3]. Notably, these effects sizes are similar to those for the use of statins to prevent an acute myocardial infarction during a 5 year period[2].

However, the large majority of prevention trials concern psychological therapies administered to motivated people with sub-threshold symptoms. In addition, studies are limited to short-term outcomes and effects decrease over time, suggesting that repeated age-adapted exposures are essential. Active comparators are rarely used, and higher quality studies report substantially smaller effects. In addition, adherence is far from optimal. Populations at the highest risk are often the least motivated to participate in psychological therapies.

The biggest problems of current prevention are that it does not target the strongest determinants of risk and is not structurally embedded in major social systems.

Strong proximal determinants include exposure to poor parenting (risky prenatal behavior, emotional neglect, rejection, lack of structure, over-control and over-involvement, inter-parental conflict, family instability), as well as children's maladaptive personality traits (negative affectivity, low self-control) and poor social and problem-solving skills[4-6]. These have well-established long-term effects on a broad range of outcomes[4,7]. When both poor parenting and child risks are present, maladaptive person-environment transactions may develop that often result in intractable personality problems which are resistant to change.

It is therefore essential to target simultaneously both parent- and child-related determinants of risk. Thus, prevention needs to start early in life, address both child and parent, be long-term and structural, and improve parenting skills and children's self-control, negative affectivity and life skills, partly through better parenting and partly through better education.

Negative affectivity and self-control are especially important, given the prospective significance of early-onset phobia, hyperactivity and oppositional-defiant behavior[8]. Also of interest, but less thoroughly investigated, are the mental health effects of distal socio-economic and cultural factors, such as inferior social status, income inequality, migration, and their effect mediators[9].

The second problem of current prevention is that it is not structurally and socially embedded. Large-scale, long-term implementation and utilization of prevention can only be successful if prevention is embedded at local, district/state, and national levels. Two forms of embedment are important. First, the "socio-political form", in which local administrations and national governments embed prevention (programs/activities) in existing institutions in the domains of education, pregnancy and child care, health and social work. Second, the "social-psychological form", in which mental health values and behaviors develop into widely accepted social norms (as is happening with smoking).

The first form of embedding is probably the best way to guarantee structural funding, political collaboration and thus long-term implementation. The second form is important as it rewards (mental) health behaviors. For instance, if life skills become part of the regular curriculum of schools (in smaller classes!), repeated age-adapted exposure to universal "prevention" becomes a normal component of preparation for adult life.

Mental health professionals and organizations cannot achieve this alone. As advocated by the World Health Organization, it requires the joint collaboration of multiple parties at multiple levels of organization (community, municipality, district, state).

The major advantages of embedded universal programs are that they: a) may normalize prevention activities because they are anchored in systems that are (virtually) mandatory (education, obstetric, child care); b) reduce risk of stigma; c) improve parenting, child characteristics and life skills (and hence lifestyles), which d) will benefit multiple domains of life. This may range from mental and physical health to educational attainment, occupation and income, but even relationships, social embeddedness and crime rates. Although ceiling effects certainly exist, even parents and children who do relatively well on all fronts may benefit from universal programs[4].

Despite the expectation that population effects will be substantial, universal programs will not involve everybody at the desired level. Some people will need additional input: remedial prevention, analogous to remedial teaching for pupils with unsatisfactory academic progress. In this way, selective/indicated prevention supplements universal prevention.

We are facing a remarkable paradox. On the one hand, stakeholders (policy makers, consumers, insurance companies,

professional organizations and researchers) consider prevention a very self-evident idea and agree that prevention of mental disorders is their top priority. On the other hand, structural and socially embedment of preventive activities and research in mental health is minimal.

We believe the only way to substantially scale up and anchor prevention at all levels in society to such an extent that it will reduce the population prevalence of depression (and improve functional outcomes and quality of life) is large-scale structural and social embedding of universal and "remedial" prevention programs targeting the big determinants. It should start very early in life and target parenting skills of parents and life skills of children, and be long-term and structural.

Substantial investments are required to develop, implement, and evaluate the proposed prevention. It is also crucial that research evaluating prevention use methodological rigor and target long-term outcome, as these limitations continue to fuel doubts and reservations about the effectiveness of prevention.

If politicians really want to reduce the burden of depression, there should be proportionality between burden and expenditures (treatment, prevention, research). It is about time to catch up with cancer and cardiovascular disease prevention. Together with other relevant parties such as public health, police, insurance companies and educational authorities, mental health professionals will also need to step up their political influence and persuade politicians and the public to embed multi-target and multi-level mental health promotion and prevention.

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Implementing the WPA Action Plan 2017-2020: community orientation for learning, research and practice

With each new term of Presidency at WPA, an Action Plan is implemented that builds on our preceding work. Our 2017-2020 Plan[1,2] strengthens the community orientation of our profession. It addresses the contribution of psychiatrists to responses to conflicts, emergencies and adversities, and provides a targeted strategy for reaching young women and men who face adversity and disadvantage and associated mental ill health or risks.

In March 2018, we took the first major steps toward executing this strategy, when WPA representatives met with leaders from citiesRISE, the Juan José López-Ibor Foundation and senior psychiatrists from the Colombian city of Bogotá[3]. We were joined by experts from the Department of Mental Health and Substance Abuse of the World Health Organization and the International Medical Corps. We talked about how, through collective efforts, we can link local action with global networks to accelerate the uptake of best practices and models and support psychiatrists to contribute to community-based work in practical, creative ways. We considered how WPA and partners might best develop tools and strategies to support those at high risk of developing mental health problems (for any reason) and those who are already experiencing these problems, as well as ways to promote mental health for the wider population.

We have now established the WPA-citiesRISE partnership. The WPA is a founding partner of the citiesRISE platform[4] and has been instrumental in shaping its strategy and collective action program, implemented initially in five cities and focussed on the mental health of young people. The program is supported by a range of philanthropic and industry funders. The WPA has participated in collective action workshops in Chennai and Nairobi, as well as supporting foundational work in Bogotá. Existing initiatives in these cities, many of them led by small grassroots entities, are examples of what community orientation in mental health looks like in practice.

The WPA is helping to stimulate productive exchanges between people who rarely have an opportunity to talk to one another. In Nairobi, for example, there have been joint meetings with senior psychiatrists, the national directorate of mental health, researchers, civil society leaders and young people such as participants in Amazing Minds (a creative network of students dedicated to reaching zero stigma for mental health and increasing help seeking among campus students). These kinds of encounters are characteristic of the WPA-citiesRISE partnership. They are an exciting way to support mutual understanding between diverse organizations as they join the global program.

As well as supporting citiesRISE by access to the best available technical and conceptual evidence and experience, the WPA will lead specific programs. Psychiatry will contribute to better community capacity to respond to the mental health needs of children and young people in emergencies and adversities. Across the cities we will work towards: a) improved perinatal mental health, and b) support for prevention programs that reduce the prevalence of depression, anxiety and suicidal behaviour among young people. The recent announcement of the Lancet-WPA Commission "Reducing the global burden of depression"[5] is a further step in this direction.

The work will consolidate the perception and role of psychiatrists as members of a profession with a community orientation. It will demonstrate the practice of psychiatry within a framework of community care and multi-sector collaboration across low-, medium- and high-income settings. It will show how sustained support can be achieved for networks of psychiatrists engaged in community-based work and for psychiatrists working in community development related to the improvement of mental health.

The WPA-citiesRISE partnership gains life from the committed leadership of psychiatrists in each of the engaged cities. In the first phase, WPA is appointing a global task force to guide the development of the partnership activities. We are also identifying interested psychiatrists in each city. They will be encouraged to form local representative groups positioned to assist the work of citiesRISE and develop the community-oriented work of psychiatrists in their country of operation. Each group will ideally include diverse practitioners, drawn from a range of backgrounds and from different points in their careers.

The WPA is appointing psychiatrists as program leaders. They will have multi-faceted roles that include facilitating the development of the local representative groups and the interaction between them and the global task force. They will take a lead in developing the tools and guidelines for the planned activities.

We are actively pursuing other activities. These include support for best practice in working between practitioners, people with lived experience of mental ill health and family carers[3,6]. The WPA Executive Committee has approved the establishment of a service user and family carer consulting group to advise on new initiatives, including reviewing and improving the participation of service users and family carers in our congresses. This work is a priority in the new WPA meetings policy. Examples of best practice will be gathered as the WPA-citiesRISE partnership work proceeds, and will be disseminated through the newly launched WPA website[7] and other channels.

The WPA participated in preparation and launch of the Lancet Commission on Global Mental Health[8], a landmark document in the field. We are concerned with quality of care and human rights in psychiatry. Consequently, we are designing a project with a member society to examine how to create conditions in mental health services that are free from violence and abuse and that minimize coercion.

To conclude, I am pleased to report these developments in implementing the WPA Action Plan. Other activities under the Action Plan have been and will be

described in detail on other occasions. There are major changes underway in the WPA meetings program, in the work of the Early Career Psychiatrists programs, and in WPA communications. A global survey of psychiatry is being developed in conjunction with a survey of training programs, and other programs are detailed separately by our active officers[9-11].

My fellow officers and I are above all encouraged by the active engagement and support of the WPA Secretariat, our Member Societies, Scientific Sections, hard-working Standing Committees and all components of the Association.

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WPA President

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Collective action for young people's mental health: the citiesRISE experience

Globally, most young people with mental health problems lack the support and access to the care they need[1]. The rapidly urbanizing, technology-based societies of today present social, political, economic and culture changes that increase both risks to, and opportunities for, young people's mental health.

However, current approaches to supporting the mental health of young people typically lack an integrated understanding of the pressures and challenges they face, especially at critical life transitions. They do not address the rapidly increasing disparities experienced by young people, particularly by those who are marginalized[2]. Beyond scaling up a single model, we believe that the most promising path forward for mental health leverages place-based solutions, taking services to young people through a range of access points and intervention methods.

citiesRISE is a multi-stakeholder initiative. It was formed as a response to the concern that fragmented and small-scale efforts are failing to address the rising tide of mental health problems among young people worldwide, despite the existence of effective approaches in several parts of the world[3]. citiesRISE is using proven methodologies of collective action and a network approach to introduce and scale up interventions backed by evidence and experience.

citiesRISE is working now in four countries: India, Kenya, the US and Colombia.

Organizations at the local, national and global levels are working together to implement programs in the first five cities of Chennai, Nairobi, Seattle, Sacramento and Bogotá. In each of these cities we are convening young leaders, psychiatrists and other mental health professionals, government and civil society stakeholders, as well as cross-sectoral partners, to learn about local initiatives, and connect to global ideas, insights and resources.

We are jointly designing interventions that will address supply (e.g., the scale of services and support available for early intervention) and demand (i.e., awareness, help-seeking behavior) for services as well as relevant societal factors. The vision of this initiative and the approach has attracted a range of investors from philanthropy and industry.

citiesRISE is currently developing five key offerings:

- City platforms that are testing a collective action approach: identifying the needs of the city, connecting different sectors, and evaluating opportunities to scale up existing community interventions while also recommending new and promising approaches.
- Youth leadership: it is critical to tap into the insights and energy of young people in the design and delivery of mental health interventions. Our early work in Nairobi and Chennai has demonstrated that youth are engaged in improving local mental health locally, bringing energy and passion to the cause; just as young people everywhere are found at the center of movements for social change, in the process of growing into the leaders of tomorrow.
- The Learning Collaborative is a knowledge forum that will pool and provide access to information. Cities will use it to compare local information and experiences and learn about emerging best practices. The Collaborative will collect data from each city, contribute to city-level processes, and provide opportunities to share ideas and knowledge.
- The Accelerator was launched with Grand Challenges Canada to support promising social businesses and young innovators. It has been working to identify innovative approaches to improving mental health as well as proven models that are ready for scaling up, such as the Friendship Bench, StrongMinds, Atmiyata, Drumbeat and others. In this initial phase it is being set up to provide financial and technical assistance to test and scale ideas rapidly. The vision is to offer cities and communities new tools for adoption into their core programs along with the scaling up of proven models.
- A global framework for monitoring and evaluating the work in each city is being finalized, with site-specific and shared indicators.

Partnerships are vital to implement strategies on prevention and treatment of mental illness and the promotion of mental health through the citiesRISE platform. The WPA-citiesRISE partnership, for example, gives the opportunity to demonstrate the community orientation of psychiatry while contributing to the local and global efforts to improving the mental health of young women and men in adversity[4,5].

The citiesRISE concept differs from approaches that focus primarily on mental health care delivery by trained specialists alone. citiesRISE aims to mobilize all available resources, including young people, non-specialists and sectors beyond health care. Psychiatrists and other mental health specialists are centrally involved in several roles such as advocates, advisors, clinical supervisors and trainers, as well as in direct clinical care.

Building on successful models sourced from cities around the globe, our process involves:

- Identifying local leaders, specifically among a city's youth population.
- Hosting a series of working sessions to identify community needs and capabilities.
- Building consensus on shared goals and a framework for monitoring and evaluation.
- Providing funding and technical assistance to accelerate the work at the city level.
- Evaluating the work with the goal of building sustainable initiatives and strategies that can scale.
- Sharing and implementing successful initiatives in cities worldwide.

Achieving better mental health needs a broad strategy that engages many disciplines and sectors, such as neighborhood safety, commercial development, public spaces, and cultural life, including education, arts and sports[1]. Including and activating young people at every stage has provided energy and insight for this work. With the right kind of leadership from public and private sectors, we believe that affordable support for mental health can be developed by connecting formal and informal services across housing, transport, law enforcement, education and health systems.

Accessible psychosocial support services can mitigate the impacts of contemporary urban problems such as homelessness, poverty, and loss of education and job opportunities. Cities can therefore lead the way in accelerating the scaling up of solutions and catalyzing local collective action towards addressing mental illness and improving mental health.

In this way, we encourage a broad approach to include, for example, awareness-raising and education programs, the use and design of public spaces, and the role of technology to support communities and complement the development of clinical services for those that use and need them.

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ICD-11 sessions within the 18th World Congress of Psychiatry

Within the 18th World Congress of Psychiatry, held in Mexico City from 27 to 30 September 2018, one presidential symposium, one course and several individual presentations focused on various aspects of the chapter on mental and behavioural disorders of the 11th edition of the International Classification of Diseases and Health Problems (ICD-11).

The statistical version of the chapter, containing the hierarchical structure, the category names, the code numbers, brief definitions of each disorder, and inclusion and exclusion terms, was released to the World Health Organization (WHO) Member States in June 2018 to prepare for implementation. This version is available online at https://icd.who.int/dev11/l-m/en.

The ICD-11 is scheduled for approval by the World Health Assembly in May 2019. The Clinical Descriptions and Diagnostic Guidelines, intended for use by health professionals in clinical settings, will be published as soon as possible after that.

A primary care version of the chapter is also being developed, whereas a research version may be developed later.

The field testing of the chapter has been now completed. It is important to emphasize that it was conducted before the finalization of the chapter (not after, as often happened for other classification systems), so that changes to some sections of the chapter could be made on the basis of the results of the trials.

The field studies included: a) two large international surveys of views of psychiatrists and psychologists about the features that could increase the clinical utility of the classification of mental disorders; b) formative field studies, aimed to guide decisions about the basic structure and content of the classification by exploring clinicians' conceptualization of the interrelationships among categories of mental disorders; c) Internet-based field studies, implemented through the Global Clinical Practice Network (which includes now more than 15,000 mental health and primary care professionals from 155 countries, comprising more than 5,000 from Europe, more than 3,000 from the Americas, more than 3,000 from Western Pacific, more than 600 from South East Asia, more than 400 from Eastern Mediterranean, and

more than 300 from Africa), which used case vignette methodologies to examine clinical decision-making in relationship to the proposed ICD-11 diagnostic categories and guidelines; d) clinic-based (or ecological implementation) field studies, to assess the reliability and clinical utility of the diagnostic guidelines with real patients in ordinary clinical settings; e) service user/carer studies, providing feedback on the diagnostic guidelines.

The results of the Internet-based and ecological implementation field studies were presented at the Congress.

In the Internet-based field studies, the diagnostic agreement for disorders specifically associated with stress was consistently higher for the ICD-11 as compared with the ICD-10 categories (e.g., 81.8% vs. 76.8% for post-traumatic stress disorder; 75.8% vs. 71.8% for adjustment disorder). The same applies to feeding and eating disorders (e.g., 96.8% vs. 95.1% for anorexia nervosa; 87.5% vs. 78.4% for bulimia nervosa).

In the ecological implementation field studies (whose detailed results have been recently published in this journal[1,2]), the clinical consistency (reliability) ranged from moderate to almost perfect (.45 to .88) for the various disorders and was generally superior to results obtained for

ICD-10. Concerning clinical utility, the diagnostic guidelines for schizophrenia and other primary psychotic disorders, mood disorders, anxiety and fear-related disorders, and disorders specifically associated with stress were perceived as easy to use, corresponding accurately to patients' presentations (i.e., goodness of fit), clear and understandable, providing an appropriate level of detail, taking about the same or less time than clinicians' usual practice, and providing useful guidance about distinguishing disorder from normality and from other disorders. Clinicians evaluated the guidelines as less useful for treatment selection and assessing prognosis than for communicating with other health professionals[3], although the former ratings were still positive overall.

At the Congress, the good reliability in the use of the diagnostic guidelines was confirmed in the course, in which clinicians from all regions of the world were presented with clinical vignettes relevant to the sections on psychotic disorders, mood disorders, anxiety and fear-related disorders, and disorders specifically associated with stress.

In the presidential symposium, several general issues concerning diagnosis and classification of mental disorders were addressed, including culture fairness, validity in predicting response to treat-

ments, and the possible complementary role of systems or models based on psychopathological dimensions, neurobiological variables, the network theory of mental disorders, or a transdiagnostic approach[4-14].

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