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World Psychiatry

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2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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Subjectivity, psychosis and the science of psychiatry

The significance for psychiatry of a patient's subjective or "lived" experience seems obvious even on casual reflection, especially in cases of severe mental illness. It is likely that curiosity and concern about what a patient is experiencing is a prerequisite for building trust or a therapeutic alliance, particularly when the experiences seem highly unsettling and unusual. Few would deny that grasping something of the patient's viewpoint should play a role both in developing and selecting therapeutic techniques.

Beyond this, it seems likely that some understanding of patients' subjective life is relevant to psychopathology as a scientific enterprise. The *explanandum* at issue in what we term "delusion", "hallucination" or "thought disorder" may, for instance, be found to involve quite different experiences across different individuals, diagnoses or subgroups, and such knowledge can improve the pathogenetic modelling of mental disorders. It is possible, in fact, that the lackluster results of neurobiological research on severe mental illness in recent decades (widely acknowledged) be in part due to neglect of this subjective dimension and the distinctions it would allow.

Given all this, it is striking to note how limited the study of patients' experiences has been in the mainstream of psychiatry and clinical psychology. One may wonder why. An obvious reason is the influence of exclusionary and reductive forms of empiricism and materialism, which have stressed the difficulty both of observing subjective life and of incorporating it into the causal order of the universe. Subjectivity can indeed seem what phenomenological philosopher M. Merleau-Ponty termed "the flaw in the great diamond of the world"[1] – a recalcitrant explanatory outlier, albeit one that is lodged at the center of each one of us (our consciousness) and is the condition for whatever knowledge we possess.

A second reason is a widespread discomfort with and incomprehension of the states of mind that characterize severe forms of mental or emotional disorder, especially psychoses. Though many scientists and scholars are fascinated by the limit-experiences that can occur in psychotic conditions, many are ready to accept what are, in scientific terms, extremely vague and potentially misleading characterizations, often involving defect and deficit assumptions that do little more than register the absence of a norm (e.g., "inappropriate affect", "false belief"). Deficit models are often criticized on ethical grounds as being condescending or even insulting to the patient's dignity, but their modes of objectification may also be *scientifically* inadequate, since they fail to register what may be qualitatively distinct about the condition being studied[2]. Conventional approaches also tend to downplay the *agentic* role of the patient – i.e., the subtle ways in which a patient's orientation or attitude, partly under his/her control, can impact the nature of delusions, hallucinations or "thought disorder"[3].

The study by Fusar-Poli and numerous co-authors published in this issue of the journal[4] is an exceptionally important contribution. There have been previous attempts, especially by phenomenologists and qualitative researchers, to collaborate intensively with patients whose experiences they study, but never on such a broad-based, quantitative scale. As the authors note, their results are in fact consistent with the rich phenomenological tradition which stemmed from K. Jaspers and the Heidelberg school and included, among the others, K. Schneider, K. Conrad, W. Blankenburg, E. Minkowski and the various contemporary experts cited in the paper.

Phenomenological psychopathology did influence mainstream British psychiatry in the 1950s through a textbook by the German-Jewish émigré W. Mayer-Gross, and penetrated North American consciousness with the anthology *Existence* in 1958[5] and Laing's *Divided Self* of 1960; but then it languished for several decades prior to its more recent renaissance beginning in the 1990s. Fusar-Poli et al's study vindicates this most venerable approach to a rigorous understanding of mental life in psychiatric illness.

The present study is mainly in the tradition of *descriptive* phenomenology, offering diverse accounts largely in the vocabulary of everyday language, eschewing attempts at explanatory synthesis[5]. Another type of phenomenology, more speculative and theoretical, does try to account for the heterogeneity of some subsets of symptoms by identifying a core or generating disorder, thereby providing models for pathogenetic research that can account for the variety and variability of certain psychotic conditions – e.g., "loss of vital contact"[6] or altered "basic-self experience"[7].

There is much to be learned from Fusar-Poli et al's report, a superb compendium of all the major experiences characteristic of psychosis, and perhaps especially of the contested category of schizophrenia. Like earlier phenomenological work, their research shows that signs and symptoms can seem very different from *within* a mental condition compared to what common sense or standard psychiatry often claims. Hallucinated voices may not exactly be "heard". What we call "delusions" may or may not be taken literally and, rather than being "erroneous beliefs", may sometimes involve withdrawal into a private or subjective world that the patient himself actually recognizes as such[8]. So-called "poverty of content of speech" – a type of "formal thought disorder" – may sometimes contain profundities.

Among the many insights to be gleaned is the prominence (at least for *some* patients *some* of the time) of the experience of insight and illumination. Confronted with "madness", the academic observer or man-on-the-street stresses metaphors of darkness, confusion, and subterranean journeys, and this sometimes accords with the patient's viewpoint. But, as Fusar-Poli et al[4] report, patients may describe some "psychotic" states as shot through with a sense of almost blinding clarity and revelation. We must beware of projecting our own yearnings and value judgments onto the patients. They, at least, can sometimes feel not beneath, but far above the quotidian realities of "normal" people, who

neglect more encompassing and foundational though ineffable truths – truths perhaps accessible only to forms of self-conscious or hyperreflexive awareness unavailable to most of us[3].

In closing, one must acknowledge some gaps in our grasp of subjectivity and its significance for psychiatry. It may be obvious to common sense that the exercise of free will, together with a person's experience of meaning or significance, do play a role in human behavior and thereby affect the material plane of brain functioning (if I choose to close my eyes, in prayer, patterns in visual cortex are altered). But it is also true that we have difficulty incorporating the domains of conscious life and its physical substrate within a single explanatory account (the mind/body problem). In particular, we have difficulty integrating "act" with "affliction" aspects of psychological existence[3] – that is, appreciating the subtle but decisive ways in which defensive or other goal-directed forms of thought or behavior can interact with aspects of mental life over which the person has little or no control.

Even more basic is the challenge of observing and describing consciousness itself, whose ever-changing, all-encompassing flow we, as human beings and language speakers, are constantly tempted to misperceive or misdescribe. We succumb to this temptation by using words that stress the substantive over the transitory aspects of experience, or by focusing on particular objects of awareness while ignoring subtle alterations in, for example, the experience of space, time, or the overall atmosphere of reality. In fact, no approach can be fully "bottom-up" in the sense of being purely empirical or a-theoretical: when it comes to describing experience, patients as well as professionals are burdened (though also blessed) with the objectifying prejudices of their language and their worldview. The study of "lived experience" may then be impossible as a foolproof, quasi-empiricist venture. It is, however, also indispensable – and to both the ethical and the scientific enterprise of psychiatry[9].

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What is good acute psychiatric care (and how would you know)?

There is an old joke told of a tourist asking for directions, only to be advised by a local: "Well, I would not start from here". We have the acute mental health services we have inherited. Asylums closed during the great era of deinstitutionalization, clunkily evolving into our current inpatient estates. Crisis teams were established (without any real evidence) to provide choice and less coercive treatment, but often seem to function solely for – in dreadful contemporary management-speak – "admission avoidance".

As a thought experiment, if you were to start afresh, setting up services without the baggage of existing buildings and services, what would you create? And dream some more: your budget is limitless, and recruitment and retention of staff is not a problem. You would not build what we have now – but why not, and what would you replace it with? Would you have inpatient wards? Sure – better equipped, with finer facilities and more staff; but how many, and why, and what exactly would happen on them? Home treatment teams: not everyone wishes to be in hospital in a crisis, but which interventions should they provide? How creative might you get with new models of treatment, engaging social care, the third sector, and local communities?

So, first we hit a wall of reality as we are reminded that we have budgets, staff shortages, and buildings in various levels of disrepair. We enter a world of opportunity costs: maintaining a ward might mean reducing a community service or hiring fewer occupational therapists. And then we hit an evidence wall. What are wards for, what do they do? Containment, safety, care? All of these surely, but perhaps the emphasis has been on the first two (and many people are unaware that much of the initial "locking of wards" was with intent to stop the public walking into space containing people at their most vulnerable, not the other way around). But does "containment" work? German data suggest that locked units do worse than open ones in terms of suicide[1]. Parallel challenges can be thrown at home treatment teams. The evidence supports them saving money (not a bad thing of itself) and reducing hospital admissions[2], but their impact on safety and reducing coercive care is limited, and data on patient experience are modest[3].

One can ask what "effectiveness" means: are "preventing harm" and "avoiding admission" the limits of our vision and ambition for acute care? Evaluations have often emphasized these, as they are easier to measure. What might you alternatively explore (and how would you weigh that sunlight)? More short-term crisis-focused psychological interventions (which ones?); a more trauma-focused service philosophy; better working with housing and domestic violence teams? As a follow-on, we bet your answers will be very different depending upon whether you use, work in, manage, or commission services.

In this issue of the journal, Johnson et al[4] provide a comprehensive overview of the existing evidence in acute mental health care, and the gaps and opportunities for innovation. They argue convincingly that key steps are reducing coercion, addressing

trauma, diversifying treatments and workforce, and making decision making and care truly collaborative. They rightly recognize and call-out the complex ethical realities of research with individuals often at their most vulnerable.

We were particularly struck by their description of presentations at the emergency department. Who can fail to be struck by the frequent inadequacy of such environments, and high reported rates of prejudicial treatment of mental health crises? A second area that resonated loudly is the description of initiatives working with the police. These have grown out of concern that such crisis-interfaces can be common, but, without adequate training or resource, they risk actually causing harm. In the UK, this has recently been brought into sharp focus by public concern about a specific intervention – the Serenity Integrated Mentoring model – whose underpinning evidence base and the lack of clear service-user input into its design have been heavily criticized.

We need to move beyond preoccupations with "avoiding admission", "bed numbers", and "length of stay". The first sets-up services that perceive inpatient care as failure; to the latter two, we are never sure what the "right" number is, and which person, upon being admitted to a ward, would ever inquire or care about a unit's average length of stay?

We can hold a basket of all the agreed necessary parts: co-design and co-production; compassionate, thoughtful care; and a range of psychosocial and pharmacological interventions. The first of these is surely self-evident, yet inadequately truly practiced – if you work in acute care, ask those who use your service how engaged they feel in this process. The second is not rewarded by systems that prioritize "avoiding harm" over "doing good". Johnson et al note how the existing literature on inpatient care often highlights poor practice: this is important, but "good" is not the absence of "bad", and we need to do better at welcoming sunshine. The detail of the type and range of services and care remains, perhaps, the trickiest and least understood part. But therein is the opportunity for growing, testing, and evaluating models and outcomes. Why something works (or does not), which factors underpin this (the clinical issues, intervention, clinicians, or geography/environment), and what is transferable, especially to low- and middle-income countries.

To us, there appear to be two major contemporary opportunities. First, we agree with Johnson et al on the need for better co-design and co-production of services, and research with those who use them. On Twitter, the hashtag *#CrisisTeamFail* has gained traction as individuals describe their poor experiences of care: this needs to be heard, understood, and engaged with, not responded to in a defensive manner by professionals. There could be none more invested in improving services, knowing where the gaps are, and measuring what matters than users and their support networks.

Everyone appreciates real-world budgets, but we must still be having thoughtful conversations about what we can nevertheless all do together with the resources that we have. The call from those using services is consistent. Clear routines and fostering of healthy habits, not days seemingly solely built around medication and meal times. More occupational therapy and meaningful activities, ensuring that these are a focus for staff engagement, managerially emphasized and supported above note-keeping and computer entries, and not disrupted or stopped by inanities such as missing batteries and lost pieces of equipment. People understand that home treatment teams operate shift-systems and staff turnover, but personalizing care to understand individuals' perspectives and concerns, including around home visits and possible illness-triggers, is not complex. Above all, respect and kindness, not least in the emergency department: the time has long-passed to hear prejudicial comments from professionals.

Second, there is an international trend to more "integrated services". In the UK, a quiet but profound shift is occurring towards integrated care systems[5] that join mental health, acute and community physical health, social care, and local resources with served populations. Johnson et al note the growth of innovations such as "crisis cafés" and "crisis houses", and correctly identify how voluntary sector services helpfully work in different ways to (the often monolithic) health care industry. There are many fertile opportunities for collaboration. True population-based research is needed: messy data sets outside the gold-standard randomized controlled trials – in other words, real people in their daily lives. We might not have chosen to start from where we currently are but, to mix our metaphors, the longest journey begins with a single step.

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D.M. Phillips has lived experience of using crisis and inpatient services.

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The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics

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Psychosis is the most ineffable experience of mental disorder. We provide here the first co-written bottom-up review of the lived experience of psychosis, whereby experts by experience primarily selected the subjective themes, that were subsequently enriched by phenomenologically-informed perspectives. First-person accounts within and outside the medical field were screened and discussed in collaborative workshops involving numerous individuals with lived experience of psychosis as well as family members and carers, representing a global network of organizations. The material was complemented by semantic analyses and shared across all collaborators in a cloud-based system. The early phases of psychosis (i.e., premorbid and prodromal stages) were found to be characterized by core existential themes including loss of common sense, perplexity and lack of immersion in the world with compromised vital contact with reality, heightened salience and a feeling that something important is about to happen, perturbation of the sense of self, and need to hide the tumultuous inner experiences. The first episode stage was found to be denoted by some transitory relief associated with the onset of delusions, intense self-referentiality and permeated self-world boundaries, tumultuous internal noise, and dissolution of the sense of self with social withdrawal. Core lived experiences of the later stages (i.e., relapsing and chronic) involved grieving personal losses, feeling split, and struggling to accept the constant inner chaos, the new self, the diagnosis and an uncertain future. The experience of receiving psychiatric treatments, such as inpatient and outpatient care, social interventions, psychological treatments and medications, included both positive and negative aspects, and was determined by the hope of achieving recovery, understood as an enduring journey of reconstructing the sense of personhood and re-establishing the lost bonds with others towards meaningful goals. These findings can inform clinical practice, research and education. Psychosis is one of the most painful and upsetting existential experiences, so dizzyingly alien to our usual patterns of life and so unspeakably enigmatic and human.

Key words: Psychosis, lived experience, experts by experience, bottom-up approach, phenomenology, premorbid stage, prodromal stage, first-episode stage, relapsing stage, chronic stage, recovery, psychiatric treatment

(World Psychiatry 2022;21:168–188)

Psychotic disorders have a lifetime prevalence of 1%[1], with a young onset age (peak age at onset: 20.5 years)[2]. They are associated with an enormous disease burden[3], with about 73% of healthy life lost per year[4].

Psychosis is characterized by symptoms such as hallucinations (perceptions in the absence of stimuli) and delusions (erroneous judgments held with extraordinary conviction and unparalleled subjective certainty, despite obvious proof or evidence to the contrary). The nature of these symptoms makes psychosis the most ineffable experience of mental disorder, extremely difficult for affected persons to comprehend and communicate: *"There are things that happen to me that I have never found words for, some lost now, some which I still search desperately to explain, as if time is running out and what I see and feel will be lost to the depths of chaos forever"*[5].

K. Jaspers often refers to the paradigm of "incomprehensibility" with respect to the primary symptoms of psychosis that cannot be "empathically" understood in terms of meaningful psychological connections, motivation, or prior experiences[6]. However, psychotic disorders – especially schizophrenia – have, more than any other mental condition, inspired repeated attempts at comprehension.

In the two-hundred-year history of psychosis, numerous medical treatises and accurate psychopathological descriptions of the essential psychotic phenomena have been published. However, this top-down (i.e., from theory to lived experience) approach is somewhat limited by a narrow academic focus and language that may not allow the subjectivity of the lived experience to emerge fully.

Some evidence syntheses have summarized various aspects of the lived experience of psychosis[7-13], but again they were written by academics. On the other hand, numerous reports describing the subjective experience of psychosis have been produced by affected individuals[14-26] (see Table 1). Although useful, these reports are often limited by fragmented, contingent and contextual narratives that do not fully advance the broader comprehensibility of the experience.

To our best knowledge, there are no recent studies that have successfully adopted a bottom-up approach (i.e., from lived experience to theory), whereby individuals with the lived experience of psychosis (i.e., experts by experience) primarily select the subjective themes and then discuss them with academics to advance broader knowledge. Among the various forms of collaboration available in the literature, co-writing represents an innovative approach that may foster new advances[27,28]. It can be defined as the practice in which academics and individuals with the lived experience of a disorder are mutually engaged in writing jointly a narrative related to the condition. Co-writing is based on the sharing of perspectives and meanings about the individual's suffering. Collaborative writing must honour the challenge of maintaining each subject's diction and narrative style without capturing or formatting them in pre-established narrative models[29].

The present paper aims to fill the above-mentioned gap in the literature by providing a bottom-up co-written review of the lived experience of psychosis.

In a first step, we established a collaborative team of individuals with the lived experience of psychosis and academics. This core writing group screened all first-person accounts published in *Schizophrenia Bulletin* between 1990 and 2021[30], and retrieved further personal narratives within and outside the medical field through text reading (e.g., autobiographical books, see Table 1) and qualitative research (e.g., narratives from clinical records or service users' magazines or newsletters). The material was included if consisting of primary accounts of the lived experience of psychosis across its clinical stages (premorbid, prodromal, first episode, relapsing, and chronic). Primary accounts of the experience of recovery or of treatments received for psychosis were also included.

We performed automated semantic analyses on *Schizophrenia Bulletin* first-person accounts, extracting the list of experiential themes relating to the disorder across its clinical stages and their interconnections, loading them into Gephi software, and building up network maps.

In a second step, the core writing group selected the lived experiences of interest, tentatively clustered them into broader experiential themes, and identified illustrative quotations. The material was stored on a cloud-based system (i.e., google drive) fully accessible to all members of the group.

In a third step, the initial selection of experiential themes and quotations was collegially shared and discussed in two collaborative workshops, which involved numerous individuals with the lived experience of psychosis as well as family members and carers, to ensure that the most prominent themes were being considered and to collect users' and carers' interpretation of these themes.

The workshops involved representatives from the Global Mental Health Peer Network (https://www.gmhpn.org); the Global Alliance of Mental Illness Advocacy Networks (GAMIAN) - Europe (https://www.gamian.eu); the South London and Maudsley NHS Foundation Trust (https://www.slam.nhs.uk); the Young Person's Mental Health Advisory Group (https://www.kcl.ac.uk/research/ypmhag); the Outreach And Support in South-London (OASIS) (https://www.meandmymind.nhs.uk) Service Users Group; the South London and Maudsley NHS Recovery College (https://www.slamrecoverycollege.co.uk); the Black and Minority Ethnic Health Forum Croydon (https://cbmeforum.org); the UK Mental Health Foundation (https://www.mentalhealth.org.uk); the Faces and Voices of Recovery (https://facesandvoicesofrecovery.org);

Table 1 Selection of publications on the lived experience of psychosis considered for the present review

Beers CW. *A mind that found itself*[14]
Boisen AT. *Out of the depths*[15]
North CS. *Welcome, silence*[16]
Sommer R et al. *A bibliography of mental patients' autobiographies: an update and classification system*[17]
Clifford JS et al. *Autobiographies of mental health clients: psychologists' uses and recommendations*[18]
Saks ER. *The center cannot hold*[19]
Colori S. *Experiencing and overcoming schizoaffective disorder: a memoir*[20]
Weijun Wang E. *The collected schizophrenias*[21]
Sechehaye M. *Autobiography of a schizophrenic girl*[22]
Benjamin J, Pflüger B. *The stranger on the bridge*[23]
Geekie J et al (eds). *Experiencing psychosis: personal and professional perspectives*[24]
Williams S. *Recovering from psychosis: empirical evidence and lived experience*[25]
Stanghellini G, Aragona M (eds). *An experiential approach to psychopathology: what is it like to suffer from mental disorders?*[26]

and the Asociación Española de Apoyo en Psicosis (AMAFE) (https://www.amafe.org).

In a final step, the selection of experiential themes was revised and enriched by adopting a phenomenologically-informed perspective[31-33]. The revised material was then shared again across all collaborators in google drive and finalized iteratively. All individuals with lived experience and researchers who actively contributed to this work were invited to be co-authors of the paper. Representatives from service user and family groups were reimbursed for their time according to the guidelines by the UK National Institute for Health Research (https://www.invo.org.uk).

In this paper, the words spoken or written by individuals with the lived experience of psychosis are reported verbatim in italics, integrated by co-authors' comments and phenomenological insights.

THE LIVED EXPERIENCE OF PSYCHOSIS ACROSS ITS CLINICAL STAGES

This section addresses the subjective experience of psychosis across the clinical stages of this condition: premorbid, prodromal, first episode, relapsing, and chronic[34-37].

The premorbid stage starts in the perinatal period and is often asymptomatic; it is generally associated with preserved functioning[38], although delays in milestones may emerge[39]. Accumulation of further risk factors during infancy and young adulthood[40] may lead to the emergence of a clinical high-risk state for psychosis; this stage is often termed "prodromal" in the retrospective accounts of individuals with the lived experience. The prodromal stage is characterized by attenuated psychotic symptoms that can last years, do not reach the diagnostic threshold for a psychotic disorder, but are typically associated with some degree of functional and cognitive impairment[41-45]. These manifestations can then progress to a subsequent stage of fully symptomatic mental disorder (first episode of psychosis) and then persist, especially if treated sub-optimally, leading to a relapsing stage and, for a proportion of cases, a subsequent chronic stage[38].

Premorbid stage

An early, inner experience of loneliness and isolation

"When growing up I was quite a shy child… I was usually uncomfortable around kids of my own age"[46]. Figure 1 shows that the most frequent cluster of lived experiences in the premorbid stage of psychosis is represented by feelings of loneliness and isolation – variably referenced as being "introverted"[47], "loner"[48-50] or "isolated"[51] – already reported during childhood: *"I admitted I was a loner and was probably somewhat backwards socially. I had never had a boyfriend, rarely even dated, and my friendships with girls were limited and superficial"*[48].

This weak "attunement" in social interactions during childhood[52] has been captured by Bleuler's[53] concept of "latent schizophrenia" and Kretschmer's[54] definition of "schizothymic" and "schizoid" temperaments. Recent meta-analyses have confirmed that loneliness is a core experiential domain during subclinical psychosis[55]. Loneliness has been frequently associated with experiences of social anxiety[46,56] and recurring fears[51,57-60], ob-

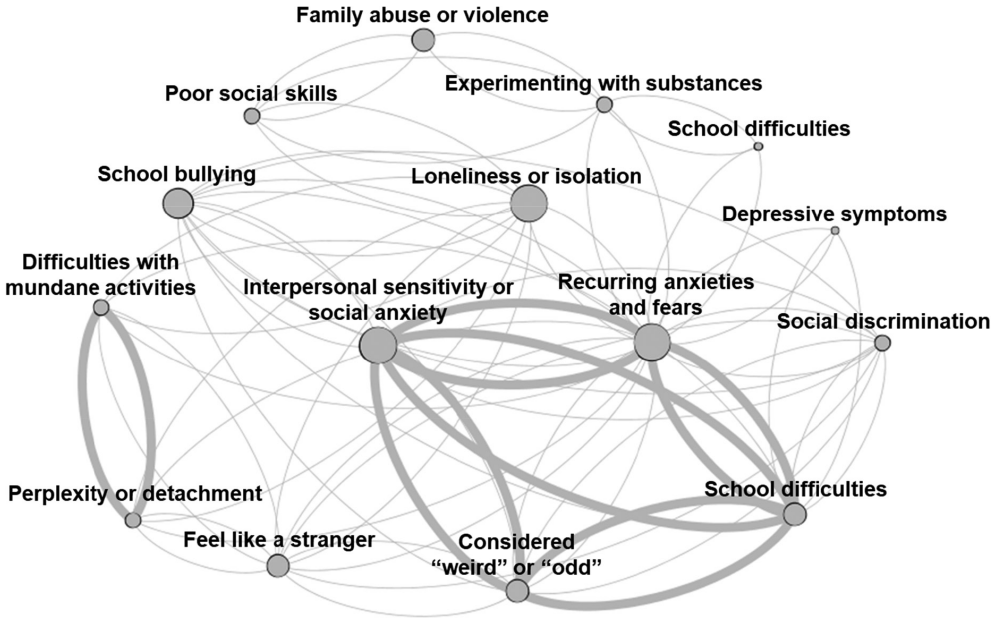

Figure 1 Network map of lived experiences of psychosis during the premorbid stage. The nodes represent the experiential themes, and the edges represent the connections between them. The size of each node reflects the number of first-person accounts addressing that experiential theme. The thickness of the edges reflects the number of connections between the themes.

sessive ruminations[59], depressed mood[57], and a heightened sensitivity to social interactions[14,60,61]: *"I was too shy to raise my hand, and although my parents were very sociable and outgoing, I would hide behind my mum when meeting strangers"*[23].

These experiences color the emotional life of the individuals before the emergence of attenuated psychotic symptoms[51,58]. Loneliness is also frequently associated with early adverse experiences, such as social discrimination[60,62], school bullying[50,60,63,64], abuse or exposure to prolonged familial conflicts and violence[65,66], which further amplify the sense of subjective alienation, fear and isolation (see Figure 1): *"The abuse I had in my years of schooling... exacerbated anger and fear, which as I remember had always been there anyway"*[60].

Loss of common sense and natural self-evidence

"*When I was younger, I used to stare at the words on the pages of a book until they became so unfamiliar that they were practically incomprehensible to me even if I had learnt their meanings before. Then I would wonder, why do words mean anything anyway? They are just letters put together by some unspoken rule... What is this hidden rule? The hidden rules that govern thoughts and behaviors were not transparent to me although others seemed to know them*"[67]. Another core experiential theme during the premorbid stage of psychosis is this diminished intuitive grasp of how to naturally conduct natural, everyday tasks like reading a book or interactions: *"I was forever making remarks and behaving in a way that would slightly alienate people. This was because I would have to grasp situations by apprehending their parts rather than grasping them intuitively and holistically"*[60].

Common sense is defined by Blankenburg[68] as the tacit (implicit) understanding of the set of "rules of the game" that disciplines and guides human interactions. A "crisis in common sense"[68] is the main root of the premorbid subjective experience of psychosis since childhood, intensifying over the subsequent stages[69]: *"Rules about how to deal with others were learnt and memorized instead of being intrinsically felt. What should come naturally, and without effort, became a difficult cognitive task"*[67].

Fragile common sense erodes interpersonal attunement (and vice versa) and may drive individuals towards an eccentric self-positioning that is marginal to commonsensical reality, situating them at the edges of socially shared beliefs[70] and values[69,71]. Fragile common sense relates to the subjective feelings of being *"odd"*[60,72] or *"weird"*[56] (see Figure 1). Individuals may feel ephemeral, lacking a core identity, profoundly (often ineffably) different from others and alienated from the social world, a state that has been termed "diminished sense of basic-self"[73,74]: *"I remember it very precisely. I must have been 4 or 5 years old. I was starting dance class, and I was looking in the mirror. I was standing next to the other kids, and I remember that I looked alien. I felt like I sort of stuck out from that large wall mirror. As if I wasn't a real child. This feeling has been very persistent from very early on"*[75].

Empirical studies have confirmed that this odd *"feeling like a stranger"*[62] (see Figure 1) and isolated (e.g., schizoid or schizotypal) personality organization may present features qualitatively similar to psychosis[76], and be associated with an increased risk of later developing the disorder[52]. Detachment from common sense is also related to a pervasive sense of "perplexity" (see Figure 1), frequently characterizing the premorbid stage of psychosis[51,67]: *"A certain perplexity has always been a part of how I experience the world and its inhabitants"*[67].

Abnormal body experiences, such as the sense of being a *disembodied self*, may also be reported: "*The first disturbing experience I remember was discomfort in my very own body. Because I didn't feel it. I didn't feel alive. It didn't feel mine. I was just a kid, but ever since, I never felt a feeling of fusion or harmony between 'me' and 'my' body: it always felt like a vehicle, something I had to drive like a car*" (*personal communication during the workshops*).

Overall, the disconnectedness from common sense translates into real-world feelings of inadequate social skills[48,56,60,66], difficulties at school[57], and problems in mundane daily activities[51]: *"It made me inept about mundane things such as washing up, getting a haircut when I needed it, doing the bins, and little things like that – which really have to be done, just to get on with life"*[51]. These impairments can be so profound as to disrupt the individual's identity[51,58,60] (Jaspers' awareness of the identity of the self, or ego-identity[6]).

Prodromal stage

A feeling that something important is about to happen

The subjective experience of the psychosis prodrome is marked by an intense feeling that something very important is "about to happen"[77], that the individual is on the verge of finding out an important "truth" about the world[78,79] (see Figure 2). K. Conrad calls this initial expectation phase the *Trema* (stage fright)[77]. The *Trema* can last from a few days to months, or even years[6], and is characterized by delusional mood (*Wahnstimmung* in the German tradition): an "uncanny" ("*unheimlich*" in the German tradition), oppressive inner sense of tension, as if something ominous and impending is about to happen ("something seems in the air"[6]), but the individual is unable to identify what this might be precisely[77]: *"Something is going on; do tell me what on earth is going on"*[6].

During this experience, time is suspended. Individuals live in an elusive and pregnant "now", in which what is most important is always about to happen. Premonitions about oneself (*"I felt something good was going happen to me"*[60]) and about the external world (*"Something is going on as if some drama unfolding"*[60]) are common.

Delusional mood, according to Jaspers, marks the irruption of a *primary* psychotic process (i.e., not due to other conditions) that interrupts the development of personality[81]. As the

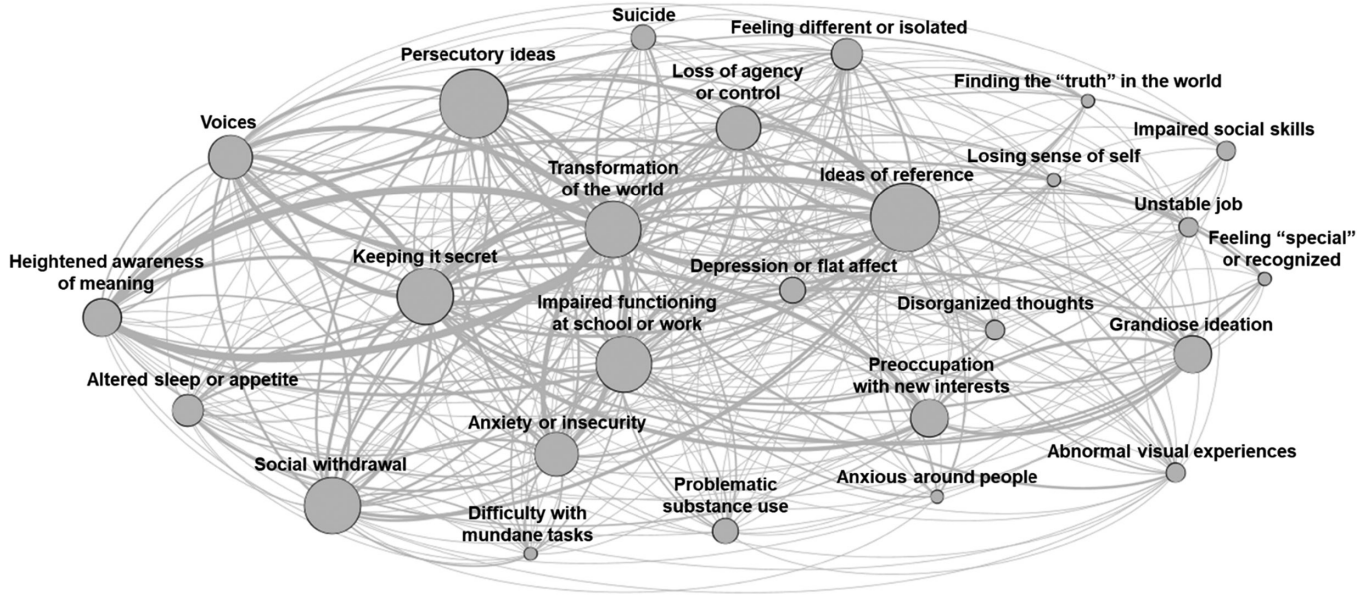

Figure 2 Network map of lived experiences of psychosis during the prodromal stage. The nodes represent the experiential themes, and the edges represent the connections between them. The size of each node reflects the number of first-person accounts addressing that experiential theme. The thickness of the edges reflects the number of connections between the themes.

world transforms, the crisis of common sense of the *Trema* intensifies, and known places or people become strange[57,82] and lose their familiarity[83], often acquiring a *"brooding"*[47] or threatening connotation[62,67,82,84]: *"Suddenly the room became enormous, illuminated by a dreadful electric light that cast false shadows. Everything was exact, smooth, artificial, extremely tense; the chairs and tables seemed models placed here and there. Pupils and teachers were puppets revolving without cause, without objective. I recognized nothing, nobody. It was as though reality, attenuated, had slipped away from all these things and these people. Profound dread overwhelmed me… I heard people talking, but I did not grasp the meaning of the words"*[22].

Individuals feel as if they are the only ones noticing these changes: *"I felt I was the only sane person in the world gone crazy"*[62]. In contemporary terms, the uncanniness of the delusional mood has been described as "living in the Truman Show", quoting a movie in which the protagonist, Truman, gradually starts to realize that he has been living his life in a reality television show, becoming increasingly suspicious of his surrounding world[85,86]: *"All seemed ever more unreal to me, like a foreign country… Then it occurred to me that this was not my former environment anymore. Somebody could have set this up for me as a scenery. Or else someone could be projecting a television show for me… Then I felt the walls and checked if there was really a surface"*[67].

Heightened salience of meanings in the inner and outer world

During the prodromal phase of psychosis, individuals feel assaulted by events personally directed to them[67,79,82,88], accompanied by a strong need to unravel their obscure meaning[67,79]: *"A leaf fell and in its falling spoke: nothing was too small to act as a courier of meaning"*[69]. Seemingly innocuous everyday events assume new salient meanings[78,83,89]. Previously irrelevant stimuli are brought to the front of the perceptual field and become highly salient[90]. This perceptual background, until then unnoticed, now takes on a character of its own[77]: *"At first, this started with sudden new perspectives on problems I had been struggling with, later the world appeared in a new manner. Even the places and people most familiar to me did not look the same anymore"*[83].

The enhanced salience of the environment can become an overwhelming experience[79,89]: *"It was shocking the amount of detail I found in this new world. In a day, there are so many things the mind relegates to background information"*[79]. Therefore, individuals become increasingly preoccupied with new themes and interests – often involving religion[48,91], the paranormal[59,91], or sciences[49,92] – and ideas of reference emerge[46,47,51,62,72,82,84,92-95] (see Figure 2).

Perturbation of the sense of self

Another core experience is described as follows: *"I thought I was dissolving into the world; my core self was perforated and unstable, accepting all the information permeating from the external world without filtering anything out"*[67]. The normal lived experience of the world is intertwined with a stable sense of selfhood[96] (*"core self"*[67]), which demarcates the individuals from the surrounding world. During delusional mood with heightened salience of meanings and paranoid interpretation, the bounda-

ries of the self are "*perforated*"[67], the self becomes *"permeated"*[67] by the external world[51] and *"unstable"*[67] (see Figure 2).

A pre-reflective sense of "mineness" ("ipseity" and Jaspers' awareness of being or existing[6]) is the necessary structure for all experience to be subjective, i.e. to be someone's experience, instead of existing in a free-floating state appropriated *post-hoc* by the subject via an act of reflection[74,97,98]. This sense of ownership and agency (sense of "I") of actions and emotions, that healthy people typically take for granted[99], is essentially based on self-presence and immersion in the world. The person's experience of being a vital *subject* of experience[97] is disrupted in psychosis, leading to experiences of dissolution[67] and losing one's sense of identity[51,66]: "*This vacuousness of self… one cannot find oneself or be oneself and so has no idea who one is*"[51].

A key component of ipseity disturbances is hyper-reflexivity (exaggerated self-consciousness and self-alienation), in which inner mental processes such as thoughts become reified and spatialized, resulting in hallucinatory experiences[97]. During the prodromal phase, these abnormal perceptual experiences are reported as brief and remitting[100], or intensifying over time[47,101]: *"At first, hallucinations are often small or momentary and can be as small as the appearance of eyes or a whisper of a voice"*[100]. Perceptual experiences include hearing indistinct chatter or distorted sounds[61,95,101], voices[61,67,102], or visions [78,82,88].

The "mineness" of thinking and emotions is gradually compromised (diminished self-affection[97]): *"Some thoughts didn't seem to be my own. They seemed foreign, as though someone was putting them there"*[88]. Individuals complain about intrusive thoughts or impulses[103], losing control over their emotional and cognitive processes[51,79,104,105], or feeling under the influence of external forces[82], although these experiences are typically transient.

Perplexity as lack of immersion in the world

An intense sense of perplexity is the hallmark of the emotional experience during the prodromal stage of psychosis[67,77,78]: *"During that time reality became distant, and I began to wander around in a sort of haze, foreshadowing the delusional world that was to come later"*[78]. Perplexity here refers to a lack of immersion in the world, an experience of puzzlement and alienation[106] which may acquire a threatening quality: *"The sense of perplexity and feeling threatened by others preceded the fully formed voices by just over two years"*[67].

A pervasive sense of insecurity starts to creep in[82,84,89], potentially leading to panic attacks[107] and experiences such as feeling empty, shut-off, depressed[50,62,88,101,108], angry or frustrated[57,105]. Substance use and social withdrawal are typical coping mechanisms (see Figure 2)[84,101,103].

However, the prodromal phase of psychosis is not always tainted by anxiety[109]. Pleasurable emotional experiences can coexist[49,58,61,110]: *"At that time I was working on an entirely new reality… with emotional gratification beyond any reasonable comprehension. In fact, I experienced it, but I also experienced terror and hell"*[110].

Compromised vital contact with reality

During the prodromal phase of psychosis, individuals tend to lose vital contact with the world, experiencing increasing difficulties in interacting and communicating with others[92,111]: *"People were incomprehensible, as well as the world. I did not understand my peers why they could have so much 'fun' just by engaging in gossip or in a party. I much preferred my own company"*[67].

Individuals describe withdrawing from family and friends[62,95] from the early years gradually, over a long time[60,64,112], and experiencing emotional distress, a sense of isolation[46,66], and impairment of social skills[66,82] (see Figure 2). They feel out of place or unable to communicate with others[113] or grasp commonsensical implicit social codes[60,67], or feel excluded[46,114] as if they were different or inferior[51,57] (see Figure 2): *"I felt different and alone. Seeing so many people in the school halls made me wonder how my life could be significant. I wanted to blend in the classroom as though I were a desk. I never spoke"*[57].

These experiences have been variously linked to the concept of "autism"[115] in psychosis, which has been understood as a "withdrawal to inner life" (Bleuler[53]), or as the "loss of vital contact with reality" (Minkowski[116]) and, more recently, quantified by deficits in the related construct of social cognition[117-120].

Keeping it secret

During the prodromal phase of psychosis, individuals typically keep their anomalous subjective experiences secret: *"These things caused me considerable anguish, but I continued to act as normal as I could for fear that any bizarre behavior would cause me to lose my job"*[62].

Individuals often hide their experiences from family and friends over a very long time[82,111] because they feel ashamed[58,79] of negative consequences[82], and fear being labeled as "crazy" or "insane"[51,78,108] or being laughed at[64], hoping for their problems to *"clear up"*[121]: "*At 18, I couldn't study or focus but still kept everything to myself. My behavior looked 'normal' to others, as I was always a quiet child, an introvert"* (*personal communication during the workshops*). Help-seeking during the prodromal phase may be hindered by this difficulty of sharing the unusual experiences with others[122]. For children and young adolescents, it is generally harder to conceal their emerging symptoms[123].

On the other hand, because of the insidious onset of the abnormal experiences, individuals may not realize that something "might be wrong"[67,82]. They may believe that it is common for other people to have these experiences[64,67], or consider them *"plausible"*[49].

Notably, not all individuals describe a prodromal phase, but some report an abrupt onset of the first episode[89,92,124,125]: *"I ex-*

perienced a great and normal life I was thoroughly enjoying, then I went straight into the first episode phase" (*personal communication during the workshops*).

First episode stage

A sense of relief and resolution associated with the onset of delusions

The first psychotic episode is characterized by an intensification of abnormal experiences, as visually shown by the increased density of Figure 3 compared to Figures 1 and 2.

A sense of resolution emerges as a core experiential theme (see Figure 3): *"It really feels as if I am suddenly capable of putting things in perspective, that the light has suddenly switched on inside of my head and that because of this I am capable of reasoning again"*[63]. The pervasive sense of uncanniness and perplexity of the *Trema* is replaced by Conrad's *Apophany* (revelation)[77], an unexpected experience of clarity or insight[60,83,126,127]. The individual suddenly "*puts the pieces together*"[89,126,127], becoming aware of the *"truth"* in the world[79] or the *"essence"* of things[83], discovering a delusional motif behind the abnormal perceptions and distressing experiences[79,83] ("*aha experience*"[77]): "*All of a sudden there came this 'intuition': that they had chosen me for the experiment. I was chosen to incarnate myself in one body and come to earth. That explained why I felt a stranger in my body. And a stranger on the earth too*"[128].

Individuals report being unable to shift away from or transcend[77] these new delusional perspectives[83,113,129-131]: *"I told myself that I suddenly saw the real truth of the world as it was and as I had never seen it before"*[79].

The onset of delusions can provide the individual with a newfound role in the world that is more thrilling and meaningful than the uncanny reality of the *Trema*[60,67,83,89,132,133], alongside a sense of excitement[60,61,126] or relief[67,83,89] (see Figure 3): *"A relationship with the world was reconstructed by me that was spectacularly meaningful and portentous even if it was horrific"*[60]; "*My destination after this is a place where everything is vibration, a pure state of consciousness, so elevated that everything is peace"*[128].

However, the sense of relief associated with *Apophany* is frequently contrasted with a difficult personal situation: *"There was going to be a nuclear holocaust that would break up the continental plates, and the oceans would evaporate from the lava… My future wife and I were going to become aliens and have eternal life. My actual situation [however] was a sharp contrast. I was living in a downtown rooming house with only cockroaches for friends"*[112].

Delusions can be understood as new beliefs providing a satisfactory explanation of a strangely altered and uncanny reality and a basis for doing something about it – rather than incomprehensible and meaningless phenomena. Delusional beliefs can alleviate distress by replacing confusion with clarity, or promoting a shift from purposelessness to a sense of identity and personal responsibility[134,135]. Delusions can indeed enhance a person's experience of meaning and purpose in life[136], contrib-

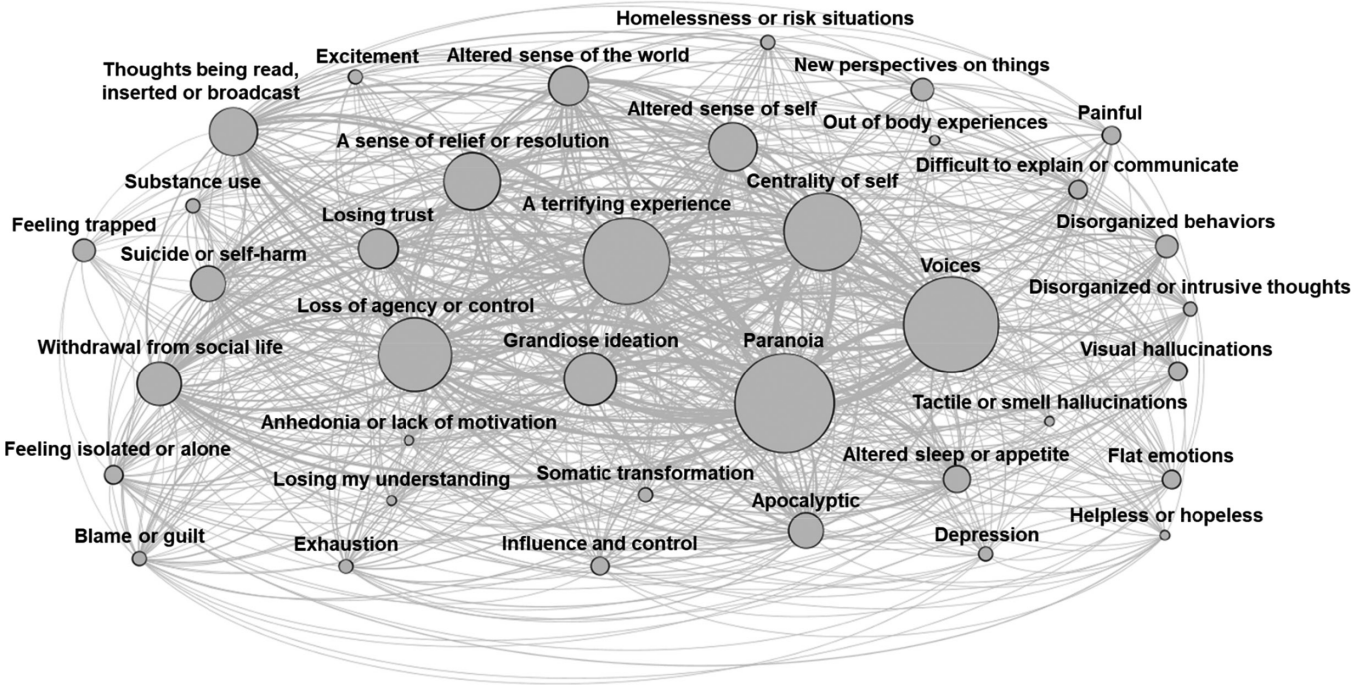

Figure 3 Network map of lived experiences of psychosis during the first episode stage. The nodes represent the experiential themes, and the edges represent the connections between them. The size of each node reflects the number of first-person accounts addressing that experiential theme. The thickness of the edges reflects the number of connections between the themes.

ute positively to establishing a "sense of coherence"[137] and partially provide a sense of purpose, belonging and self-identity[138].

Feeling that everything relates to oneself

The experience of delusion is often subjectively reported as: *"Everything I 'can' grasp refers to 'me,' even the tone of every voice I hear, or the people I see talking in the distance"*[139]. In Conrad's model, *Anastrophe* ("turning back" of meanings) is the third phase following the "*aha experience*"[77]. All events and perceptions are experienced as revolving *around the self* (the "middle point")[140]: "*I have the sense that everything turns around me*", "*I am like a little god, time is controlled by me*", "*I feel as if I were the ego-center of society*", "*I became in a way for God the only human being, or simply the human being around whom everything turns*"[141].

The increased centrality of the self during a first psychotic episode (see Figure 3) is substantiated by the delusional self-reference of messages on the radio or television[57,60,88], the gestures or conversations of people in the street[57,100,139], or even the color of people's clothes[130]: *"Colors of jeans got more realistic"*[142]. This is typically accompanied by a transformation of the experience of the lived space (i.e., the meaningful, practical space of everyday life). Individuals feel they are uncomfortably center-stage. Other people look at them, spy on them, send them messages, or hide something from them. While in the center of the stage, individuals feel things directed to them bearing personal meanings: *"Cat jumping cardboard box signified a spiritual change in me"* or *"TV, radio, people on buses refer to me"*[142]. Individuals eventually become *"overwhelmed"*[79,89], *"flooded"* or *"swarmed"*[139] by these external or internal stimuli, and the subjective experiences become exhausting[60,79,89,139,143].

The self-referential experiences are frequently associated with grandiose delusions[49,57,60,79,89,91,104,124] ("*To feel like I have everyone following me around, whether it's negative or positive, that alone is a force of power… knowing that you can influence people's mind in the right way*"[144]), or with Truman-like[49,72] delusions[85,145] (*"I deduced that I had been on a secret TV show all of my life, similar to the Truman Show"*[49]) (see Figure 3).

Losing agency and control of the boundaries between the inner subjective and the outer world

In the *Anastrophe* stage, the individual's sense of agency and control over the delusional belief is lost (see Figure 3): *"As my delusional system expanded and elaborated, it was as if I was not 'thinking the delusion': the delusion was 'thinking me'!"*[60]; *"My paranoid delusions spun out of control. I was a slave to madness"*[79].

The experience of hallucinations dissolves the boundaries between the self and the surrounding world: *"When I am psychotic, I feel as though my awareness is happening to me. It's a passive experience. I'm at the mercy of 'my' thoughts and 'my' perceptions of people"*[139]. Individuals report single or multiple voices[100,104,146-148], distorted sounds or whispers[149] or physicalized thinking[150], visions[104,111], tactile sensations of radiation[65], electricity[151] or burning[149] on the skin (see Figure 3).

Some reported experiences seem to support phenomenologically-informed models suggesting that hallucinations represent an organization of the inner dialogue[152] emerging from the ipseity disturbances described above[97]: *"I avoid the use of 'voice' to describe what occurs in my thinking. Instead, I prefer to conceptualize these occurrences by saying it is as if I hear 'voices'… It's difficult to really concretely define 'voices' for someone else. Sometimes it seems they serve as reminders of things I should or shouldn't do – doubts vocalized"*[150].

The sense of agency and ownership[153] and the boundaries of the self are particularly disrupted by commanding voices giving orders[104,139,146], warnings[147], insults[104], soothing[104,150] (more rarely encouraging[66]): *"I felt trapped in a bewildering hole; felt like wreckage on a derailed and deranged alien train; felt like I was about to be destroyed"*[64]. The emotional correlates of these experiences are ontological fear[78,89] and pervasive terror[84,126,139] (see Figure 3). The word *"nightmare"*[89,126,151] is often used to describe such intense anguish. A sense of entrapment is frequently reported[84,88,89], along with feelings of guilt, embarrassment[66,103,151] and self-blaming[111,154] (see Figure 3): *"My shame at even hearing these words in my head ran deep, but I couldn't make them stop. I tried my best to suppress them, but they welled up like poison in a spring"*[79].

The experience of an increased permeability of ego boundaries or the blending of the internal and the external fields[78,155-157] is sometimes explicitly mentioned: *"I lost my ego-boundary which meant everything external and internal seemed like one blend"*[156] ("transitivism" for Bleuler[53], "loss of ego-demarcation" for Jaspers[6]).

A dramatic dissolution of the sense of self and devitalization

The dissolution of the sense of self, already present during the prodromal phase (see Figure 2), becomes more intense: *"I had the feeling that I was dissolving and that pieces of me were going out into space, and I feared that I would never be able to find them again"*[78]. Individuals feel different from the usual self[65,101,114] (*"I felt distinctly different from my usual self"*[114]; "*I am only a response to other people; I have no identity of my own*"[158]; "*I am only a cork floating on the ocean*"[158]), split, divided or scattered into various pieces[57,63,78] (Jaspers' loss of awareness of unity of the self, or ego-consistency and coherence[6]).

The disorder of the basic sense of self leads to a disruption of the feeling of "mineness" in relation to one's psychic or bodily activity (Jaspers' awareness of activity of the self, or ego-activity[6]) and to experiences of deanimation or devitalization[159] (Scharfetter's[160,161] loss of awareness of being or existing, or ego-vitality): *"It was not me who was engaging in such behaviors. I was unaware of my actions, observing myself in the third person"*[155]; "*I walk like a machine; it seems to me that it is not me who is walking, talking, or writing with this pencil*"[122]; "*A feeling of total emptiness frequently overwhelms me, as if I ceased to exist*"[162].

The experience of dissolution of the self is more marked when the ego-world boundaries are compromised by passivity phenomena involving feeling under the influence of external forces[114,155]; thoughts being read, inserted or broadcast[88,114,163] (see Figure 3); body boundaries being violated by entities or forces (*"Someone cut open my head and inserted a bag", "Areas of the body where forces enter"*[164]) or parts of the body being displaced ("*Mouth was where hair should be", "Arms sticking out of chest"*[164]). Some individuals may even feel that their body or parts of it are projected beyond their ego boundaries into outer space ("*Arms disjointed from the body", "Legs and arms dropped off"*[164]). Altered corporality experiences such as the disembodiment or distancing from one's own body or mental processes[157] often co-occur, sometimes leading to somatic delusions[78,110,112] (see Figure 3): "*I thought my inner being to be a deeply poisonous substance*"[78].

These experiences are often associated with the sense of the world turning into an unfamiliar place[57,65], at times chaotic and frightening[57], which can resolve in apocalyptic beliefs about incoming wars[65,89] or the inevitable end of the world[88,110,112], or nihilistic delusions[114,155]: *"I had the distinct impression that I did not really exist, because I could not make contact with my kidnapped self"*[114].

The dissolution of the self can result in extreme self-harm behaviors: "*When one's ego dissolves, it becomes a part of everything surrounding him; but at the same time, this unification entails the annihilation of the self – hence the suicidal ideation*"[155].

Feeling overwhelmed by chaos or noise inside the head

The disorganization of thoughts is a prominent experiential theme[66,84,108,163,165] (see Figure 3): *"My head is 'swarming' with thoughts or 'flooding.' I become overwhelmed by all the thinking going on inside my head. It sometimes manifests itself as incredible noise"*[139]. Words such as *"rollercoaster"*[124], *"whirlwind"*[114], *"vertigo"*[79] or *"maelstrom"*[5] are used by individuals to try to convey an experience of inner chaos and confusion, which is difficult to articulate accurately through language[151] (see Figure 3): *"Being in a whirlwind is not a very good metaphor for that experience, but I have trouble finding words to describe it"*[114].

As one individual describes, thought disorder can be experienced as a *"weakening of the synthetic faculty". "My thoughts seemed to have lost the power to squeeze things to clear organization"*[84]. The weakening of the natural "core self" that organizes the meaning and significance of events[166] can lead to a disturbed "grip" or "hold" on the conceptual field[97].

Losing trust and withdrawing from the world

During the first episode of psychosis, individuals frequently report losing trust in others (see Figure 3): *"While I was in hospital, I was frightened, but at the same time I felt safe. I knew the workers were there to help me, but I just couldn't trust anyone"*[66].

Persecutory delusions disrupt the atmosphere of trust that permeates individuals' social interactions and familiar environments[167]: *"For me, it was about losing trust to everyone"* (*personal communication during the workshops*). The loss of trust extends to the individual's immediate social network, with suspiciousness towards neighbors, family members, friends or colleagues[78,92,95,107]: *"I was afraid of people to the extent that I wouldn't come out of my room when people were around. I ate my meals when my family was either gone or asleep"*[78].

A sense of helplessness[101,155] can be associated with these experiences: *"You feel very much alone. You find it easier to withdraw than cope with a reality that is incongruent with your fantasy world"*[111]. Therefore, the first episode is lived as an intensely isolating and solipsistic experience[60,101,111,155] (see Figure 3): *"Having no friends to visit and living alone in my apartment… I began to spend weekends sitting on the couch all day"*[147]. Individuals frequently withdraw (Figure 3) from family and friends[66,147], college or school[79,88], adopting a reclusive lifestyle[104].

Withdrawal from social life is often associated with the subjective inability to cope with the disrupted sense of self and the world[5,111], the loss of pleasure and interest in social relationships[66], delusion-fueled fears[78,104], increasing difficulties in understanding social interactions[79], or communication difficulties[58,91,101,114]: *"I thought that I must be in hell and that part of the meaning of this particular hell was that no one else around understood that it was hell"*[78].

Relapsing stage

Grieving a series of personal losses

"At the time, my diagnosis was equal to the death sentence. Nothing could have been more devastating. Not even death itself"[62]. During the relapsing phase of psychosis, individuals are frequently confronted with a series of losses, leading to an experience of grief for their pre-psychotic self[124,168] (ego-identity[6]) that impacts their confidence and self-esteem[102,169,170] (see Figure 4): *"It's hard to recall the past. Hard to accept things will be like this from now on"* (*personal communication during the workshops*).

These losses frequently include their past identities, as individuals often feel that they have to assume the new role of "mental patient": *"I entered the hospital as Robert Bjorklund, an individual, but left the hospital three weeks later as a 'schizophrenic'"*[171]. Individuals also grieve their individuality[65,171], as they feel different compared to others[133]: *"At first, it made me think that I was weird and different from everyone else. I didn't like feeling that I wasn't a part of the main group of people in life who were healthy and/or "normal"*[156].

Public stigma[94,156,170,172,173] towards mental disorders fuels feeling of rejection[50,56,126,156,174], further reducing social networks[50,66,101,130,169,174,175] and personal relationships[105,107,156,169,173] (see Figure 4): *"People would constantly joke about mental illness, and it was difficult for me to deal with"*[172]. As a result, individuals typically hide their diagnosis[92,94,102,156,173,174,176]:

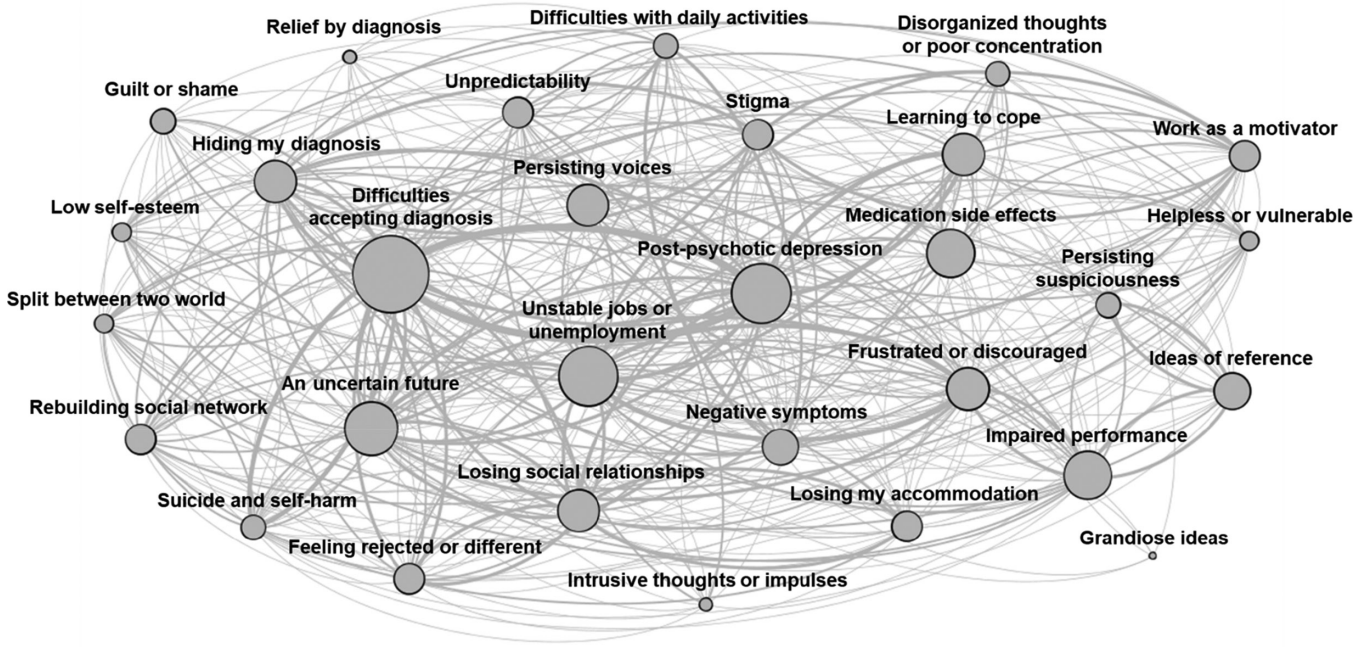

Figure 4 Network map of lived experiences of psychosis during the relapsing stage. The nodes represent the experiential themes, and the edges represent the connections between them. The size of each node reflects the number of first-person accounts addressing that experiential theme. The thickness of the edges reflects the number of connections between the themes.

"I struggled with accepting the diagnosis, and I never told anyone about it"[156].

Another personal grief is for the premorbid sense of autonomy, as even the most mundane activities can now represent enormous challenges[89,94,102] (see Figure 4): *"Something as basic as grocery shopping was both frightening and overwhelming for me. I remember my mom taking me along to do grocery shopping as a form of rehabilitation… Everything seemed so difficult"*[94]. Difficulties in completing daily activities, performing at school or work[57,58,78,102,110,175-177] and maintaining employment[47,57,94,95,101,110,114,124,174] trigger sentiments of frustration and discouragement[47,57,59,101,102,169,177] (see Figure 4).

Individuals also mourn the loss of the sense of meaning or purpose that psychotic symptoms provided during the "*aha*" and *Apophany* phases[132,133]: *"In my delusions, I had been a heroine on a mission; now that I was back on medication, I spent most of my days lying in bed, hating myself with a vengeance. Grief? Who knows?"*[133]. Commonly, individuals struggle with post-psychotic depressive mood following the remission of acute symptoms[101,108,112,132], feeling *"flawed"*[94] by a lack of accomplishments[169], leading to feelings of hopelessness and fragility[178] or the belief of being a *"failure"*[94] (see Figure 4).

Feeling split between different realities

Following remission of florid symptoms, individuals can feel "split" between the outer world and the private delusional worlds[78,155,176] (see Figure 4): *"A constant during most of these years under psychiatric care and in the three years leading up to them was the existence of an inner reality that was more real to me than the world's outer reality"*[78]; *"The difference between normal reality and psychosis feels extraordinarily subtle. It can, in its subtlety, encroach on me without my even noticing… That's why, today, I have a healthy respect for the cunningness of psychosis"*[139]. Individuals can also feel split about the diagnosis and the need for ongoing medication: *"I find it difficult to accept the continued professional opinion that I should take medication for my 'condition' over the long term"*[107].

This phenomenon of "double awareness"[179], in which the person continues to simultaneously live in two realities[98] (i.e., the real and the delusional world), was originally referred to by Bleuler[53] as "double-entry bookkeeping".

An uncertain future

Following remission of acute psychosis, individuals face the task of rebuilding their identities and goals[124,154,169]: *"Eventually, as discharge from my two years of treatment drew close, I was asked the big questions. What did I want to do now?"*[154]. In this context, a psychotic relapse can be interpreted as a threat or even the complete abolition of a person's goals and future. Individuals can feel that past aspirations and plans in life are now completely out of reach[94,127,177]: *"In my eyes, my life was over. Everything I had dreamt of doing, and all my aspirations in life, were now nonexistent. I felt completely nullified"*[66].

The sense of uncertainty is enhanced by the lack of a clear

roadmap ahead: *"That's what getting out of schizophrenia is like: there are no clues, no map, no road signs like 'wrong way,' 'turn here,' 'detour,' 'straight on.' And it's dark, lonely, and very frightening. You want nothing to do with it, but your return to sanity is at stake"*[139]. The unpredictable evolution of the disorder also contributes: *"However, now what I want more than anything else is to be sure that the things that I went through will never happen again. Unfortunately, that is not an easy thing to guarantee"*[46].

The acceptance of the diagnosis and the related uncertain future typically begins during this stage, but often requires several years of inner struggles[66,88,92,139,156].

Chronic stage

Coming to terms with and accepting the new self-world

During the chronic stage of psychosis, individuals often report feeling more optimistic about the future or believing that the worst is now behind them[47,57-59,61,62,78,91,94,95,101,124,129,150,170,177] (see Figure 5): *"After more than 40 years of psychosis, I can now say, I feel better than I have ever felt in my life"*[95]. Individuals may also report feeling more satisfied with their occupational activities than before[47,49,50,59,62,78,82,91,101,112,129,133,173,177,180,181] (see Figure 5).

As the intensity of psychotic symptoms and the associated distress frequently decrease[127,147], they can be more easily dismissed (see Figure 5): *"I go out among people almost every day and, although I still feel 'stared at' and occasionally talked about, I do not believe, even if I am psychic, that I am an agent of God"*[91].

During this stage, individuals have often also learned how to cope more effectively with their symptoms, for instance ignoring the voices and delusional ideas, partially regaining a sense of agency or control[50,112,127,150] (see Figure 5): *"I think the quality of the thought-voices evolved as my health evolved. I no longer hear suggestions to run into traffic; if I did, I would refuse. I'm able to judge the appropriateness of the advice"*[150].

All this aids the individuals to come to terms with the diagnosis and its impact: *"At 42, I think I'm slowly getting better or at least getting better at dealing with the difficulties that remain. I feel stronger and more stable now than ever before"*[58]. Acceptance of psychosis and the new self[60,150,169,170,180,182,183] is a slow process that typically takes several years: *"For a long time I searched for a lesson from my experience. What I learned was to build a new life and new dreams based on what I find myself capable of doing today"*[89].

However, a sense of grief and loss for the old self and the life before the disorder can still persist[124,133,150,168,175,184]: *"Though I am working again, I have a pervading sense of loss about my life. This illness has affected all aspects of how I perceive myself and how others perceive me"*[184]. This is accentuated when the individuals with lived experience of psychosis compare themselves with healthy peers[108], feeling worthlessness or inferior[124,133,185,186] (see Figure 5).

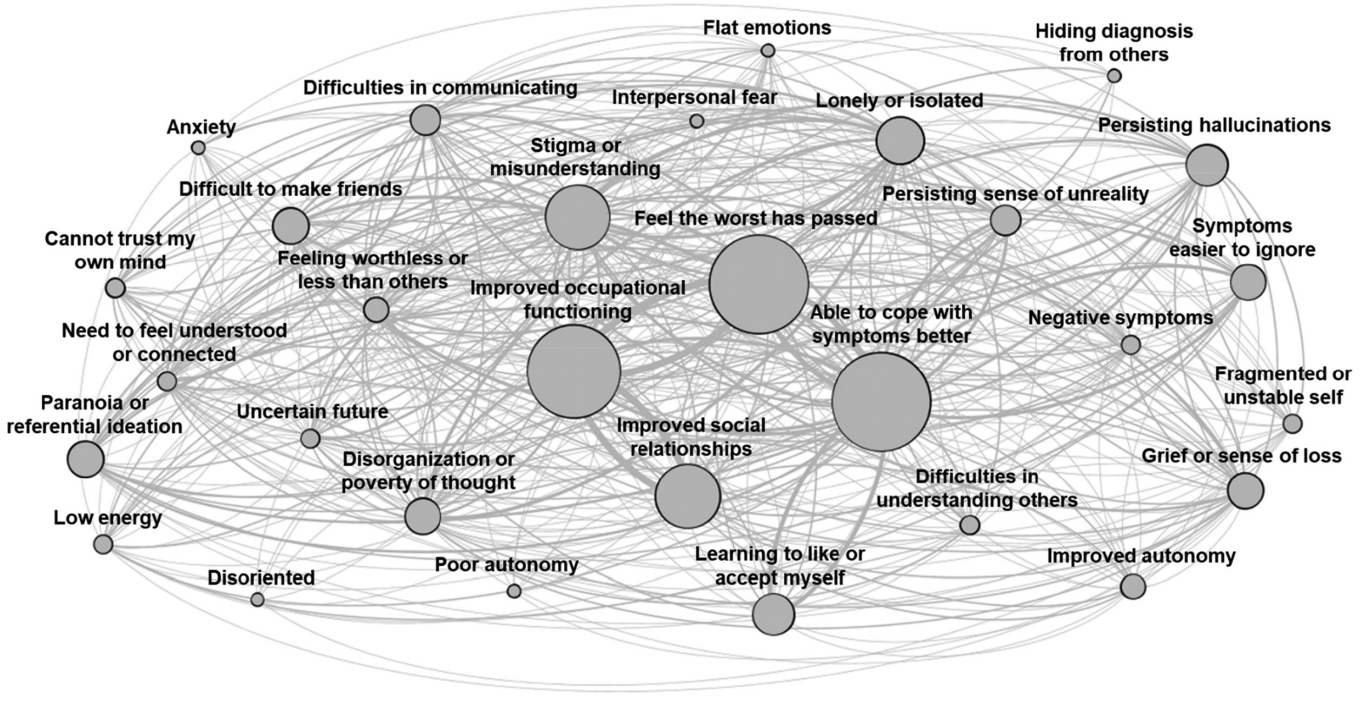

Figure 5 Network map of lived experiences of psychosis during the chronic stage. The nodes represent the experiential themes, and the edges represent the connections between them. The size of each node reflects the number of first-person accounts addressing that experiential theme. The thickness of the edges reflects the number of connections between the themes.

Persisting inner chaos not visible from the outside

An unstable sense of self and the world can persist in this stage: *"The clinical symptoms come and go, but this nothingness of the self is permanently there"*[157]. These experiences can include an ongoing sense of unreality of the world[58,155] and disorientation[139,157], and disorders of the sense of the self, such as devitalization, disintegration or disconnectedness[155,157,185], loss of agency[149,187], and fear of doing something that might have negative consequences[103,139] (see Figure 5).

A tumultuous inner world may be described, even if it is not "visible" from the outside[5], with a constant feeling on edge from slipping away from reality: *"Although on the outside things seem to have calmed down greatly, on the inside there is a storm raging, a storm that frightens me when I feel that I am alone in it"*[5]. The experience may be aggravated by the feeling of not being able to trust one's own mind[5,185,188] (see Figure 5).

Loneliness and a desperate need to belong

While some improvements in socialization may be reported[47,49,50,82,101,114,127,133,175,180,181] (see Figure 5), social relationships tend to remain a major concern during the chronic stage of psychosis[63,112]: *"I look at people, and I don't feel like one of them. People are strangers"*[185].

Pervasive feelings of loneliness and isolation[63,112,133,168,181,183,185,186,188], including feeling *"cut off from humanity"*[185], are commonly reported, and have been confirmed at meta-analytical level[189]. There is often a strong and desperate call to feel understood, connected and accepted[5,133,185] (see Figure 5): *"I need people to accept me enough to want to build a relationship with me… I feel cut off, cut off from humanity… I am already separated… I isolate myself on purpose because when I'm around others, that chasm between me and the world gets more pronounced; at least when I am alone, I can pretend I'm normal"*[185].

This desire for human warmth and closeness can be frustrated by equally intense fears of reaching out to people[5], difficulties in communicating with others[185], and not being able to convey the nature of psychotic experiences[5,58] (see Figure 5): *"The more I try to speak, the less you understand me. This is why we stop trying to communicate… Not being able to communicate my basic feelings, not identifying with another human being, and feeling completely alone in my experience are killing me"*[185]. Stigma and misunderstandings about mental disorders[58,110,133,139,168,173,180,184,186,188,190] and feelings of shame[185] amplify the experience of loneliness[49,173] (see Figure 5).

Difficulties in establishing and keeping social relationships[108,112] reiterate a weak attunement to the shared world of "unwritten" codes of social interactions (see Figure 5)[187]: *"Making friends is pretty much a mystery to me. Even though I have made some friends in my life, I cannot seem to master or understand the skill"*[188]. Individuals express this hypo-attunement to the social world with statements such as: *"I cannot associate with other persons", "I always felt different, as if I belonged to another race"*, or *"I lack the backbone of the rules of social life"*[191].

THE LIVED EXPERIENCE OF RECOVERY AND OF RECEIVING TREATMENTS FOR PSYCHOSIS

This section explores the lived experience of recovery and of receiving treatments for psychosis. As the latter is determined by the type of care delivery platform and contexts, we first address the subjective experiences of receiving treatments across different mental health settings and subsequently focus on specific treatments. To reflect the multitude of possible experiences, we emphasize both core positive and negative aspects.

Recovery as a journey towards meaningful goals

Individuals feel that recovery extends beyond symptomatic improvement[192] (*"It is not necessarily the disappearance of symptoms"*[101]), but rather is about achieving a sense of subjective control and being able to *"do something about it"*[193]: *"Recovery to me means that, even if the delusions are not completely gone, I am able to function as if they are"*[72]. Notably, *"The road of recovery is totally different for each person and different in each stage and across different ages"* (*personal communication during the workshops*).

Recovery from psychosis is commonly experienced as a cyclical and ongoing process that requires active involvement[94], and is hardly ever "complete"[194]. This recovery *"journey"*[133,192] is filled with back-and-forth, rather than being a linear path with a set endpoint: "*a long, solitary journey, with almost as much shock and fear at its outset as with the psychosis*"[133]. It is, therefore, a dialectical process on its own. Or, as described in another account: *"Recovery can be a process as well as an end… Recovery means finding hope and the belief that one may have a better future. It is achieving social reintegration. It is finding a purpose in life and work that is meaningful. Recovery is having a clear direction"*[101].

In more practical terms, recovery appears as a deep and protracted struggle to restore meaning and one's sense of self and agency[193,195,196], re-establishing an active relationship with the world[83,183]: *"As I recover, I am also faced with rebuilding my identity and my life. Making the decision to end my career profoundly affected my sense of identity and self-worth, and I have been left since searching for meaning and for a means by which I can continue to help others"*[183]. As such, recovery is often understood by individuals as the ability to move towards meaningful goals[94,183,197]: "*Recovery for me means serving a purpose; I think it is important for me because I felt 'useless' when I struggled through psychosis" (personal communication during the workshops)*.

The recovery process also involves a strengthening of the person's ego-identity by building a sense of continuity with the past and a projection towards the future. Following a first episode, some young people view recovery as going back to their old selves, to *"the way I was"*[195]. For others, the recovery process requires a personal transformation of their identity and goals[183]

and the acceptance, not only of the disorder[193], but also of one's limitations: "*For me, recovery has been about admitting something is wrong, about acknowledging my limitations. Recovery language focuses on what the person can do; I had to look at what I couldn't do before I could start to get better*"[185]. A such, recovery is not necessarily about returning to the "past self"[192], but implies assimilation of the experience into a new sense of self and a transformed understanding of the world and the person's role in it[83].

Some young people feel that the recovery experience lead them to mature or make essential changes in their social relationships[195,196,198]. Psychosis can also provide new perspectives on life and relationships, including insights into one's life history[183], increased empathy towards others[94,124,172], or a rebalancing of life's priorities[56,101,169]: *"I have more empathy for others and have a deeper understanding of what the human body is capable of. These components that make up my reality, to me, are the essence of life"*[66].

Supportive relationships are critical facilitators of the recovery journey: *"The key to recovery for me was having really good supporting relationships that didn't break when everything else was breaking" (personal communication during the workshops)*. A relationship is perceived as helpful when it transmits hope for the future[58,94,105,177,197,199]: *"Most importantly, my care team believed in the certainty of my recovery in a period of life when I just wasn't able to"*[126]. Supporting relationships also facilitate understanding of the unusual experiences[6,200,201] in the context of compassionate[139,202] and positive attitudes[150], and realistic expectations[203].

The lived experience of receiving treatments across different health care settings

Inpatient care: a traumatic experience or a respite

"The attendants carried me into the dark corridor. A jumble of voices bounced off the walls – harsh bellows, still murmurs, and authoritative orders – but to me, the sounds blended together in a common senselessness"[48]. Admission to a hospital commonly occurs in the context of fear, chaos and confusion[48,66,84], fuelled by delusional ideas[49,124,182].

Negative experiences of being admitted to inpatient wards can trigger a sense of isolation[132], hopelessness and uncertainty for the future[49,66,204]: *"I wondered if I was ever going to recover; I wondered if I was ever going to be normal"*[66], and are often more pervasive for young people who are inappropriately admitted to adult mental health services[205]: *"There were only a few younger ones in their twenties or thirties... I had heard someone use the term "chronic wards"... It didn't sound like a nice term"*[48].

The subjective experience of compulsory treatment or physical restraint during inpatient care is typically recalled as traumatic: *"The first time was very traumatic... I refused medication, and I was held down and injected by six staff. What I feel strongly about is that no one gave me a choice... [this] added to the trauma that I'd already experienced in my home, being yanked out to an ambulance... It was a very nasty experience"*[206]. The experience is associated with feeling powerless[108] and lacking privacy[207], which can be re-traumatizing for those with previous histories of abuse[206].

A perceived *"lack of compassion"*[208] from the staff can lead to a sense of being *"dehumanized"*[209]: *"'Noncompliant,' passive dependent, passive-aggressive... they all mean the same thing: you're not really you"*[209]. Negative experiences of inpatient care can discourage future attempts to seek help[84,151,204] and hamper long-term trust in the health care system: *"I think if you don't come out and get a good experience right after that, then that's how you perceive the whole system"*[208].

However, in other cases, hospitalization can bring a much sought-after sense of safety and relief, particularly during acute psychosis[66,78,114]: *"The hospital was a safe haven"*[210]. Hospitalization can also alleviate the personal exhaustion which follows the efforts to maintain a semblance of normalcy: *"It was a relief to be in a place where it did not matter if you went off somewhere in the middle of a conversation. It was a relief not to have to fight all the time to maintain a semblance of sanity... It was a relief to be able to be honest"*[78].

The hospital can therefore provide a *"respite"* from the stress of life outside[205], at times providing opportunities for recreation and the incorporation of healthy habits[66,108], as well as time to reflect on the past and plan for the future: *"It gave me a chance to think about what I really wanted to do with my life. I no longer wanted to continue working at a dull job where I was unhappy... There should be more to life"*[57].

Following discharge, the hospital can remain a safe haven to go back to during times of distress: *"At those points in my life, the safety (albeit restrictive safety) offered by an institution was preferable to the responsibilities I felt I could not handle outside"*[211]. As such, individuals can develop an ambivalent relationship with hospitalization, given the mixture of negative and positive experiences, especially when compulsory treatment was involved: *"It would be a while before I realized hospital was there to help me in crisis rather than to further torture me as the voices had threatened"*[84].

Social relationships in the ward may have a solid positive impact on the subjective experience: *"I found the staff usually kind, competent, and extremely tolerant of me and my fellow patients"*[211]. Positive experiences are also linked to opportunities for inward socialization that counter the sense of isolation[48,132,172,199]. For some individuals, the ward experience provides support networks that can persist after discharge: *"Being in hospital is a painful experience, but it's also a personal journey, and for me, it was forming friendships on the ward that pulled me through (and continues to do so)"*[172].

Preventive and early intervention services: promoting and restoring hope

The subjective experience of individuals accessing specialized preventive (e.g., clinical high-risk) or early intervention services

for psychosis is markedly different compared to standard inpatient units. These services provide specialized and youth-friendly care during a clinical high-risk state or first episode of psychosis[34,212,213]. Their focus on recovery is greatly valued by young users[214-216]: "*They get me more active. They encourage me to be interested in things and think that I have a future. I thought my life was coming to an end and they kind of encouraged me to see that there is life after psychosis*"[216].

Individuals value the support with everyday practical challenges – such as social relationships, employment and housing – suited to their actual needs and concerns[215-217], provided by these services. In addition, when services are located within a youth-friendly setting outside the "mainstream" psychiatric institutions, they are perceived to reduce the feeling of shame and self-stigma often attached to accessing mental health care[217], providing a "*human touch*"[214] and high quality of relationships with the care team that are key in the recovery process[208,215-218].

In particular, individuals appreciate the opportunity to be involved as "partners" in the treatment decisions, as well as the experience of being treated "*as a human being*"[214,217], since staff *"listen and ask your opinion"*[214], while at the same time being allowed to *"describe what I was experiencing"* with their own words, rather than over-relying on diagnostic labels[208].

In addition, availability of staff[214,216] and continuity in care[216, 218] are emphasized as positive aspects: *"I was seeing my key worker every week or two, which was very good"*[218]. Continuity in care has been highlighted as a key trust-enhancing factor[219]: *"Opening-up to the therapist requires trust; it takes time to build up that relationship" (personal communication during the workshops)*.

Young users also value how these services support them in developing a positive sense of self by sharing their experiences with others[216-218]: *"I've met quite a few people with similar problems to me, and it's helped because we've discussed how we're different and tried to suggest ways that can sort of help each other or help ourselves"*[216]. Preventive and early intervention teams also provide a sense of certainty and safety[215,216]: *"This is what I've been looking for, somebody who actually knows what they're talking about"*[220].

For young individuals at clinical high-risk of psychosis, specialized care provides an opportunity to disclose the distressing experiences often kept hidden from family, friends and professionals. Understanding can emerge through a process of shared exploration and creation of links[221] between symptoms and life experiences: *"This 'normalization' of my difficulties was one of the most helpful elements of therapy, as it very quickly reduced my fear of being 'mad,' which had been the most disturbing of my worries"*[222].

On the other hand, discontinuity of care due to high staff turnover, whenever present, is felt like an essential source of frustration also within these services, as "*it takes a whole load of time to build up trust in someone*"[218]. Furthermore, following symptomatic and functional improvements, individuals can gradually lower their engagement with preventive or early intervention services, that are perceived as an unnecessary and undesired reminder that they are under mental health treatment[218,220]: *"As I've got better, it's not nice having somebody come in all the time, because it constantly reminds you that you're suffering from an illness"*[218].

Outpatient care: opening the gates to the community

In the lived experience of persons with psychosis, practical and accessible outpatient services promote autonomy and control: "*You can come for the treatment, and the gates are open for you to come*"[223], as well as fostering the sense of feeling welcomed: "*It gives you an idea of home, it does not have that mystification that it is that closed, trapped thing and that you are hospitalized behind closed bars*"[223]. As a result, the experiences of receiving outpatient community care can provide an opportunity for strengthening social bonds and networks.

Friendly and easily accessible outpatient multidisciplinary teams are perceived of utmost importance to achieve this: *"I feel good, this is a family, if I'm not feeling good, they reach out for me. So here I found the people that really helped me. Every single one of them, from the cleaning mister to the service coordinator"*[223]. These positive experiences are also crucial for promoting treatment adherence: *"What gets me here is fraternity… They gave me so much fraternity that I end up saying to the doctor that out there, in my first life, second life, third life and present life I never had as much fraternity as I'm having here, I'm not drooling, it is the truth"*[223].

On the contrary, negative experiences of outpatient care result from fragmented services that expose users to repeated assessments and excessive waiting lists due to inter-professional miscommunication[126,224]. Individuals often feel struggling with ever-changing care teams and limited appointment times that are not enough for professionals to get to know them beyond the diagnostic label: *"The various mental health professionals I saw at three separate psychiatric hospitals reinforced my narrowly defined diagnosis. Little effort was made to look beyond the many incongruences of my condition"*[171]. In addition, the competing theories about psychosis can cause confusion, as individuals can feel as if *"[clinicians] see what they want on your psychosis" (personal communication during the workshops)*.

The impersonal nature of some services can lead to an amplification of the inner feeling of objectification characterizing the experience of psychosis: *"If you enter the psychiatric business as a patient, then you have a high chance of being reduced to a disturbing object or to the disorder itself. Only that which is significant to the diagnostic examination is seen and heard. We are examined but not really seen; we are listened to but not really heard"*[65]. As a result, excessively bureaucratic clinical settings foster stigma and isolation[209].

Individuals may also feel rejected by the service due to lack of expertise among staff: *"There are no guidelines to do that"*[65]. Additionally, outpatient services can be perceived as insufficient in their treatment offers when there is a narrow focus on one-size-fits-all approaches[214].

The lived experience of receiving specific treatments for psychosis

Social interventions: finding one's own space in the world

"*I finally felt independent again. I was beginning to manage my mental illness. I was responsible again for my own space in the world*"[225]. Social interventions are perceived as supporting individuals in rebuilding their disturbed sense of self by fostering autonomy and independence[96]. As previously discussed, one core component of psychosis is the disruption of the person's natural engagement with the world. Following a first episode, young individuals often view their recovery as being able to feel "normal" again[195], which essentially means reintegrating into society[192], re-entering the workforce or going back to study in socially valuable roles[193]. Therefore, they feel that interventions supporting their study or work help them in regaining their sense of purpose[177,202] and confidence[226]: *"I waged this war not because I am so brave but because I absolutely had to in order to keep my job"*[170].

Interventions supporting an independent housing are also key in the process of strengthening personal agency, fostering stability, autonomy and independence[224,227]: "*Here [in the new house] I met new friends who accepted me. My attention shifted to pleasure and was increased through meeting new friends and enjoying the courses on offer*"[202].

Social interventions are also essential to reduce the experience of isolation and shame. This applies in particular to peer-support groups[180], which "normalize" the psychotic experiences[208,217], allowing the affected individuals to feel *"liberated"* and hopeful: *"They just told me that the fact was, there are other people like you, and you can get better from it"*[217]. Peer-support groups also help individuals to feel connected[228] and more accepted[184]: *"[The peer-support group] allows people to share their experiences, rediscover their emotions, and prepare for new journeys… where we can all support each other toward the goal of recovery and a better life"*[228].

Social interventions are also felt as helpful to overcome the passive role of affected individuals, stimulating a more proactive engagement in their care: "*I feel less like an outsider and more like someone with something to offer*"[229]. The positive experience of receiving these interventions is enhanced by the dialogic co-responsibility of the partnership established across various social actors, involving the community and the family[230].

The negative aspects of the experience of social interventions occur when the personal values of affected individuals are not prioritized, becoming purposeless[186]: "*Occupational therapy was supposed to engage me in what the professionals deemed meaningful activity. So I painted, I glued, and I sewed. I was occupied, but where was the meaning*?"[132]. These adverse experiences are widespread when individuals are asked or expected to conform and socially perform like everyone else: *"I have to do things differently… It is unfair for others to expect us to finally finish that college degree and finally get that job… It makes us feel ashamed and hopeless and depressed"*[185].

Furthermore, people with chronic psychosis often point out that adequate community integration requires a delicate balance between socially-promoting activities and having the space for solitary time[78,231,232]. This feeling has been confirmed by ethnographic studies, indicating that people with psychosis may develop a particular way of feeling integrated within society by keeping "at a distance" (i.e., neither too close nor too distant)[233,234]: *"I need to be alone… If I were living in the countryside, nobody would care about my solitude, but in the city, no one is allowed to live like a hermit"*[234].

Psychological treatments: sharing and comprehending one's experiences

Psychological treatments are perceived as essential to provide the first channel to open oneself about difficult-to-communicate psychotic experiences[226,235]: "*I wanted to learn to talk about my psychotic experiences, to communicate about them, and to learn to see their meaning*"[65].

For many individuals, recovery requires developing a complex and meaningful understanding of their distressing experiences, which re-establishes a sense of continuity in their life narrative and overcomes the disturbances of the awareness of identity[65,183,193,196,236-239]: *"Psychotic episodes don't happen out of nothing. There's always a reason for it. Unless the person is helped to make sense of that, they are not properly recovered" (personal communication during the workshops)*.

Given the intense search for explanations during the *Trema* phase of psychosis onset[240], finding meaning through a shared collaborative process allows the individuals to feel understood by others[237], reducing their sense of isolation and loneliness: *"So powerful is this desire that I often speak fervently of the wish to place my therapist inside my brain so that he can just know what is happening inside me"*[5]. However, not all individuals will necessarily succeed in discovering new meanings for their disorder: *"I've never been good at the 'finding meaning' thing" (personal communication during the workshops)*.

The experience of receiving psychological treatments is valued when it flexibly allows individuals to experiment[241] different approaches and strategies: "*My initial strategy for change was to take a break from the high-stress activities that have historically triggered symptoms and to instead focus on 'anchoring activities' that I find personally meaningful, intellectually challenging, and conducive to 'connectedness' with others*"[183]. Therefore, the experience of these treatments is highly personal, as reflected by the range of psychological coping strategies subjectively preferred, including improving mental health literacy and recognizing early warning signs[94,151,172,210], self-monitoring[151,197,242,243], developing meaningful alternative activities[108], setting a routine[63,108], learning to interact with the voices[150,238], reducing stress or "triggers"[46,180,183,244], relaxation[151,202] or distraction[245,246] techniques, sharing and discussing the experience with others[82,150,172,242,245,246], or employing reality-testing and disconfirmation strategies[46,88,131,232].

On the contrary, psychological treatments are felt unhelpful when they are "forced" upon the individual or deny his/her individuality[186]: *"The person needs to identify what psychotherapy works best for them – what works for me does not necessarily work for someone else" (personal communication during the workshops)*. Poor attentive listening is also perceived as impeding the affected individuals to speak in their voice and share their meanings appropriately[247]. Moreover, during psychological treatments, individuals feel that voices should be balanced, with no dominant voice, even if there are different views[248].

Psychotherapeutic relationships are also seen as not valuable if both parts are not allowed to contribute and learn: *"Clinicians need to give space to the patient and learn from the patient. There's a lot to learn from the patient" (personal communication during the workshops)*. Judgmental, preaching or lecturing attitudes[235] can lead to individuals feeling invalidated, which increases the experience of lacking agency, and feelings of isolation and discrimination: "*When I have been preached or lectured in talk therapy, I felt my thoughts were far less valuable and contributed less to the conversation*"[235].

An excessive emphasis on a rationalistic (reality-testing) approach in the psychotherapy of delusions and hallucinations is often perceived to aggravate[146] the sense of self-alienation, potentially through the intensification of hyper-reflexivity[249,250]. Under these circumstances, the experience of receiving psychotherapy may amplify the ipseity disturbance, perplexity, lack of common sense and sensation of being different from others that have been described above[251]: *"My recollections of any professionals challenging my hallucinations or delusions [during psychotherapy] are filled with feelings of hostility and resentment. After that, I would just tell them whatever they wanted to hear about my progress"*[146].

Similarly, a psychotherapeutic attitude that discredits the lived experience of psychosis as "meaningless" aggravates the sense of self-alienation: *"Untold damage can be caused by ignoring or trivializing [the experiences]. When regarded as just bizarre or symptomatic of the illness and not psychologically treated with appropriate validity, the intrinsic states of withdrawal are often exacerbated"*[186].

Medications: struggling with ambivalent feelings

The experience of receiving medication for psychosis, in particular antipsychotics, is often complex and ambivalent: "*The lesson is that psychiatric medications have two sides, on the one hand creating adverse effects and on the other hand alleviating and preventing psychiatric symptoms*"[203].

Medication is frequently considered helpful in alleviating distressing symptoms[61,92,127,243] or creating the necessary conditions for add-on psychosocial or psychological interventions[60,88,252]. Medications are often perceived to rescue the core self from the perturbation of the disorder: *"The experience of medication was such that there has never been any feeling that it has turned me into someone I am not; on the contrary, I always have felt that haloperidol removed all the barriers that were preventing me from being who I am"*[60]. Medication can provide a sense of being normal, even if it does not wholly restore premorbid functioning: *"I consider myself to be normal when I am on medication… And I do function normally when I am medicated, except for my inability to make friends"*[188].

These positive experiences often clash with the distressing side effects, which can impact the person's daily life abilities: *"After two weeks, the side effects of risperidone became intolerable. I slept at least 16 hours a night. I had a voracious appetite, akathisia and severe anhedonia"*[104]. In particular, for young people during a first episode, side effects are often perceived as severely limiting their social functioning abilities[195]. This is a common reason for medication abandonment or rejection [104,130,147].

The person can thus feel conflicted[186,203], due to having to choose between two challenging scenarios: *"It is hard realizing that I probably will have to continue taking medications for the rest of my life, but the misery without them is terrible"*[147]. The decision becomes then *"a question of personal values"*[253]: *"[The person] must decide what side effects and what degree of symptoms are intolerable"*[253]. It is worth emphasizing that shared decision-making enhances the sense of personal agency and autonomy[61,108,148,150,172,186,210].

Another negative experience of receiving antipsychotics is the feeling that one has not really recovered[195] or that something is "wrong" with oneself: *"During each psychotic episode, my family tried to get me medical help. Medications were prescribed, but I refused to take them. I didn't believe anything was wrong with me… Those pills were for crazy people!"*[92]. The associated desire to feel "normal"[48] may be asserted: "*I refused to go to any more doctors or take any more meds. I wanted to live a normal married life; normal people don't have to take pills to think clearly and act appropriately*"[254].

Antipsychotics may be also perceived as necessary but not sufficient to promote a complete recovery: "*I have found that, although psychiatric medication aids in the management of some of my symptoms, it only treats part of the problem*"[61]. As a result, the combination of medication with other treatments is often regarded as more acceptable[57,127,243,255], with varying combinations across the different phases of the recovery process: *"At the beginning stage, pharmacological treatment was more important for me; it allowed me to be stable and be able to go on with my life. As I started to improve, the psychosocial treatments were more important" (personal communication during the workshops)*.

Indeed, while providing symptomatic alleviation, medication may not address the underlying basic-self disturbances described above that fuel and sustain symptom formation: *"Medications can and do help with many of the frightening and distressing symptoms of schizophrenia, but they do not resolve anything beyond the apparent manifestation itself. What lies behind the symptoms is a tormented self, a highly personal experience unchangeable and irreplaceable by any physical treatment"*[157].

DISCUSSION

This paper is based on the lived experience of individuals who have gone through the semi-darkness and shadows of a psychotic crisis. We have followed and transcribed the words of these individuals, their emotions and forms of expression, their anguish and despair, their hopes and their silent cry for help. The paper, therefore, belongs to all the individuals with a lived experience of psychosis who have co-written it with researchers.

This double perspective on psychosis represents an innovative methodological attempt in the existing literature. It is only by following different paths and languages that it is possible to look at psychosis with fresh eyes that can capture the vividness of the subjective experience of suffering. This is best achieved by allowing personal insights to re-emerge into life and putting ideologies and traditional ways of thinking in brackets.

Such an approach also helps to minimize injustices, especially those related to exclusion and silencing of the affected persons' voices, distortion or misrepresentation of their emotions, meanings, values and understanding of oneself and the other, unfair distribution of power, and unwarranted distrust[256] – i.e., preventing these persons from speaking for themselves about their own views and purposes because of others claiming to know what those views and purposes are.

We attempted to prioritize the patients' first-person perspective rather than confining ourselves to descriptions of psychosis from a third-person perspective. Although this paper is dedicated to outlining some of the essential (paradigmatic) ways psychosis expresses itself, there is no assumption that the material presented is necessarily comprehensive or generalizable to all individuals affected. Although psychosis may have a formal framework common to all its clinical expressions, the contents and ways of being manifested in it are personal and idiosyncratic. It is, therefore, evident that is no such thing as a unique experience of psychosis that can be delineated. Instead, a plurality of experiences has been captured, reflecting the intrinsic heterogeneous nature of psychotic disorders. Bleuler himself coined the term "schizophrenias" to acknowledge heterogeneous syndromes characterized by multiple presentations and different possible trajectories[53,257].

Within these limitations, the present paper has first decomposed the experience of psychosis across core clinical stages. We have found that the early phases (i.e., premorbid and prodromal stages) are characterized by core existential themes spanning from loss of common sense, perplexity and lack of immersion in the world with compromised vital contact with reality, heightened salience and feeling that something important is about to happen, perturbation of the sense of self, and need to hide the tumultuous inner experiences. The first episode stage is denoted by some transitory relief associated with the onset of delusions, intense self-referentiality and permeated self-world boundaries, tumultuous internal noise and dissolution of the sense of self with social withdrawal. Core lived experiences of the later stages (i.e., relapsing and chronic) involve grieving personal losses, feeling split and struggling to accept the constant inner chaos, the new self, the diagnosis and an uncertain future. While these experiences partially blur across the different stages, the life-course of psychosis is marked by an inner experience of loneliness, stemming during the premorbid phase and persisting until the chronic stage.

Finally, we analyzed the positive and negative subjective experiential aspects of inpatient and outpatient care, social interventions, psychological treatments and medications. The experience of receiving these treatments is determined by the hope of achieving recovery, understood as an enduring journey of reconstructing the sense of personhood and re-establishing the lost bonds with others towards meaningful goals[258]. Good practices of care for persons with psychosis are first and foremost based on the understanding of what it is like to live with psychosis and receive psychiatric treatments.

Although it is not easy to listen to and understand the human and experiential reality of patients who are about to relive or re-express their stories, it is not possible to "do" psychiatry and to provide treatments without starting from these inner realities – from these lacerated subjectivities that yearn to be heard and understood. The present paper is a reminder to clinicians not to be afraid to descend in the therapeutic relationship with their patients affected with psychosis to penetrate their subjective world.

By comprehensively improving the understanding of what it is like to live with psychosis, this paper may additionally benefit several other areas. We hope that it will be widely disseminated across clinical networks as well as patient and family organizations, to substantially improve the mental health literacy of individuals affected with the disorder, their families and carers. The paper may also hold an educational potential to train junior doctors in psychiatry, medical students and other health care professionals. Furthermore, health care providers may access this co-developed source of core subjective experiences to refine the design and delivery of mental health services.

On a research level, this paper resurfaces the psychological and existential essence of psychosis, going against the current tide of a psychiatry "without psyche"[259], which reifies scientific epistemology silencing the fundamental expression of the human experience of psychosis. This observation is empirically corroborated by the imbalance on top-ranking scientific journals (with some exceptions) between neuroscientific articles and the field of phenomenology and first-person accounts. It is not possible to grasp the real and dialectical dimension of psychosis without a deep-rooted phenomenological approach that goes beyond the categories of natural sciences. The experiences described here may help to unmask the series of prejudices and misunderstandings with which natural sciences often reduce the complexity of psychosis, and to reflect on the limits of knowledge in psychiatry and on the meaning of research in this area.

Overall, this paper reminds us that psychosis is one of the most painful and upsetting existential experiences, so dizzyingly (apparently) alien to our usual patterns of life and so unspeakably enigmatic and human.

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Emerging experience with selected new categories in the ICD-11: complex PTSD, prolonged grief disorder, gaming disorder, and compulsive sexual behaviour disorder

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Among the important changes in the ICD-11 is the addition of 21 new mental disorders. New categories are typically proposed to: a) improve the usefulness of morbidity statistics; b) facilitate recognition of a clinically important but poorly classified mental disorder in order to provide appropriate management; and c) stimulate research into more effective treatments. Given the major implications for the field and for World Health Organization (WHO) member states, it is important to examine the impact of these new categories during the early phase of the ICD-11 implementation. This paper focuses on four disorders: complex post-traumatic stress disorder, prolonged grief disorder, gaming disorder, and compulsive sexual behaviour disorder. These categories were selected because they have been the focus of considerable activity and/or controversy and because their inclusion in the ICD-11 represents a different decision than was made for the DSM-5. The lead authors invited experts on each of these disorders to provide insight into why it was considered important to add it to the ICD-11, implications for care of not having that diagnostic category, important controversies about adding the disorder, and a review of the evidence generated and other developments related to the category since the WHO signaled its intention to include it in the ICD-11. Each of the four diagnostic categories appears to describe a population with clinically important and distinctive features that had previously gone unrecognized as well as specific treatment needs that would otherwise likely go unmet. The introduction of these categories in the ICD-11 has been followed by a substantial expansion of research in each area, which has generally supported their validity and utility, and by a significant increase in the availability of appropriate services.

Key words: International Classification of Diseases, ICD-11, diagnosis, complex post-traumatic stress disorder, prolonged grief disorder, gaming disorder, compulsive sexual behaviour disorder, clinical utility, mental health care

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The eleventh revision of the World Health Organization (WHO)'s International Classification of Diseases (ICD-11) was approved by the World Health Assembly, comprising the health ministers of all WHO member states, on May 25, 2019[1]. Reporting of health statistics to the WHO based on the new diagnostic system began on January 1, 2022[2]. WHO member states are now transitioning from the ICD-10 to the ICD-11, a process that will take several years to implement fully around the world. Countries that have not yet implemented the ICD-11 in their health information and reporting systems will use conversion algorithms in order to comply with the WHO reporting requirement in the meantime.

The primary purpose of the ICD classification is to provide a framework for the collection and reporting of information on mortality and morbidity by WHO member states, including disease surveillance and national and global health statistics. The ICD is also used by member states in the organization of clinical services from the institutional to the national level, and as an integral part of the framework for defining their obligations to provide free or subsidized health services to their citizens[3]. For individual users, the ICD organizes and facilitates clinical practice and research.

Over the past decade and within the context of the overall development of the ICD-11, the WHO Department of Mental Health and Substance Use has developed Clinical Descriptions and Diagnostic Requirements (CDDR) for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders, which are intended to provide sufficient information for reliable implementation in clinical settings[4]. The Department had previously published Clinical Descriptions and Diagnostic Guidelines (CDDG) for ICD-10 Mental and Behavioural Disorders[5] simultaneously with the publication of the ICD-10. The development of the ICD-11 CDDR, 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[6]. In part, the structure and methodology for developing the ICD-11 CDDR were specifically intended to address some of the shortcomings of the ICD-10 CDDG[4]. The change in title from CDDG to CDDR relates to the development by the WHO over the past decade of a body of policies that define guidelines in a specific way that is not applicable to the CDDR.

Among the important changes introduced in the ICD-11 classification of mental disorders[6] is the addition of 21 new categories, shown in Table 1. Proposals to add new categories are invariably intended to increase the recognition and prominence of a disorder that does not appear as a specific entity in the prior edition of the classification. The most frequent rationales for such addi-

Table 1 New disorders introduced in the ICD-11 classification of mental, behavioural or neurodevelopmental disorders

Type 1 additions (novel disorders previously not specifically classifiable)
Body dysmorphic disorder
Olfactory reference disorder
Hoarding disorder
Excoriation disorder
Prolonged grief disorder
Rumination-regurgitation disorder
Body integrity dysphoria
Gaming disorder
Compulsive sexual behaviour disorder
Intermittent explosive disorder
Type 2 additions (novel categories emerging from extension, expansion or subtyping of ICD-10 disorders)
Partial dissociative identity disorder
Binge eating disorder
Avoidant-restrictive food intake disorder
Complex post-traumatic stress disorder (PTSD)
Factitious disorder imposed on another
Substance-induced anxiety disorder
Substance-induced obsessive-compulsive or related disorder
Substance-induced impulse control disorder
Secondary neurodevelopmental syndrome
Secondary obsessive-compulsive or related syndrome
Secondary impulse control syndrome

tions include the needs to: a) collect morbidity statistics on a new but currently unclassifiable mental disorder that has important public health significance; b) facilitate recognition of a clinically important but poorly classified mental disorder so that appropriate management can be provided; and c) stimulate research into the development of more effective treatments for that condition.

In principle, there is an ICD category available for every conceivable clinical presentation of a mental disorder, based on the provision of what are called "residual categories". Residual categories include "other specified" and "unspecified" categories for each disorder grouping (e.g., other specified mood disorder; unspecified neurocognitive disorder). "Other specified" is used when there is no ICD-11 category that corresponds to a particular presentation, and "unspecified" is used when there is insufficient information about a patient's condition to assign a more specific diagnosis at a particular point in time.

If the clinician determined, for example, that a particular presentation involved clinically significant abnormal eating behaviours not explained by one of the specific feeding or eating disorders, another mental disorder or medical condition or the effects of a substance or medication, the category "Other specified feeding or eating disorders" could be assigned. If the clinician considered the presentation to constitute a mental disorder but it was not clear to which grouping it belonged, the category "Other specified mental, behavioural or neurodevelopmental disorders" or "Mental, behavioural or neurodevelopmental disorders, unspecified" could be used. However, using such residual categories as diagnoses for frequently occurring clinical presentations runs counter to the core purpose of the ICD to record unambiguous health data, because the same diagnostic label and code could be applied to a wide array of heterogeneous and potentially unrelated presentations. This situation often gives rise to the perceived need to add a new category.

From a classification perspective, new categories can be divided into two types. The first type involves diagnostic entities that represent a novel phenomenon which is qualitatively different from existing entities in ICD and was thus not specifically classifiable. In Table 1, new mental disorder categories in ICD-11 that fit this description are designated as Type 1. For example, the phenomenology of hoarding disorder bears some resemblance to obsessive-compulsive disorder (e.g., the irrational need to save items may resemble an obsession; excessive acquisition of possessions may resemble a compulsion). However, unlike in obsessive-compulsive disorder, in hoarding disorder these behaviours are not undertaken with the goal of neutralizing or reducing concomitant distress and anxiety, and may be associated with pleasure or enjoyment. In addition, important treatments for obsessive-compulsive disorder are not effective for hoarding disorder[7]. Based on its review, the ICD-11 Working Group for this diagnostic area concluded that there was sufficient evidence to regard hoarding disorder as a separate mental disorder that had previously been under-recognized and undertreated[8]. In the ICD-10, presentations of hoarding disorder would most likely have been classified as "other specified neurotic disorder", which is neither clinically informative nor statistically useful.

The second type of new disorder category emerges from extending, expanding or subdividing the conceptualization of an existing disorder so that it identifies a group of symptomatic presentations that are relatively homogeneous with respect to the underlying pathophysiology, course, prognosis or treatment, and sufficiently distinct so as to justify being considered a new disorder rather than a subtype of the original category. In Table 1, new ICD-11 mental disorder categories that fit this description are designated as Type 2. For example, bulimia nervosa is a well-established disorder defined by recurrent binge eating accompanied by repeated inappropriate compensatory behaviours, such as self-induced vomiting or misuse of laxatives or enemas, to prevent weight gain. It has long been noted clinically and in the literature that there is a group of individuals who recurrently engage in binge eating but not in purging or other compensatory behaviours. The symptoms of these individuals do not meet the diagnostic requirements for bulimia nervosa, but they experience high levels of distress, elevated rates of other mental disorders, and substantial general health risk[9,10]. In the ICD-10, these individuals might be diagnosed with "atypical bulimia nervosa", "other eating disorder", or "eating disorder, unspecified", making unified statistical reporting and tracking of this group of patients difficult. The new ICD-11 condition, binge eating disorder, is much more common than bulimia nervosa[11], and also differs in terms of prognosis and treatment[12], justifying its addition to the ICD-11.

Given the major implications for the field and for WHO member states of adding new mental disorders to the official global classification system, it is important to examine the impact that their introduction has had. Although it has been too short a time since the official approval of the ICD-11 by the World Health As-

sembly for the effects of these changes to be fully evaluated, a draft version of the ICD-11 was made publicly available in 2012[13], and many papers have appeared in the scientific literature related to proposals for the classification of mental disorders in the ICD-11[6]. Therefore, the WHO's intention to add the mental disorder categories shown in Table 1 to the ICD-11 has been publicly communicated for a decade, and relevant research and clinical evidence has become available.

In this paper, we focus on the addition of four new categories to the ICD-11 classification of mental disorders: complex post-traumatic stress disorder (PTSD), which represents a modification of the ICD-10 category "enduring personality change after catastrophic experience" as well as an extension of the category of PTSD; two completely novel disorders, prolonged grief disorder and gaming disorder; and one disorder, compulsive sexual behaviour disorder, which replaces a related but poorly defined disorder that had existed in the ICD-10, "excessive sexual drive". The "essential (required) features" from the CDDR for these four disorders are provided in Tables 2-5.

Essential features in the CDDR represent those symptoms or characteristics that a clinician could reasonably expect to find in all cases of the disorder[4]. In this sense, they resemble diagnostic criteria in the DSM. However, artificial precision, such as using exact symptom counts and specific duration requirements as diagnostic cutoffs (unless these have been well established with appropriate global evidence), has generally been avoided. This allows for broader exercise of the professional's clinical judgment depending on the characteristics of the patient – including cultural variations in presentation – and local circumstances. It is important to note that the essential features represent only a portion of the material provided for each disorder; the CDDR also include disorder-specific information on additional clinical features, which describe important aspects of the clinical presentation that are not diagnostically determinative, boundary with normality (threshold), course features, developmental presentations, culture-related features, gender-related features, and boundaries with other disorders and conditions (differential diagnosis)[4,14].

The four disorders discussed in this paper are of particular interest because they have been the focus of considerable activity and/or controversy, which is in part related to the fact that their official inclusion in the ICD-11 as diagnostic categories represents a different set of decisions than had been made by the developers of the DSM-5[15]. Categories similar to prolonged grief disorder and gaming disorder were included in the DSM-5 section on "Conditions for Further Study", outside the main classification. A counterpart to compulsive sexual behaviour disorder was proposed and then not included in the DSM-5 at all[16]. Some symptoms similar to those of complex PTSD were added to the DSM-5 criteria for PTSD[17], but complex PTSD was not distinguished as a separate disorder.

Table 2 Essential (required) features for complex post-traumatic stress disorder in the ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR)

- Exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible. Such events include, but are not limited to, torture, concentration camps, slavery, genocide campaigns and other forms of organized violence, prolonged domestic violence, and repeated childhood sexual or physical abuse.
- Following the traumatic event, the development of all three core elements of Post-Traumatic Stress Disorder, lasting for at least several weeks:
  - Re-experiencing the traumatic event after the traumatic event has occurred, in which the event(s) is not just remembered but is experienced as occurring again in the here and now. This typically occurs in the form of vivid intrusive memories or images; flashbacks, which can vary from mild (there is a transient sense of the event occurring again in the present) to severe (there is a complete loss of awareness of present surroundings), or repetitive dreams or nightmares that are thematically related to the traumatic event(s). Re-experiencing is typically accompanied by strong or overwhelming emotions, such as fear or horror, and strong physical sensations. Re-experiencing in the present can also involve feelings of being overwhelmed or immersed in the same intense emotions that were experienced during the traumatic event, without a prominent cognitive aspect, and may occur in response to reminders of the event. Reflecting on or ruminating about the event(s) and remembering the feelings that one experienced at that time are not sufficient to meet the re-experiencing requirement.
  - Deliberate avoidance of reminders likely to produce re-experiencing of the traumatic event(s). This may take the form either of active internal avoidance of thoughts and memories related to the event(s), or external avoidance of people, conversations, activities, or situations reminiscent of the event(s). In extreme cases the person may change their environment (e.g., move house or change jobs) to avoid reminders.
  - Persistent perceptions of heightened current threat, for example as indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises. Hypervigilant persons constantly guard themselves against danger and feel themselves or others close to them to be under immediate threat either in specific situations or more generally. They may adopt new behaviours designed to ensure safety (not sitting with ones' back to the door, repeated checking in vehicles' rear-view mirror). In Complex Post-Traumatic Stress Disorder, unlike in Post-Traumatic Stress Disorder, the startle reaction may in some cases be diminished rather than enhanced.
- Severe and pervasive problems in affect regulation. Examples include heightened emotional reactivity to minor stressors, violent outbursts, reckless or self-destructive behaviour, dissociative symptoms when under stress, and emotional numbing, particularly the inability to experience pleasure or positive emotions.
- Persistent beliefs about oneself as diminished, defeated or worthless, accompanied by deep and pervasive feelings of shame, guilt or failure related to the stressor. For example, the individual may feel guilty about not having escaped from or succumbing to the adverse circumstance, or not having been able to prevent the suffering of others.
- Persistent difficulties in sustaining relationships and in feeling close to others. The person may consistently avoid, deride or have little interest in relationships and social engagement more generally. Alternatively, there may be occasional intense relationships, but the person has difficulty sustaining them.
- The disturbance results in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.

In developing this paper, the lead authors (GMR and MBF) invited experts on each of these disorders to address the following questions: a) from a clinical perspective, why was this category considered important enough to be added to the ICD-11 and what was the evidence available at the time?; b) how were individuals with this disorder diagnosed prior to the ICD-11 and what were the implications for care of the absence of the diagnosis in the ICD?; c) what were the controversies (if any) about adding the disorder?; and d) what evidence has been generated and what other developments have occurred in relation to this category (e.g., changes in availability of clinical services) since the WHO signaled its intention to include it in the ICD-11 classification?

COMPLEX POST-TRAUMATIC STRESS DISORDER

The need for a complex PTSD diagnosis

Clinical presentations that extend beyond those described by the ICD-10 diagnosis of PTSD, particularly among individuals who experienced extreme, prolonged or multiple forms of trauma, have been reported by clinicians and researchers over several decades[18,19].

The WHO conducted two global surveys as a part of the early development of the ICD-11 classification of mental, behavioural and neurodevelopmental disorders, the first in collaboration with the World Psychiatric Association[20], and the second with the International Union of Psychological Science[21]. Among 3,222 psychiatrists and psychologists from 35 countries who participated in either survey in English or Spanish, complex PTSD was the most frequent diagnosis suggested for inclusion in the ICD-11[22]. Participants indicated that the diagnosis was needed to better account for the distinct characteristics and consequences of complex trauma.

Based on its review of the evidence, the ICD-11 Working Group on Disorders Specifically Associated with Stress recommended inclusion of complex PTSD in the ICD-11[23]. The essential features of this condition as outlined in the CDDR are shown in Table 2.

The diagnosis of complex PTSD requires the presence of all three core symptoms of PTSD (re-experiencing in the present, avoidance, and an ongoing sense of threat). In addition, complex PTSD is characterized by what are referred to as disturbances in self-organization: severe and persistent problems in affect regulation; beliefs about the self as diminished, defeated or worthless; and difficulties in sustaining relationships and in feeling close to others.

The ICD-11 diagnosis of complex PTSD acknowledges the existence of more diverse and pervasive symptoms that may particularly occur in response to certain types of traumas, such as prolonged or repetitive events from which escape is difficult or impossible (e.g., torture, slavery, prolonged domestic violence, repeated childhood sexual or physical abuse). The new category also flags the potential need for greater mental health resources in the form of longer, multi-part or multimodal therapies.

History of the disorder

In 1992, the ICD-10 had introduced a new category called "enduring personality change after catastrophic experience" (EPCACE). The ICD-10 CDDG indicated that the personality change should be enduring and manifest as inflexible and maladaptive features leading to an impairment in interpersonal, social and occupational functioning. It also required the development of features not previously characteristic of the individual, such as a hostile or mistrustful attitude towards the world, social withdrawal, feelings of emptiness or hopelessness, a chronic feeling of being "on edge", as if constantly threatened, and estrangement. The ICD-10 CDDG also noted that PTSD could precede this type of personality change, which could therefore be seen in some cases as a chronic sequela of PTSD when it occurred in response to certain types of events. Examples of potential causes of EPCACE provided in the ICD-10 CDDG included "concentration camp experiences, torture, disasters, prolonged exposure to life-threatening circumstances (e.g., hostage situations: prolonged captivity with an imminent possibility of being killed)"[5, p.163]. Conceptually, therefore, EPCACE can be seen as a forerunner of ICD-11 complex PTSD.

However, the diagnosis was neither widely taken up by clinicians nor subject to much empirical investigation. Reasons for this include the absence of important symptoms that are part of more recent formulations (e.g., problems with affect regulation, negative views of the self) and what seemed to be a narrow range of application. For example, prolonged and severe intimate partner violence or childhood physical or sexual abuse, which are much more common than the types of experiences described in the CDDG as causes of EPCACE, were not mentioned at all. Moreover, the description of symptoms of EPCACE was very broad and general, which made clinical application and research difficult[24,25].

Concurrent with the development of the ICD-10, the DSM-IV was considering the inclusion of a new diagnosis based on a formulation of complex PTSD developed by Herman[18], which was given the name "disorder of extreme stress not otherwise specified" (DESNOS). The DSM-IV field trial for PTSD[26,27] indicated that individuals who had experienced early and chronic interpersonal trauma reported a greater number and severity of DESNOS symptoms particularly related to emotion regulation difficulties, negative self-concept, and relational disturbances, in comparison to those without such a history. DESNOS did not include any of the symptoms traditionally understood to comprise PTSD, but rather was viewed as a distinct disorder that might complement PTSD. Ultimately, DESNOS was not included in the DSM-IV on the grounds that there was not enough empirical support to warrant the addition of a distinct trauma-induced disorder. The symptoms ended up being included in the "associated features" section of DSM-IV PTSD, which facilitated clinicians' awareness of their existence as possible post-traumatic stress reactions.

The ICD-11 proposal for complex PTSD[23] was derived from the ICD-10 EPCACE diagnosis, but many aspects of its operationalization were based on the empirical literature that emerged

from the DESNOS investigations. First, the ICD-11 CDDR identify a wider variety of types of chronic and sustained trauma exposures as risk factors for the disorder, including childhood abuse and intimate partner violence. Second, while the diagnosis of EPCACE, like other ICD-10 diagnoses reflecting personality changes, was intended to describe difficulties in three domains (i.e., affect, identify and relationships), these were only broadly described. The selection of specific symptoms and symptom clusters reflecting difficulties in these domains was guided by the DESNOS formulation in the DSM-IV field trials[26] as well as by an expert consensus survey on complex PTSD[19]. These aspects of complex PTSD are formulated in the CDDR as severe and persistent problems with affect regulation, a deep and enduring negative sense of self, and persistent difficulties in sustaining relationships and in feeling close to others. Lastly, while ICD-10 EPCACE had identified the sense of threat as a key symptom, ICD-11 complex PTSD includes all three PTSD core symptoms as part of the profile (i.e., re-experiencing in the present, avoidance, and an ongoing sense of threat). This decision was supported by the observation in the DSM-IV field trial that nearly all individuals whose symptoms met criteria for DESNOS also met criteria for these three symptoms of PTSD[26].

In summary, ICD-11 complex PTSD derived from the general conceptualization of EPCACE, which included both traditional PTSD symptoms as well as an emphasis on disturbances in affect, identity and relationships. In the ICD-10, EPCACE was included in a grouping called "enduring personality changes, not attributable to brain damage" (along with enduring personality change after psychiatric illness), which was adjacent to the specific personality disorders. In contrast, in the ICD-11, complex PTSD is grouped together with other disorders in which a stressor is required as causal agent.

The presence of re-experiencing, avoidance and threat symptoms in both PTSD and complex PTSD highlights the continuity between the two disorders. However, the greater number and diversity of symptoms in complex PTSD, the greater impairment associated with it, and the relative dominance of the disturbances in self-organization (i.e., affect dysregulation, negative self-concept, and relational difficulties) over the PTSD symptoms indicate the importance of describing complex PTSD as an independent disorder rather than as a subtype of PTSD. The CDDR specify that an individual can be diagnosed with either ICD-11 PTSD or complex PTSD, but not both.

Controversies related to the diagnosis of complex PTSD

A debate about the clinical utility and validity of the diagnosis of complex PTSD has been ongoing since its formulation in the 1990s[28]. Several reasons have been given for rejecting its adoption in official classification systems. These include: a) the lack of a consistent definition of the disorder; b) the lack of standardized and validated measures; c) the argument that it simply represents a severe form of PTSD; and d) difficulty differentiating it from borderline personality disorder[29].

These concerns have been addressed in substantive ways. The introduction of complex PTSD into the WHO's diagnostic nomenclature has brought with it a clear definition of the disorder. This established definition has provided the foundations for the development of reliable measures. A self-report measure has now been validated[30], translated into over 25 languages, and made available to the international community (see www.traumameasuresglobal.com). In addition, there has been significant progress in the testing of a clinician interview[31]. The suggestion that complex PTSD is simply a more severe form of PTSD has not been supported but rather countered by over 15 studies indicating that the two diagnostic categories identify distinct trauma populations with qualitatively different patterns of symptom endorsement[32,33].

Lastly, a growing number of studies indicate that, while complex PTSD and borderline personality disorder have some overlapping symptoms, they are more distinct than similar, particularly in regard to key symptoms and treatment implications. In fact, while the affect dysregulation symptoms overlap between the two disorders, recent research shows that other borderline personality disorder symptoms are quite distinct from the disturbances in self-organization occurring in complex PTSD[34]. Specifically, borderline personality disorder is marked by instability in identity, fluctuating and volatile relationships, and the salient presence of self-injurious and suicidal behaviours, while complex PTSD tends to be characterized by a negative but stable identity, a consistent tendency to avoid or break off relationships, and relatively lower levels of impulsivity. There is some indication that differences in identity characteristics may most effectively distinguish the two disorders[35].

Review of the evidence

The validity of the complex PTSD diagnosis has been supported by a number of studies using a variety of methods and statistical approaches.

Initial investigations focused on determining whether trauma-exposed populations are best described under the umbrella of a single diagnosis, as has been done by the DSM-5 (i.e., as a part of PTSD), or if they fall into different groups based on symptom profiles and do so consistently across different settings and cultures.

In an initial validation study[36], latent profile analyses revealed that trauma-exposed individuals fell into two different subgroups, with one displaying a complex PTSD symptom profile and the other a PTSD profile. Moreover, membership in the complex PTSD subgroup was strongly predicted by a history of chronic trauma, while membership in the PTSD subgroup was predicted by exposure to single-incident trauma.

A 2017 review of studies investigating ICD-11 complex PTSD[32] reported an additional nine investigations using latent profile/class analyses, eight of which replicated the finding of distinct complex PTSD and PTSD subgroups. The studies included a variety of samples, such as individuals with histories of child-

hood sexual abuse, military veterans, war-exposed civilians, and mixed trauma samples, and represented research from different regions of the world, including the US, the UK, Israel, Uganda and Bosnia, indicating the consistency of PTSD and complex PTSD profiles over many types of trauma populations and regions in the world.

More recent summaries have indicated that, relative to PTSD, complex PTSD is associated with greater comorbidity, greater impairment, and lower quality of life[33]. A prospective study has found that complex PTSD is associated with poorer health and greater cognitive decline over time[37]. A functional magnetic resonance imaging (fMRI) investigation[38] has provided evidence of distinct neural profiles of complex PTSD and PTSD patients during the processing of threatening stimuli, with increased insula and right amygdala activation in complex PTSD, a finding similar to other studies[39,40] and consistent with disturbances in emotion regulation and self-concept as described for that condition in the ICD-11.

Clinicians' capacity to accurately distinguish between the two disorders has also been documented. Using a vignette-based experimental design, an ICD-11 field trial assessed whether clinicians would be able to accurately diagnose ICD-11 complex PTSD as compared to ICD-10 EPCACE, and whether clinicians would successfully distinguish ICD-11 complex PTSD from ICD-11 PTSD on the basis of the presence or absence of disturbances in self-organization[41]. The accuracy rate for complex PTSD was significantly higher than for EPCACE, indicating the benefits of the conceptual revision and symptom specification in ICD-11. Clinicians were also able to successfully differentiate complex PTSD from PTSD with high accuracy.

The factor structure of the symptoms comprising complex PTSD is also supportive of its construct validity. Several studies have found that each of the six symptom clusters demonstrates good to excellent internal consistency[42]. In addition, the studies have reported that higher-order factors of PTSD and disturbances in self-organization (affect dysregulation, negative self-concept, and relational difficulties) were either the best fit or a very strong fit to the data. This evidence supports the conceptualization of complex PTSD as having two higher-level symptom components (PTSD and disturbances in self-organization). It should be noted that studies with certain populations have not found this higher-level organization[e.g.,43], a finding that is of interest and requires further investigation.

A series of network analyses assessing the symptoms of complex PTSD across four nationally representative samples (Germany, Israel, the UK, and the US) found that – despite differences in traumatic experiences, symptom severity and symptom profiles – the networks (e.g., clustering of symptoms) were very similar across the four countries, providing evidence of the stability and relative invariance of the symptom clusters[44]. In addition, the analyses indicated that negative self-concept was the most central aspect of the complex PTSD formulation, followed by affect dysregulation, while the PTSD symptoms were less central to the disorder and significantly influenced by the disturbances in self-organization. This finding supports the ICD-11 decision to identify complex PTSD as a separate disorder rather than as a subtype of PTSD, because the most dominant and influential symptoms are those unique to the new diagnostic category. This finding also has implications for assessment and treatment planning.

Implications of the complex PTSD diagnosis

One important implication of the diagnosis of complex PTSD is its potential impact on treatment. Although no systematic data have been published, clinical reports indicate that, prior to the availability of the new diagnostic category, individuals with complex PTSD were likely to be diagnosed with PTSD along with one or more co-occurring disorders, in an attempt to account for the full range of presenting symptoms[45]. Additional diagnoses might include recurrent depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, and personality disorder, most commonly borderline type, but also schizoid or avoidant.

The implications for care under this scenario are significant. First, multiple diagnoses involve a risk that the patient will "fall through the cracks" or have an overly long and disorganized treatment program. Second, patients might view themselves as very sick or feel stigmatized, including by health professionals, due to being diagnosed with numerous mental disorders. Third, diagnosing complex PTSD as PTSD can lead to treatment needs being underestimated. There is evidence that standard PTSD treatments primarily designed for single traumatic events may provide inferior outcomes for complex PTSD patients. A recent meta-analysis indicated that patients with childhood trauma, a group of people more likely to have a complex PTSD diagnosis, received less benefit from standard PTSD treatment than those without childhood trauma with respect to numerous symptom outcomes, including PTSD symptoms, emotion regulation difficulties, negative self-concept, and interpersonal problems[46,47].

While much remains to be determined, particularly about treatment implications, the announcement of the intention to include complex PTSD in the ICD-11 prompted considerable research interest. A PubMed search (search terms: CPTSD or "complex PTSD" or "complex posttraumatic stress disorder" or "complex post traumatic stress disorder") identified 16 publications in 2014, the year after the first formal report[23]. In the following years, the number of publications steadily increased each year, such that by 2020 a total of 322 studies had been published on this condition. This is more than double the number of publications in the 21 previous years (1992-2013) during which the term complex PTSD had existed[18].

Papers have included psychometric studies of the validity of the diagnosis, development of standardized measures, epidemiological surveys, risk factor and treatment research, and comparisons with PTSD in the DSM-5. Importantly, and consistent with the mission of the WHO, the validity of complex PTSD has been supported in studies on four continents and in a wide range of cultures. Also of interest are studies supporting the validity of

the diagnosis in samples of children and adolescents[48], and its particular relevance to occupational groups such as police officers exposed to chronic and repeated stressors[49].

Research funding specific to complex PTSD has emerged, which will contribute to the progress of knowledge about how best to treat the disorder. The existence of the complex PTSD diagnosis should help draw attention to the importance of chronic trauma-related symptoms as a prominent aspect of mental health. It is hoped that the designation of complex PTSD as distinct from PTSD will have a public health benefit derived from the development of population-tailored interventions, leading to greater efficiency in the deployment of global health resources as well as better outcomes for people with these disorders.

PROLONGED GRIEF DISORDER

In the ICD-11, prolonged grief disorder is described as persistent longing or yearning for the deceased and associated intense emotional pain, difficulty accepting the death, feeling to have lost a part of oneself, an inability to experience positive mood, emotional numbing, and difficulty in engaging with social or other activities[14] (see Table 3). The severe grief response needs to persist beyond 6 months after bereavement, or for a time that clearly exceeds the norms of the person's culture. It is expected that the symptoms be associated with impaired personal, social or occupational functioning.

The need for a prolonged grief disorder diagnosis

There has been accumulating evidence over many years validating prolonged grief disorder as a specific and identifiable condition that can severely impact a minority of bereaved people. There are many factor-analytic studies indicating that the construct of persistent yearning and emotional pain, together with its associated symptoms, is a well-defined syndrome, and that this syndrome is distinct from other related disorders such as depression and PTSD[50-52]. Furthermore, studies using network-analytic approaches to model the centrality of prolonged grief disorder symptoms have converged on the conclusion that yearning for the deceased and associated emotional pain have a cascading effect on other symptoms[53,54].

It is important to note that studies of the nature of prolonged grief disorder symptoms indicate that these symptoms are not different from those typically reported in normal grief reactions[55]. The defining feature of prolonged grief disorder is that these reactions do not abate over time and continue to cause severe distress and impairment.

One of the major rationales for recognizing prolonged grief disorder as a distinct syndrome is that persistent grief can cause many physical and psychological symptoms as well as problems with functioning. Persistent grief reactions have been associated with marked occupational and social impairment[56], impaired sleep[57], increased rates of cancer and cardiovascular problems[58] and other medical conditions[59], and poor health behaviours, such as increased alcohol and tobacco use[60,61]. There is also overwhelming evidence that persistent grief reactions are associated with elevated rates of other mental disorders and symptoms, including depression[62,63], PTSD[52], suicidality[64,65], and panic[66]. Importantly, it has been shown that the symptoms of prolonged grief disorder contribute to impaired functioning beyond the effects of co-occurring depression and PTSD[67]. Taken together, these findings indicate that there is a public health need for recognition of this new diagnostic category in order to identify and successfully treat a disorder that contributes to considerable impairment amongst people who suffer from it.

Traditional conceptualizations of grief

Although having a diagnostic category for problematic and persistent grief is new, the study of grief has a long tradition in psychiatry. The importance of bereavement and loss in mental health has been extensively theorized about for many years by Freud, Lindemann, Parkes and Bowlby[68].

In his seminal text *Mourning and Melancholia*[69], Freud distinguished between normal and pathological grief by postulating that melancholia (which had some similarities to current descriptions of prolonged grief disorder) was a maladaptive form of mourning in which the object loss was so severe that affected individuals could not transfer their attachments to new relationships.

A consistent theme across earlier theorists was the role of fragmented attachments. This was articulated most clearly by Bowlby in his work on how fragile attachment tendencies acquired

Table 3 Essential (required) features for prolonged grief disorder in the ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR)

- History of bereavement following the death of a partner, parent, child, or other person close to the bereaved.
- A persistent and pervasive grief response characterized by longing for the deceased or persistent preoccupation with the deceased accompanied by intense emotional pain. This may be manifested by experiences such as sadness, guilt, anger, denial, blame, difficulty accepting the death, feeling one 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 pervasive grief response has persisted for an atypically long period of time following the loss, markedly exceeding expected social, cultural or religious norms for the individual's culture and context. Grief responses lasting for less than 6 months, and for longer periods in some cultural contexts, should not be regarded as meeting this requirement.
- The disturbance results in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.

early in life can predispose people to pathological grief reactions in the wake of bereavement later in life[70]. Comparable to current conceptualizations of prolonged grief disorder, Bowlby recognized that yearning for the bereaved was central to the condition, as the person strives to re-connect with the lost attachment figure. The emphasis placed on the role of fragmented attachments has been supported by many studies showing that anxious attachment tendencies are associated with prolonged grief disorder[71,72].

Although these earlier theorists paved the way for the current conceptualization of prolonged grief disorder, there has been a long-standing reluctance to introduce a diagnosis of pathological grief. In the DSM-III and DSM-IV, problematic but normal grief reactions were included in the chapter "Other conditions that may be a focus of clinical attention", which included phenomena that are not mental disorders but might bring a person into contact with a mental health professional, such as parent-child relational problems. Psychiatric presentations occurring in the wake of bereavement that were sufficiently severe or impairing to be considered a mental disorder would be diagnosed based on the pattern of symptoms; for example, a major depressive episode triggered by bereavement would be diagnosed in the same way as if it had been triggered by the termination of a romantic relationship.

This DSM conceptualization of mood disturbance following bereavement was qualitatively distinct from current conceptualizations of prolonged grief disorder because, rather than placing yearning for the deceased at the core of the condition, bereavement issues were considered through the lens of depression. Moreover, because of the prevalence of depressed mood amongst the bereaved, editions of the DSM prior to the DSM-5 advised against diagnosing major depressive disorder after bereavement if such episodes were better understood to be manifestations of normal bereavement[e.g.,73].

Controversies related to the diagnosis of prolonged grief disorder

For many years, controversy has surrounded the optimal way to categorize the psychological distress that can persist after bereavement. Despite strong proposals being put forward to introduce a problematic grief diagnosis, these were rejected in earlier iterations of the DSM[74,75]. This hesitancy has been based, in part, on a view that psychiatry should not be medicalizing a nearly universal experience. That is, most people will experience grief following bereavement, and it was argued that introducing a grief diagnosis would pathologize normal grief reactions and potentially lead to over-prescription of psychotropic medication for the bereaved[76]. Moreover, the experience of grief is often culturally bound and linked to distinct religious mourning rituals, and so there have been concerns that any attempt to categorize persistent grief as a disorder may ignore this variability. To consider the merits and potential limitations of a prolonged grief disorder diagnosis, it is worth considering the evidence pertaining to the most frequent concerns held by commentators.

The concern that a diagnostic category of prolonged grief disorder may over-medicalize the common grief response that most people experience after bereavement is countered by the evidence that only a small proportion of bereaved people actually have symptoms that meet the requirements for that diagnosis. Studies estimate that only 7-10% of bereaved people may suffer from this condition[77,78]. Prevalence is low even in groups characterized by exposure to the traumatic deaths of close family members. For example, in a study of refugees fleeing a war zone, only 16% of bereaved people developed symptoms meeting diagnostic requirements for prolonged grief disorder[79]. At the level of the general population, estimates indicate that only 2-3% of people may experience prolonged grief disorder, in contrast with the nearly universal experience of bereavement[62,77]. These findings suggest that prolonged grief disorder does not over-pathologize problematic grief reactions, because only a small minority of bereaved people would qualify for the diagnosis.

The concern that the prolonged grief disorder diagnosis may be problematic because of cultural differences in how people mourn and express grief can be considered in two ways. First, the diagnosis requires that the persistent grief reaction needs to be outside the realm of what is normative in the person's cultural context, especially in terms of duration. Second, the diagnostic features of prolonged grief disorder have been observed in Western and non-Western countries that comprise many different cultures and religions[80-82].

There have also been concerns regarding the amount of time that needs to elapse before the grief response is considered prolonged. This issue is particularly important, because the symptoms of prolonged grief disorder are not qualitatively different from the manifestations of normative acute grief. The duration requirement, therefore, functions to achieve a balance between capturing a pathological grief reaction and not misdiagnosing normative grief. Empirical studies that have considered this question have concluded that people with severe grief symptoms persisting beyond 6 months typically have ongoing difficulties in functioning at later assessment[83,84].

Review of the evidence

The introduction of the diagnostic category of prolonged grief disorder has been supported by emerging evidence regarding both the construct validity of this category and its differentiation from other disorders. There is increasing evidence that prolonged grief disorder is a distinct syndrome that revolves around longing or yearning for the bereaved. Many factor-analytic studies have highlighted that this disorder is distinct from depression and PTSD[50-52], and is responsible for marked functional impairment beyond the effects of co-occurring depression, anxiety and PTSD[56,85]. Evidence is also emerging that prolonged grief disorder worsens the severity of co-occurring conditions after bereavement, including PTSD[86] and depression[87].

In recent years, longitudinal findings have also emerged regarding the course of prolonged grief disorder. This is critical, be-

cause the lack of evidence regarding the normative time course of grief was one of the major obstacles to the introduction of that diagnostic category in the DSM-5. Longitudinal studies assessing bereaved people at multiple time points, and using latent growth mixture modelling to map the different trajectories of grief symptoms over time, have noted the presence of a group with high grief symptoms that do not improve over time[88-90]. However, these studies are limited by small sample sizes, relatively short follow-up assessments, or other methodological issues. Further studies, particularly those with larger sample sizes or longer-term time frames, have observed distinct trajectories in which most people are resilient to the effects of bereavement, a smaller but significant proportion have grief symptoms improving over time, others have moderate and persistent symptoms, and a smaller group exhibits high levels of grief symptoms that do not improve over time (i.e., prolonged grief)[91,92]. It appears that, whereas prolonged grief disorder and depression follow some of the same trajectories after bereavement, there are also trajectories unique to each[93]. Another study found that the ICD-11 prolonged grief disorder construct is more consistent with the observed patterns than "persistent complex bereavement disorder" as described in the DSM-5 research appendix[94]. Longitudinal studies also indicate that people with prolonged grief disorder experience deterioration in functioning, and this can persist for at least 3 years post-bereavement[90].

Research has started to shed light on the neural underpinnings of prolonged grief disorder, and this work has indicated links between characteristic symptoms of the disorder – in particular, profound yearning – and a differential pattern of activation of the neural reward system compared to normative grief[95]. Affected areas include the amygdala, the orbitofrontal cortex, the subgenual anterior cingulate cortex, the nucleus accumbens and the insula[96-101]. Notably, neural responses of people with prolonged grief disorder are distinct from those of individuals with PTSD or depression[96].

The notion that prolonged grief disorder may be associated with disturbed reward processes has also been supported by other experimental paradigms. One experiment showed that bereaved individuals with prolonged grief symptoms had a greater tendency to discount the value of future rewards (operationalized as a delayed financial incentive) as compared to bereaved persons without those symptoms[102].

On behavioural tasks, people with prolonged grief disorder are drawn to stimuli reminiscent of the deceased[103,104]. This has led to theories emphasizing the role of conditioned responses associated with a range of environmental stimuli that elicit craving for the deceased and extinguish very slowly[105]. Other studies suggest these individuals avoid reminders of the deceased[106,107]. It seems that prolonged grief disorder involves both approach tendencies towards reminders of the deceased and avoidance of these reminders as a strategy to minimize the associated emotional distress[108,109].

Numerous studies have highlighted the role of cognitive processes in prolonged grief disorder[110,111]. They include studies that have pointed to the importance of rumination, in which people tend to repetitively think about the causes and consequences of the death, which then contributes to worse emotional states[112,113]. Relatedly, engaging in counter-factual thinking, in which people imagine that if they had behaved differently the situation would have turned out better, is associated with more severe prolonged grief symptoms[114]. The role of cognitions is underscored by evidence that more adaptive appraisals during the course of therapy mediate better outcomes for people with the disorder[115]. Further, longitudinal studies indicate that maladaptive cognitive appraisals, including rumination, mediate longer-term prolonged grief symptomatology[88,116].

There have also been advances in how we understand emotion regulatory mechanisms associated with prolonged grief disorder. The disorder tends to be associated with avoidance of emotions and thoughts associated with the deceased[117,118], suppression of unwanted emotions or thoughts[117,119], avoidance of external reminders that trigger negative emotions[120], and impaired emotional flexibility[121]. There is also evidence that people with prolonged grief disorder show a distinctive disconnection between the experience and the expression of emotion; specifically, whereas they report strong affective experiences, they nonetheless are less facially expressive than bereaved controls [122].

Implications of the prolonged grief disorder diagnosis

The introduction of the prolonged grief disorder diagnosis in the ICD-11 has contributed to a surge of interest in problematic grief reactions, resulting in greater understanding of these conditions. Importantly, it has clearly influenced the recent decision by the American Psychiatric Association to promote the research category "persistent complex bereavement disorder" from its status as a condition for further study to being a full-fledged disorder in the DSM-5 Text Revision (DSM-5-TR)[123]. The new DSM-5-TR category has adopted the ICD-11 name and has been placed in the chapter on Trauma and Stress-Related Disorders. Prolonged grief disorder in the DSM-5-TR is defined very similarly as in the ICD-11, with the exception that it requires 12 months to have elapsed since the loss as compared to 6 months in the ICD-11[124]. It is a huge advance for the global study of prolonged grief disorder that the two major classification systems of mental disorders used around the world are converging on the definition of this syndrome. This will promote much greater standardization in diagnosis, lead to better estimation of global prevalence rates, and facilitate better dissemination and implementation of evidence-based treatments.

One of the major aims of introducing the prolonged grief disorder diagnosis was to identify individuals who could benefit from available evidence-based treatments. There is now convergent evidence from multiple controlled trials that grief-focused psychotherapy is the treatment of choice, with most patients responding positively to this intervention[125-128]. There is also evidence that this treatment is more effective than other often-used psychotherapeutic interventions[125] as well as selective serotonin reuptake inhibitors (SSRIs)[129]. This conclusion is supported by recent meta-analysis of published prolonged grief disorder treat-

ment studies[130]. This accumulating evidence highlights that a more standardized approach to diagnosing prolonged grief disorder can be helpful in directing persons with this condition to the best available care.

GAMING DISORDER

Video-gaming has become one of the most popular and accessible leisure activities worldwide, based on which a global multi-billion-dollar industry has been built up. In recent years, the gaming landscape has evolved significantly, with the rise of e-sports (multiplayer video games played competitively for spectators) and streaming platforms fuelled by constant advancements in Internet-enabled portable and dedicated home gaming hardware.

For the vast majority of consumers of gaming products and services, recreational gaming can confer personal and social benefits[131,132], even with relatively high levels of engagement (e.g., daily use for several hours or longer). Research has shown that gaming is an activity that can fulfil basic psychological needs such as relatedness, autonomy and competence[133], especially for players able to successfully integrate their gaming activities with other important life domains[134-136].

In the context of the COVID-19 pandemic, some preliminary data suggest that involvement in gaming activities may have mental health and social compensatory benefits for those experiencing reduced face-to-face social contact due to social distancing or lockdown conditions[137,138].

The need for a gaming disorder diagnosis

Excessive video-gaming, characterized by loss of control over gaming behaviour, can lead to functional impairment and have negative consequences on physical health, social, educational and occupational domains[139-143]. Longitudinal studies have indicated that sustained problematic gaming behaviours are associated with psychopathological symptoms over time (e.g., anxiety and depressive symptoms) and predict decrements in functional outcomes (e.g., school performance)[144-146].

Problem gaming was recognized as a potential mental disorder by the American Psychiatric Association with its inclusion of "Internet gaming disorder" in the DSM-5 section on "Conditions for Further Study". With the approval of the ICD-11 in 2019, gaming disorder has been officially recognized as a mental disorder[14], included in the new grouping of Disorders Due to Addictive Behaviours, which also includes gambling disorder. The essential features of gaming disorder according to the ICD-11 CDDR are presented in Table 4.

There is mounting evidence of a relatively high prevalence of problem gaming in the general population. A recent meta-analysis based on 53 studies estimated that the worldwide prevalence of problematic gaming was approximately 1-2%[147]. The clinical research base was initially drawn predominantly from studies conducted in East Asian countries (specifically, South Korea, Japan and China) that were at the forefront of recognizing and responding to the phenomenon, but problem gaming has steadily become an internationally recognized public health issue. For example, specialized treatment services for the disorder have been developed in most American, European and Asian countries, suggesting that the condition is not primarily driven by specific cultural (e.g., collectivist as compared to individualist) or other region-specific factors.

Clinical studies describing treatment-seeking cases[148-152], including studies of large samples of patients (N>200)[148,150], have highlighted increasing referrals and associated service demands related to problem gaming. Studies examining problem gaming and co-occurring diagnoses have noted that the former can be a primary diagnosis[148,153,154], but in other cases may be a secondary clinical issue, for example, arising as a maladaptive coping strategy or compensatory mechanism[155]. Health care and counselling facilities worldwide have encountered growing demands for services related to problem gaming since the mid-2000s[156].

Prior diagnostic practice and implications for care

Prior to WHO's publication of diagnostic requirements for gaming disorder as part of the ICD-11 CDDR, individuals seeking treatment for problematic gaming behaviours were often diagnosed with alternative conditions (e.g., in the ICD-10, pathological gambling, another habit or impulse disorder, a mood disorder, an anxiety disorder). This heterogeneity in the assigned diagnosis affected the type of treatment provided and hindered

Table 4 Essential (required) features for gaming disorder in the ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR)

- A persistent pattern of gaming behaviour ('digital gaming' or 'video-gaming'), which may be predominantly online (i.e., over the internet or similar electronic networks) or offline, manifested by all of the following:
  - Impaired control over gaming behaviour (e.g., onset, frequency, intensity, duration, termination, context);
  - Increasing priority given to gaming behaviour to the extent that gaming takes precedence over other life interests and daily activities; and
  - Continuation or escalation of gaming behaviour despite negative consequences (e.g., family conflict due to gaming behaviour, poor scholastic performance, negative impact on health).
- The pattern of gaming behaviour may be continuous or episodic and recurrent but is manifested over an extended period of time (e.g., 12 months).
- The gaming behaviour is not better accounted for by another mental disorder (e.g., Manic Episode) and is not due to the effects of a substance or medication.
- The pattern of gaming behaviour results in significant distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning.

the collection of reliable data regarding individuals seeking treatment. The treatment offered to such individuals varied widely, depending on locally available mental health facilities, which often lacked relevant clinical expertise.

Outside the East Asian context, almost no national health care responses or other organized health service programs had developed in response to this need[139,156,157], even in pioneering countries that had highlighted gaming disorder in their national health or addiction strategic plans more than a decade ago[158,159]. Lack of recognition of gaming disorder as a diagnostic category in the ICD appeared to be a major obstacle to provision of specialized care for patients and their families[139,156,160].

Overall, including gaming disorder in the ICD-11 has been an important step towards providing more effective, safe and person-centered care in a timely, integrated and efficient way[161]. However, there remains some uncertainty among health professionals regarding how to respond to problem gaming. While some programs have been developed based on evidence-based treatments known to be effective for other mental health and addictive disorders, there remains a need for more methodologically robust treatment studies (e.g., large-scale randomized controlled trials with longer-term follow-up) focusing specifically on gaming disorder[162].

Furthermore, to inform the development of more effective and comprehensive policies, there is a need for improvements in systems for monitoring problem gaming and gaming disorder in the population (e.g., relevant information on prevalence; clinical profiles of individuals presenting with problem gaming; associated morbidity and mortality) as well as indicators of resource allocation, treatment coverage, treatment effectiveness, and health care quality[139,163].

Controversies related to including gaming disorder in the ICD-11

Debates and controversies related to the recognition of gaming disorder as a mental disorder have existed for decades, echoing similar debates in the field of gambling studies[164].

Criticisms of gaming disorder intensified following its inclusion in the public draft version of the ICD-11[165-167] and when the ICD-11 was officially adopted by the World Health Assembly. Critics have tended to put forward the following arguments: a) supporting evidence has mainly been the product of "confirmatory approaches"; b) recognition of the disorder might result in pathologizing non-problematic gaming; and c) the notion of problematic gaming has been driven by "moral panic" rather than by scientific evidence.

The criticism of the validity of gaming disorder due to the use of confirmatory approaches[165,167] contends that high rates of gaming were conceptualized *a priori* as an addictive disorder and this conceptualization was then confirmed when excessive gaming was observed, without considering alternative explanations[168,169]. A study employing a confirmatory approach would adapt existing addiction-based screening tools and substitute the term "gaming" for substance use, rather than developing new tools that may better reflect harmful or pathological gaming engagement[170]. The evidence base may be further compromised by lack of rigorous psychometric validation of scales and reliance on non-clinical convenience samples[171].

Another argument in opposition to gaming disorder has been the view that its diagnostic formulation, particularly the DSM-5 diagnostic criteria set intended for further study, may be poor at discriminating between normal (non-problematic) and harmful or pathological gaming behaviours[132,172,173]. The concepts of tolerance, preoccupation and withdrawal have attracted scrutiny for their imprecise operationalization when applied to gaming and other addictive behaviours. For example, the DSM-5 criteria for Internet gaming disorder operationalize tolerance as "the need to spend increasing amounts of time engaged in Internet games"; preoccupation as "the individual thinks about previous gaming activity or anticipates playing the next game; Internet gaming becomes the dominant activity in daily life"; and withdrawal as "symptoms such as irritability, anxiety, or sadness when Internet gaming is taken away"[15, p.795]. Some authors have reported that gamers who do not exhibit evidence of other psychopathology or functional impairment may endorse such items intended to parallel substance addiction[174-176], thus challenging their diagnostic utility[172].

In an attempt to address these issues, a recent international Delphi study[177] investigated the clinical validity, utility and prognostic value of the DSM-5 research criteria for Internet gaming disorder, as well as the proposed ICD-11 diagnostic requirements. Experts agreed that criteria such as tolerance, deception and mood regulation were less capable of distinguishing between problematic and non-problematic gaming and should not be used to diagnose gaming disorder. Furthermore, no consensus emerged among experts regarding the validity and clinical utility of the withdrawal or preoccupation criteria, suggesting that more research was needed before accepting them as diagnostic features of gaming disorder. On the other hand, this Delphi study supported the pivotal role of the core ICD-11 diagnostic requirements: loss of control (over gaming), persistence despite negative consequences, and functional impairment as a result of gaming. Participating experts agreed that the ICD-11 CDDR were likely to identify the condition adequately, and more likely to avoid pathologizing intensive but healthy gaming behaviours.

Some authors have further argued that support for the concept of gaming disorder may be based on "moral panic" rather than scientific evidence[165,178]. Moral panic refers to fear or anxiety that the well-being of a community or society is threatened by a particular group or by social or technological changes. These authors argue that fears related to Internet gaming are not dissimilar to past concerns about technological developments like radio and television[179].

The moral panic argument tends to advance the notion that a gaming disorder diagnosis will lead to undue concerns about the risks of gaming and will stigmatize individuals who play games, further perpetuating negative views toward gaming that predate

the scientific literature and the WHO's recognition of gaming disorder. However, the ICD-11 CDDR are clear in specifying a high threshold for classifying gaming disorder (including significant distress or functional impairment), and do not state that gaming has inherent risks or harms.

Review of the evidence

Research evidence has accumulated since WHO's proposal to include gaming disorder in the ICD-11 was made public (approximately in 2012). Epidemiological research on gaming disorder was already increasing, but has accelerated even more in recent years. This increase has been especially marked in Europe[180,182] and Asia[183,184]. The evidence base includes general population health surveys, large surveys of adolescents in schools, and targeted non-representative online surveys of adult gamers.

Systematic reviews of large-scale studies[185-188] have reported prevalence rates from 1 to 3%, with slightly higher prevalence rates of 4 to 5% for adolescents. Males are 2 to 4 times more likely to report problem gaming than females[188], and Asian countries have reported higher prevalence rates than Western countries.

Stevens et al's meta-analytic review[188] reported that the main variable affecting prevalence rates was the choice of the measurement tool for assessing problem gaming symptoms. The field has employed more than 30 different screening tools across more than 300 studies[171]. Screening approaches based on the DSM-5 research criteria for Internet gaming disorder may misclassify some highly engaged gamers as disordered[189], in line with experts' observations that some DSM-5 symptoms lack diagnostic utility[178]. Higher-quality studies (e.g., stringent sampling, cross-validation with quality of life and impairment measures) tend to report much lower prevalence rates[173], typically below 1%.

Longitudinal studies on the stability of gaming disorder are limited and have reported inconsistent data[187], including findings that less than 1%[190] or up to 26%[191] of adolescents with gaming disorder have symptoms that continue to meet diagnostic requirements at 2-year follow-up. There is a need for more robust epidemiological studies, including studies of the course of the disorder in higher-risk groups and clinical samples across different regions. Rigorous studies are needed to examine whether it is possible to predict which adolescent problem gamers are likely to experience problems into adulthood and to explore features associated with persistence (e.g., multiple types of gaming behaviours, substance use), as has been done for adolescent gambling[192].

Studies utilizing representative samples (e.g., recreational gamers, problematic gamers, treatment-seeking gamers) and/or strong research designs (experimental or longitudinal) have yielded important evidence regarding neurobiological and psychological factors involved in gaming disorder. At the neurobiological level, Yao et al[193] provided a systematic review and meta-analysis of case-control studies reporting functional and structural neural alterations in fronto-striatal and fronto-cingulate cerebral regions in problem gamers. A more recent longitudinal study of a large sample of problematic and non-problematic gamers found that problem gaming was characterized by greater dorsal striatal connectivity with the middle frontal gyrus, suggesting a ventral-to-dorsal striatal shift that aligns with other research on substance use and addictive disorders[194]. Further neurobiological similarities with addictive disorders include a stronger response to gaming on fMRI than to food (a primary reward) in problematic gamers but not in recreational gamers[195].

Numerous studies have investigated the cognitive correlates of problematic gaming (e.g., executive control, attentional bias, decision-making abilities)[196], typically involving neuropsychological testing in laboratory settings. There is robust neuropsychological evidence derived from multiple studies that problematic gaming patterns are associated with inhibitory control impairment[197], supporting the notion that loss of control over gaming is a key feature of gaming disorder. Finally, a number of studies conducted on treatment-seeking cases showed that gaming disorder is frequently associated with heightened impulsivity, affective instability, and dysfunctional personality traits as assessed using psychometric questionnaires[148,198,199].

Research on clinical interventions for gaming disorder has also accelerated during this period, particularly in countries that have developed specialized outpatient services for problem gaming[159,200]. East Asian countries – including South Korea, Japan and China – have been more proactive in developing wide-ranging public health interventions and treatment programs for gaming problems[148,201,202]. The clinical literature includes data on the experiences of hundreds of gaming disorder patients, including self-referred adult patients and families seeking help for an adolescent who may or may not be willing to attend treatment[159,162]. Moreover, some patient intake data from specialized mental health services are available, which highlight the public demand for these services.

The Kurihama Medical and Addiction Centre in Japan reported treating more than 200 patients with gaming disorder in 2019, which for many adolescent patients involved working with parents and other family members[157]. In the UK, the National Health Service (NHS)-funded specialist service for gaming disorder, positioned within the National Centre for Behavioural Addictions, received more than 50 patients between January and May in 2021[204]. Other studies have shown that individuals with gaming-related problems may also seek assistance from gambling treatment services[199], units that specialize in the treatment of behavioural addictions[151,154], broader treatment providers dealing with addictive disorders in general[204], or non-specialized services[200].

Studies that include the administration of diagnostic interview schedules to identify co-occurring conditions have reported that individuals diagnosed with gaming disorder experienced negative consequences in multiple life areas[199,205-210]. Many adolescent gaming disorder patients reported problems including reversal of day-night sleep-wake patterns, skipping meals due to gaming, physical violence toward others and hitting or breaking things when asked to stop or reduce gaming, poor school grades or work performance, and absence from school or work[201].

Ko et al[207] compared individuals formally diagnosed with gaming disorder with non-problematic gamers. They found that those with gaming disorder reported significant functional impairment across multiple domains, including academic and work performance, social functioning, and physical health (including problems related to sleep, pain, body weight, vision, and physical exercise). Psychological interventions designed to reduce gaming time and gaming disorder symptoms have demonstrated significant improvements in global measures of functional impairment[154,204].

At the same time, it must be acknowledged that, in the context of the dramatic increase in scientific publications on problem gaming, many low-quality studies have also been published. Weaker studies have relied extensively on self-selected samples that do not necessarily include regular and/or problematic gamers, have used unvalidated or psychometrically poor self-report assessment instruments, or have made causal inferences based on insufficient evidence[167,169,170]. This has fuelled criticisms about the robustness of the supporting evidence. Opponents of the disorder have selectively cited low-quality studies to advance their arguments that the totality of evidence in favour of gaming disorder is insufficient or invalid, usually via news media and social media.

Additional research is important to understand more completely the nature of gaming disorder, its pathological mechanisms, its commonalities with gambling disorder and disorders due to substance use, its long-term course and comorbidities, and its treatment. Nonetheless, there is clearly more than enough evidence to conclude that: a) individuals with gaming disorder are a legitimate clinical population for whom health services can be appropriately provided; b) it is of sufficient clinical and public health interest to WHO member states to collect and report health information about gaming disorder; and c) on this basis, the inclusion of this diagnostic category in the ICD-11 is justified. If necessary, the CDDR for gaming disorder can be modified in future updates of the ICD-11 in response to emerging evidence, but such evidence would be much less likely to become available if the category were not included in the ICD-11.

Implications of the gaming disorder diagnosis

The recognition of gaming disorder in the ICD-11, as well as its inclusion in the DSM-5 research appendix, has accelerated basic and applied research endeavours[211,212]. Research into problem gaming has advanced particularly in the areas of epidemiology, neurobiology and interventions, and has also stimulated scientific interest in problematic engagement in other online activities (e.g., social networking sites, Internet pornography use, and e-commerce)[213,214]. An advantage of the more streamlined ICD-11 conceptualization of gaming disorder as compared to DSM-5's has been its clarity regarding the scope and clinical description of the condition, eschewing some traditional addiction concepts that have been criticized or have received mixed support as applied to problem gaming[140,141,172]. The WHO has also supported several initiatives related to problem gaming, including the development of new screening and diagnostic tools, promotion of standardized decision-making tools, and support for health systems internationally[215].

Research on psychological interventions for gaming disorder is an area that has grown in conjunction with the recognition of the disorder[159,162]. These interventions, particularly cognitive-behavioural therapy (CBT), have been examined in more rigorous studies and thus far demonstrated strong short-term efficacy[147]. Recently, a randomized controlled trial evaluating the efficacy of a manualized CBT program for gaming disorder found that most patients (69%) who received the intervention showed remission compared with less than one-fourth (24%) of those in a wait-list control group[154]. Other approaches that have been tested in clinical trials include motivational interviewing and counseling, family therapy, and psychosocial rehabilitation[204,216].

Government support for research programs and public health responses to gaming disorder have varied greatly by region[217]. In East Asian countries, there have been long-standing coordinated governmental efforts to support research and public health initiatives[149,157]. In comparison, more limited funding for research and fewer public resources for treatment have been available across Western countries[218]. Examples of concrete developments following the release of the ICD-11 include the opening in the United Arab Emirates of the first outpatient clinic for the treatment of gaming disorder, and the establishment by the NHS in the UK of the National Centre for Behavioural Addictions, which provides treatment for gambling and gaming disorders. Across many countries worldwide, there remains a need for training programs for health care professionals on identifying and managing gaming disorder.

The global gaming industry has adopted a public stance in opposition to the inclusion of gaming disorder in the ICD-11[218,219]. The industry has also used its public platform and reach to endorse scholars who challenge the disorder and to direct public attention to research highlighting the benefits of gaming. To date, there has been very limited collaboration between the industry and public health stakeholders in relation to problem gaming, despite some calls from researchers for the industry to leverage its capabilities to assist in identifying and assisting vulnerable gamers. There have also been some proposals for the industry to consider more ethical game design standards and business practices[141], particularly in relation to games marketed to children[220] and monetized games (e.g., prohibiting "loot boxes" that enable in-game purchases of advantageous game features using virtual currencies or real-world money)[221].

COMPULSIVE SEXUAL BEHAVIOUR DISORDER

The need for a compulsive sexual behaviour disorder diagnosis

Compulsive sexual behaviour disorder is a new diagnostic category in the ICD-11, included in the grouping of Impulse Control

Table 5 Essential (required) features for compulsive sexual behaviour disorder in the ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR)

- A persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behaviour, manifested in one or more of the following:
  - Engaging in repetitive sexual behaviour has become 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 has made numerous unsuccessful efforts to control or significantly reduce repetitive sexual behaviour.
  - The individual continues to engage in repetitive sexual behaviour despite adverse consequences (e.g., marital conflict due to sexual behaviour, financial or legal consequences, negative impact on health).
  - The person continues to engage in repetitive sexual behaviour even when the individual derives little or no satisfaction from it.
- The pattern of failure to control intense, repetitive sexual impulses or urges and resulting repetitive sexual behaviour is manifested over an extended period of time (e.g., 6 months or more).
- The pattern of failure to control intense, repetitive sexual impulses or urges and resulting repetitive sexual behaviour is not better accounted for by another mental disorder (e.g., Manic Episode) or other medical condition and is not due to the effects of a substance or medication.
- The pattern of repetitive sexual behaviour results in marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. Distress that is entirely related to moral judgments and disapproval about sexual impulses, urges, or behaviours is not sufficient to meet this requirement.

Disorders. The essential features of this condition in the CDDR are presented in Table 5. The diagnostic category is intended to identify a clinical population of people who experience being unable to control their sexual impulses and for whom health services might reasonably be provided. The inclusion of the category in the classification is responsive to the needs of WHO member states to identify this population and to develop relevant clinical services and policies, including subsidized treatment provided by governments or via other insurance mechanisms.

Compulsive sexual behaviour disorder replaces the ICD-10 category of "excessive sexual drive", but is defined and operationalized quite differently. The ICD-10 CDDG for "excessive sexual drive" contain no specific diagnostic requirements and instead simply state that "both men and women may occasionally complain of excessive sexual drive as a problem in its own right, usually during late teenage or early adulthood"[5,p.152]. However, complaints of excessive desire alone do not identify a clinically relevant problem with public health significance[222]. The challenge in defining compulsive sexual behaviour disorder in the ICD-11 was to balance its ability to identify people in need of treatment against the risk of pathologizing variants of sexual desire and behaviour that are not inherently harmful or pathological[223,224].

Clearly, the ICD-10 description of "excessive sexual drive" would encompass a range of individuals whose sexual interests, desires and impulses are not pathological but who may experience them as excessive because they are unwanted or "morally incongruent"[225] (e.g., a woman who believes that she should not have sexual impulses at all; a religious young man who believes that he should never masturbate; persons who are distressed about their homosexual attraction or behaviour). The ICD-11 makes clear that distress related to the individual's (or others') moral judgements and disapproval related to sexual impulses, urges or behaviours that would otherwise not be considered indicative of psychopathology is not an appropriate basis for diagnosing compulsive sexual behaviour disorder. The "additional clinical features" section of the CDDR for the disorder also indicates that particular attention must be paid to the evaluation of individuals who self-identify as having the condition (e.g., calling themselves "sex addicts" or "porn addicts") in terms of whether they actually exhibit the clinical characteristics of the disorder[14].

History of the disorder

The existence of a clinical population of individuals who feel unable to control their sexual impulses and as a result engage in repetitive and problematic sexual behaviour, sometimes with very serious consequences, has long been recognized. Prior to the proposal to introduce compulsive sexual behaviour disorder in the ICD-11[223,226], there has been more than a quarter century of active research[227,228] on the symptomatology, comorbidities, etiology, and linkages to clinical outcomes (such as risk for sexually transmitted infections[229]) of a condition defined in relation to repetitive sexual behaviour, as well as on the related risks in the forensic context (especially for sexual reoffending[230]).

It is therefore not the case, as some have claimed, that this diagnostic category is simply a fashionable new label that has emerged in relation to the increased use of digital media for sexual purposes (e.g., use of Internet as a source of pornographic material or a means of finding casual or anonymous sex)[231]. However, there is no question that greatly increased opportunities to engage in sexual behaviour via the Internet without even having to leave one's home have changed the nature of these behaviours and greatly facilitated their frequent repetition[232], therefore possibly contributing to an increase in the prevalence of compulsive sexual behaviour disorder.

ICD-11 Working Groups agreed on the relevance of the clinical phenomenon, but it was less clear where to place the disorder within the classification, how to operationalize it, and how to name it[226]. The term "sexual addiction" in the US came mainly from the self-help group movement[233]. The term "sexual compulsivity" emerged in the field of human immunodeficiency virus (HIV) research, primarily from studies with samples of men

who had sex with men[234-236]. "Sexual impulsivity" was described as a symptom of borderline personality disorder[237], and "hypersexuality" had been used to describe a symptom associated with various other disorders, for example dementia[238] or Parkinson's disease[239].

A category called "hypersexual disorder" had been proposed for inclusion in the DSM-5[228]. This was conceptualized as being "characterized by an increased frequency and intensity of fantasies, urges, and enacted behaviors associated with an impulsivity component"[228, p.385]. The disorder was proposed for inclusion in the DSM-5 chapter on Sexual Dysfunctions because increased or disinhibited expressions of sexual arousal were considered to be its primary component, although some of its criteria had been modeled after those of substance dependence. There was substantial criticism of the proposal. The main arguments against it were that it represented a pathologization of normal variation (i.e., high sex drive), that there was insufficient evidence of its validity as a distinct clinical syndrome, and fears that the diagnosis could be misused in forensic settings by individuals seeking to evade responsibility for sexual misbehaviour[16,240]. In the end, hypersexual disorder was not included even in the DSM-5 section on "Conditions for Further Study", despite relatively successful application in a field trial[241].

Although there is clearly similarity between ICD-11 compulsive sexual behaviour disorder and hypersexual disorder as proposed for DSM-5, the ICD-11 entity is not conceptualized as a sexual desire disorder, and its diagnostic requirements do not focus on determining whether sexual interests and behaviour are excessive in their intensity, frequency, or time spent on them. Rather, the central feature of the ICD-11 diagnostic category is the persistent pattern of failure to control intense, repetitive sexual impulses or urges, resulting in repetitive sexual behaviour with a variety of negative consequences for the individual, including marked distress or significant functional impairment.

This conceptualization clearly aligns compulsive sexual behaviour disorder with impulse control disorders, although aspects of its description are similar to those of ICD-11 disorders due to addictive behaviours. The ICD-11 CDDR explicitly state that a diagnosis of compulsive sexual behaviour disorder should not be assigned to individuals with high levels of sexual interest and behaviour (e.g., due to a high sex drive) who do not exhibit impaired control over their sexual behaviour. The WHO explicitly decided not to classify the new diagnostic category in the grouping of Disorders Due to Addictive Behaviours (i.e., with gambling disorder and gaming disorder), because the evidence was not considered to be strong enough to support this model[223,226]. The WHO specifically declines to use the term "sex addiction".

Controversies related to the diagnosis of compulsive sexual behaviour disorder

Controversies about the nature of this phenomenon and its classification have existed since the 1990s, particularly in relation to the term "sex addiction" and the condition's etiology[227]. More than 20 years ago, Gold and Heffner[242] reviewed the available literature – comparing the competing conceptualizations as an addictive, obsessive-compulsive, or impulse control disorder – and subtitled the resulting article *Many Conceptions, Minimal Data*. These controversies were never definitively resolved, which contributed to a diversification of research in different areas independently of one another, with the result that studies based on different paradigms were often not directly comparable.

These controversies were also reflected in adversarial and sometimes *ad hominem* comments made on the ICD-11 platform about the inclusion of compulsive sexual behaviour disorder in response to the public draft version of the classification[13]. One focus of controversy revolved around whether certain patterns of sexual behaviour can reasonably be considered to represent an addiction[243,244]. A more extreme perspective reflected in some comments on the ICD-11 platform was that sex addiction is a false construct that has been promoted by profiteering providers of unvalidated services and is fundamentally based on sex-negative moral or religious judgments. The disagreement about the diagnostic construct and the lack of uniform diagnostic guidelines has fuelled discussions in the media and questions among the public regarding its legitimacy as a disorder[245], and has also hindered the development of evidence-based therapeutic approaches[227].

Nonetheless, a large number of people describe themselves as having difficulty controlling their sexual behaviour, even though it is not always clear what they mean. In a US nationally representative sample of adult Internet users, 1% of men and 3% of women reported some agreement with the statement "I am addicted to pornography"[246]. In another nationally representative US study, 10.3% of men and 7.0% of women endorsed clinically relevant levels of distress and/or impairment associated with difficulty controlling sexual feelings, urges and behaviours[247].

The WHO has attempted to sidestep many of the controversies in the area while acknowledging the existence of a clinical population of individuals who feel unable to control their own sexual behaviour and as a result experience substantial distress and sometimes quite severely negative functional outcomes. These presentations were considered to meet the basic definition of a mental disorder[223,226] and to be associated with substantial suffering for which health services might reasonably be provided. The CDDR point out that the relevant behaviours do not represent true compulsions (as defined in obsessive-compulsive disorder), but this term was adopted to describe the behaviour pattern because of the prevalence of its use in the scientific literature.

Review of the evidence

Prevalence data using the ICD-11 diagnostic requirements are not yet available at the general population level. Castro-Calvo et al[248] studied compulsive sexual behaviour disorder in two independent convenience samples in Spain, one comprising university students and the other community members who had volunteered to participate in a study about their sexual be-

haviour. The estimated prevalence of the disorder was 10.1% in the student sample and 7.8% in the community sample. Participants reporting symptoms meeting the requirements for the disorder were mostly heterosexual males, younger than the other respondents, and with higher levels of sexual sensation-seeking and interest in sex, increased offline and especially online sexual activity, more depressive and anxious symptoms, and poorer self-esteem.

Another study of US university students found that same-sex attraction was significantly correlated with compulsive sexual behaviour[249]. However, Gleason et al[250] reported that the prevalence of clinically significant compulsive sexual behaviour among gay men in the US (7.9%) was not higher than in the general population[247].

Across studies, endorsement of items related to compulsive sexual behaviour seems to be associated with male gender[247,248], younger age[246,250], religiousness[246,250], and moral incongruence (i.e., the experience of engaging in activities that violate one's moral values)[225]. In the absence of the other essential features, such subjective reports would not be sufficient for a diagnosis of compulsive sexual behaviour disorder in the ICD-11. In studies of men who have sex with men, self-reported compulsive sexual behaviour has been found to be correlated with depression[251], anxiety[252], and minority stress (i.e., the stress associated with stigma-related social disadvantage that compounds general life stress)[253], as well as to be associated with higher rates of sexual risk-taking behaviours[254,255].

A Swedish study reported a high need for health care specific to experiencing compulsive sexual behaviour[256]. During the first 7 years of its operation, 1,573 participants contacted a Swedish helpline specifically set up to provide counseling and treatment for high-risk sexual behaviours to men and women with self-identified out-of-control sexual behaviour and unwanted paraphilic arousal patterns. Compulsive sexual behaviour was reported by 69% of helpline users.

Clinical studies often investigate comorbidities between compulsive sexual behaviour disorder and other disorders. In one such study of a convenience sample of Spanish college students[257], more than 91.2% of participants with that ICD-11 diagnosis also had symptoms that met the diagnostic requirements for at least one other Axis I mental disorder during their lifetime, as assessed by the Structured Clinical Interview for DSM-IV-TR, compared to 66% of those without the diagnosis. Participants with compulsive sexual behaviour disorder were more likely to report disorders due to alcohol and other substances (mainly cannabis and cocaine), major depression, bulimia nervosa, and adjustment disorder.

In another study, 6.5% of treatment-seeking individuals with gambling disorder reported experiencing compulsive sexual behaviour[258]. The lifetime prevalence of ICD-11 compulsive sexual behaviour disorder was found to be 5.6% in patients with current obsessive-compulsive disorder[259]. Elevated rates of compulsive sexual behaviour have also been found among individuals with attention-deficit/hyperactivity disorder (ADHD)[260], bipolar disorder[261], borderline personality disorder[257,262], PTSD[263], paraphilias[264], and erectile dysfunction[264,265]. Many individuals with compulsive sexual behaviour also report a history of sexual abuse as a child[266], and the relationship between child sexual abuse and the behaviour appears to be stronger in men[267].

Neurobiological and neuropsychological evidence about compulsive sexual behaviour and compulsive sexual behaviour disorder has also been accumulating. Individuals who report compulsive sexual behaviour, as compared to individuals who do not, exhibit increased blood flow in the reward system of the brain in response to erotic cues[268-270], greater responsivity and attention to erotic cues[271-273], increased gray matter volume in the left amygdala[274], and decreased right caudate nucleus volume[275]. Men with compulsive sexual behaviour disorder, relative to controls without the disorder, also show increased anticipatory response to cues predictive of erotic rewards in the ventral striatum and anterior orbitofrontal cortex[276]. Current findings suggest that compulsive sexual behaviour disorder shares similar brain region abnormalities with both obsessive-compulsive disorder and substance addiction, although further work is needed to elucidate the underlying brain mechanisms[277].

One group of researchers has studied the pathophysiological mechanisms in men who report problems with compulsive sexual behaviour. They found that MIR4456 (an mRNA gene) had lower expression in males reporting vs. those not reporting the behaviour, and posited that this gene may play an important role in the oxytocin signaling pathway related to the expression of the behaviour[278]. They also found subtle deregulation of the hypothalamic-pituitary-gonadal axis, with increased luteinizing hormone plasma levels, but not differences in testosterone levels, between men reporting vs. those not reporting issues with compulsive sexual behaviour[279].

In terms of treatment of the disorder, there have been several relevant advances since earlier reviews on the topic[280,281]. Randomized controlled trials have been conducted using a 7-week CBT group intervention[282] as well as Internet-administered CBT[283], both of which showed significant reductions in symptoms as compared to waitlist control groups. Individuals treated with acceptance and commitment therapy reduced their Internet pornography use as compared to a waitlist control[284], as did participants in a CBT-based self-help intervention[285]. Other studies have shown beneficial effects on compulsive sexual behaviour of a 12-step self-help group[286], a mindfulness-based intervention[287], an intervention to reduce sexual risk behaviour in HIV-positive men[288], and an intervention designed to reduce minority stress[253].

With regard to pharmacological treatment, a small study with no control group found a reduction in compulsive sexual behaviour in response to 25-50 mg of naltrexone for four weeks[289]. No clear longer-term beneficial effects were seen in response to the SSRI paroxetine in a case series[290], consistent with the results of an earlier study[291]. Single case studies have been published on successful use of transcranial magnetic stimulation[292,293].

In spite of uncertainties about compulsive sexual behaviour disorder, its course, and its relationship to other disorders, there is ample evidence of the existence of a clinical population of in-

dividuals who experience themselves as unable to control their repetitive sexual behaviour, in whom the behaviour pattern is manifest over an extended period of time and is associated with significant functional impairment or marked distress that is not solely related to moral judgments and disapproval.

Compulsive sexual behaviour disorder is associated with significant suffering and may have a substantial negative impact on the health and lives of the individuals it affects. It is therefore a legitimate focus of health services and is of interest to WHO member states in their efforts to provide or facilitate subsidized health services to their populations and for the collection and reporting of health information. It is expected that the expansion of research on the disorder will continue given its status as a WHO official diagnostic entity, with its own set of diagnostic requirements for use in identifying clinical and research populations. Researchers who had previously been connected to the DSM-5 proposal for hypersexual disorder have acknowledged that the inclusion of compulsive sexual behaviour disorder in the ICD-11 will have a significant impact on clinical research and practice and have suggested possible refinements to the ICD-11 CDDR that can be tested in future research[294].

Implications of the compulsive sexual behaviour disorder diagnosis

Since the inclusion of compulsive sexual behaviour disorder in the ICD-11 was proposed, there has been a major expansion of research in this area[227]. A good deal of the early research was based on a conceptualization of "sex addiction"[242], that later began to shift to a discussion of compulsive sexual behaviour, that does not entirely map to ICD-11 compulsive sexual behaviour disorder[291,258-297], or simply "problematic sexual behaviours"[298] or "problematic pornography use"[299]. A good deal of the research in the past several years has focused on "hypersexuality"[e.g., 301,302], although this has only occasionally been operationalized as hypersexual disorder as it had been proposed for DSM-5. So, there continue to be issues with comparability across studies.

The lack of theoretical integration in the literature has also produced discrepancies in the measurement of compulsive sexual behaviour disorder[227]. The most commonly used measures include the Sexual Compulsivity Scale[234], the Sexual Addiction Screening Test-Revised[303], the Hypersexual Behavior Inventory[304], and the Compulsive Sexual Behavior Inventory[235]. Despite their popularity, there has been little methodologically rigorous research to confirm the validity and reliability of these measures in clinical populations[305].

Based on the draft ICD-11 diagnostic requirements for compulsive sexual behaviour disorder, an international group of researchers developed the Compulsive Sexual Behavior Disorder-19 (CSBD-19) scale to assess the extent of repetitive sexual urges, thoughts and behaviours and their consequences during the previous six months[306]. The scale yielded a five-factor structure (i.e., control, salience, relapse, dissatisfaction, and general and domain-specific negative consequences), and its psychometric properties were robust across the three countries involved in the initial study (Germany, Hungary and the US). In 2021, an expanded consortium of researchers launched the International Sex Survey, a large-scale multi-language study involving over 40 countries. Upon its completion, the project will make the CSBD-19 publicly available in over 30 languages for research and clinical practice[307].

Resources to equip clinicians to assess and treat ICD-11 compulsive sexual behaviour disorder have also begun to appear[231,245]. An expert group is being formed by the International Society for Sexual Medicine to launch position papers and develop guidelines on this topic. It is noteworthy that the American Psychiatric Association was the first to publish a clinical and treatment-oriented book on compulsive sexual behaviour disorder[308], despite its own decisions regarding hypersexuality in the DSM-5.

In summary, the decision by the WHO to include compulsive sexual behaviour disorder in the ICD-11 has broken the stasis due to questions about how to best conceptualize the condition. The ICD-11 CDDR very carefully address concerns about false positives and the stigmatization of non-pathological sexual behaviour. The inclusion of the disorder in the ICD-11 has facilitated the provision of appropriate services and the development and testing of empirically-supported treatments. Our understanding of the etiology, diagnostic classification, assessment, and treatment of the disorder will continue to evolve as we gain new insights from future research efforts. We anticipate that remaining controversies will be resolved over the next few years as scholarship on the disorder and related clinical experience continues to grow exponentially.

DISCUSSION

The rationale for the inclusion of each of the four disorders discussed in this paper illustrates the principles for adding new disorders in the ICD-11 that we described in the introduction: a) to allow collection of morbidity statistics by WHO member states on health conditions with public health significance; b) to facilitate identification of clinically important but poorly classified mental disorders so that appropriate management can be provided; and c) to stimulate research into effective treatments for the conditions. The ICD-11 now provides a consistent rubric and definitions for tracking and reporting of these conditions at the health system, national and global level. Having specific diagnostic requirements rather than using vague "other specified" or "unspecified" residual categories to capture the relevant phenomena obviously facilitates the identification of these conditions. Introducing these disorders into the ICD-11 appears to have been followed by a significant increase in the availability of appropriate services for each condition and an uptick in research to evaluate available interventions.

The research literature on these disorders has expanded substantially since it was publicly announced that the WHO was planning to add them to the ICD-11. A significant increase of interest in these categories was already underway, but their in-

clusion in the ICD-11 has facilitated additional research by providing investigators with standardized definitions and diagnostic requirements, which can be used as a basis for developing appropriate measures, as well as building up a more compelling case for research funding from member state governments and other agencies.

As highlighted earlier in this paper, the decisions made by the WHO to add these categories are different from those taken by the American Psychiatric Association for the DSM-5. In the case of complex PTSD, the DSM-5 Workgroup decided to broaden the PTSD criteria to include elements of DESNOS, the earlier version of complex PTSD that had been tested for DSM-IV, rather than adding a new diagnostic category. This has had the effect of substantially expanding the complexity of the PTSD diagnosis in the DSM-5[309]. A variety of studies in different populations have since demonstrated the validity of the ICD-11 approach[31,32]. Nonetheless, as the ICD-11 is adopted in clinical systems, it will be important to examine whether the DSM-5 PTSD and the ICD-11 PTSD plus complex PTSD identify different groups and whether the implementation of the ICD-11 leads to difficulties for some individuals in accessing services. This is a concern that some have expressed[310], although available data suggest that the DSM-5 criteria identify fewer cases than either the ICD-11 or the DSM-IV[311].

In contrast to the situation with complex PTSD, versions of prolonged grief disorder and gaming disorder had been included in the DSM-5 research appendix under slightly different names. Placement in this appendix suggests that there was substantial interest in the categories as candidate entries in the DSM-5, but also an overall conclusion that the proposed criteria sets had not been sufficiently validated to include these disorders in the main classification. In the past, several DSM research categories have eventually been moved to the main classification, but this does not occur invariably. The ICD has no equivalent to a research appendix; a category is either included or not. In a few cases the entity in question may be added as an index term for an "other specified" residual category to indicate the recommended ICD-11 category for classifying it, but there is no provision for including research definitions that can be tested. At the same time, the WHO has to consider the needs of the member states that form its governance. For national governments, the regular occurrence of a condition in clinical systems that appears to demand some specific treatment response is a valid reason for its inclusion in the classification.

The description of "persistent complex bereavement disorder" in the DSM-5 research appendix in part represented an attempt to reconcile two somewhat divergent models in the field[312]. Based on additional work conducted during the intervening period, the entity has been included in the main classification for the DSM-5-TR, the ICD-11 name has been adopted, and the criteria have been altered to be more similar to the ICD-11 CDDR[124]. Internet gaming disorder as described in the DSM-5 research appendix attempts to model more closely diagnostic criteria for substance use disorders, whereas the essential features of ICD-11 gaming disorder are more streamlined and more strongly emphasize loss of control over gaming behaviour. Still, they are both clearly attempting to describe the same group of people. The complete absence of a hypersexual disorder in DSM-5 (as opposed to its being placed in the research appendix or listed as an example of a sexual disorder not otherwise specified, as it was in prior editions of the DSM) was ostensibly based on concerns that there was insufficient evidence that this disorder represented a distinct clinical syndrome and that it could be misused in forensic settings, although Workgroup members opined that these concerns had been addressed[240]. The ICD-11 Working Groups attempted to avoid some of the pitfalls encountered by the proposal for hypersexual disorder, notably by describing it as a disorder of impulse control that is expressed in sexual behaviour rather than as a sexual disorder. The evidence being generated will be helpful to decisions about these categories in a future edition of the DSM.

Looking at the other entries in Table 1, eleven of the 21 disorders listed were either already in the DSM-IV or were also added to the DSM-5. These changes in the ICD-11, therefore, had the effect of enhancing compatibility between the two classifications. The ICD-11 has included a few additional syndromes caused by substances or medications or by diseases classified elsewhere that are not found in the DSM-5[17]. This leaves only three discrepant new ICD-11 categories other than those reviewed in this paper. Olfactory reference syndrome is mentioned in the DSM-5 as an example of other specified obsessive-compulsive and related disorders. Body integrity dysphoria (an intense and persistent desire to become physically disabled in a significant way, e.g., major limb amputee, paraplegic, blind) is a very rare though quite distinctive and serious condition for which a large body of evidence with specific methodologies may never be generated if that continues to be a requirement for its inclusion in the DSM. Partial dissociative identity disorder is very similar to what is described in the DSM-5 as "chronic and recurrent syndromes of mixed dissociative symptoms", included as an example of other specified dissociative disorders. These categories seem unlikely to generate the same level of interest and controversy as those reviewed in this paper.

CONCLUSIONS

The four disorders introduced in the ICD-11 that are discussed in this paper – complex PTSD, prolonged grief disorder, gaming disorder, and compulsive sexual behaviour disorder – describe populations with clinically important and distinctive features that have previously gone unrecognized in the ICD classification of mental disorders. These populations also have specific treatment needs that would otherwise be likely to go unmet if these disorders did not have a place in the classification. Overall, the impact of adding these disorders appears to have been positive in terms of health information and reporting, identifying patients in need of service, and the development and testing of interventions. Clearly, there are remaining research needs and specific targeted studies should be undertaken related to each of the four

disorders, as reviewed in this paper. However, the WHO's decision to include these categories appears to balance effectively the status of the available evidence with the information needs of WHO member states and the need of individuals with these conditions to receive appropriate care.

We do not see evidence so far of the hypothesized harms of adding these conditions to the diagnostic system (e.g., harmful stigmatization of non-pathological gaming or sexual behaviour). However, it is possible that some drawbacks may become more apparent over time as the ICD-11 is implemented around the world. Regular updates are planned for the ICD-11 (every 2 years), and it is anticipated that a greater number of changes will be made early on based on the experience of actually using the classification. This will provide an important mechanism for making refinements or clarifications to these categories, should they appear to be necessary.

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From inter-brain connectivity to inter-personal psychiatry

When it comes to symptom emergence and treatment of disorders, psychiatry and neuroscience do not always find common ground. On the one hand, neuroscientific research approaches mental disorders through their biological correlates using brain recordings; on the other, clinical psychiatry relies on self-report measures collected during face-to-face interviews. Taking into account both neural and experiential dimensions thus appears as one of the key challenges to the integration between neuroscience and psychiatry.

One aspect in which neuroscience and psychiatry do see eye to eye is in their restricted account of interpersonal dynamics. In psychiatry, the focus is primarily put on the mental state examination of the patient, although most mental disorders severely affect and are affected by social dynamics. Similarly, in neuroscience, the "social brain" has been paradoxically studied in isolated contexts, inferring that mere passive social perception and active social interaction are encoded in the same way at the brain level. Yet, research has widely shown that the development of children's social abilities requires subtle social interactions with their parents, involving an active and reciprocal co-regulation of the exchanges. Recent advancements in social neuroscience suggest that the relationship between brains and social dynamics might offer a unique opportunity for the neuroscience-psychiatry integration while acknowledging the inherent socialness of mental disorders.

In 2002, a groundbreaking functional magnetic resonance imaging (fMRI) study introduced a technique called hyperscanning[1], where the authors simultaneously scanned the brains of several participants while they were interacting through an economic game. This study paved the way for the design of realistic experimental protocols capable of capturing the crucial features of sociality, i.e. dynamicity and reciprocity, to investigate the neural mechanisms supporting social cognition and behavior.

The idea quickly spread to other brain recording techniques, such as electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS), which are cheaper and more flexible for social tasks requiring direct face-to-face interaction. This led to the discovery of specific neural circuits that support social interaction and that differ from those enabling the sole perception of social stimuli. For instance, both mirror and mentalizing networks are simultaneously engaged, with a subtle modulation of shared representations and the maintenance of a distinction between self and other.

Beyond this better understanding at the intra-brain level, the development of hyperscanning has also inspired several teams of researchers to look at the inter-brain level, i.e. between-participants brain activity. The underlying hypothesis was that communication of information across brains might follow the same principles that govern communication of information inside brains. Thus, it was expected to find coherent activity between one region and another, but extended to two or more individuals. This novel inter-personal and dynamic perspective on social cognition was strongly associated with the development of 4E cognition, arguing that the mind is not solely in the head, but is also embodied, embedded, enacted, and extended.

Thanks to hyperscanning recordings, a new type of neural correlate was identified: inter-brain connectivity (IBC)[2]. This can be defined as the synchronized brain activity of two or more people involved in a social scenario that can be attributed to their interaction rather than a shared external environment. All common neuroimaging techniques can be used to reveal IBC, from fMRI and fNIRS, which allow measuring amplitude correlation (i.e., when the brains activate regions at the same time), to EEG and magnetoencephalography, that provide sufficient temporal resolution to observe phase synchronization (i.e., when the brains present coherent oscillatory activity in time).

In the last two decades, the observation of IBC has grown from a few isolated studies to a whole new field now covering non-verbal and verbal exchanges, in dyadic and group contexts, with interaction between mother-infants, romantic couples, friends, but also complete strangers. Those experiments have identified many correlates of IBC, from behavioral synchronization and imitation of movement to language familiarity, empathic connection, and even human attachment. This massive growth has recently allowed the first meta-analyses and triggered the development of standardized IBC tools, consolidating both scientific progress and replicability in the nascent multi-brain neuroscience research.

But, how can psychiatry use this new form of multi-brain measurements? What can IBC bring to the understanding of psychiatric conditions, and how can it ultimately help in the daily practice of clinicians?

First, IBC can provide a neural correlate for core clinical features of mental disorders. For instance, the alteration of interactive social cognition may be more specific than that of perceptual social cognition[3]. In autism spectrum disorder, as an example, patients rarely mention misunderstanding of complex social plots in movies; they rather complain about their difficulties with improvising in real-time social interaction during daily life. Hyperscanning recordings can thus help in further exploring the mechanisms and manifestations of psychiatric conditions with a strong social dimension[4].

Second, IBC can provide an objective measurement of the empathic connection or other social phenomena that are fundamental to the psychotherapeutic process but remain hard to capture at the biological level. For instance, hyperscanning studies have started to uncover the biological correlates of complex inter-personal phenomena such as the analgesic effect of affective touch[5] or the therapeutic alliance[6]. In both cases, the alignment at affective and cognitive levels is reflected in the alignment at the neurobehavioral level.

So, IBC promises to better capture the underlying biological factors impacting psychiatric manifestations and treatment, with-

out necessarily reducing them to only intra-personal processes.

Beyond these recent developments, we can also wonder what are the next steps for multi-brain neuroscience, and especially what potential avenues it can open for psychiatric research and clinical practice.

First, while early work was done in humans, the recent increased interest in IBC comes from multiple papers published with animal models[7]. Not only have these studies replicated the early observation of inter-brain correlates in humans, but they have also uncovered for the first time cellular mechanisms. This move from mesoscopic to microscopic levels opens possibilities to decipher which biological mechanisms can be targeted pharmacologically to potentially enhance IBC and with them neurobehavioral inter-personal dynamics.

Second, another recent trend is the move from multi-brain recording to multi-brain stimulations. The burgeoning field of hyper-stimulation[8] may thus represent the next technological step to go from inter-brain correlational measurement to direct causal manipulation. Preliminary results already demonstrate that induction of inter-brain synchronization of neural processes shapes social interaction within groups of mice, and facilitates motor coordination in humans. If multi-brain electromagnetic stimulation provides insights about the causal factors modulating IBC and eventually sheds light onto biological mechanisms, a long-term challenge will be to move even beyond the traditional "correlation vs. causation" debate and provide an integrative explanation of the IBC phenomenon[9]. Ultimately, inter-personal neuromodulation through pharmacological compounds, electromagnetic stimulations, and even both, could open the way to new forms of therapeutics in psychiatry.

We have seen how the nascent multi-brain neuroscience may lead to transformative applications in psychiatry, from inter-brain measures for clinical characterization to inter-brain neuromodulation for treatments. Interestingly, this inter-personal psychiatry will also help take seriously our biological grounding as much as our social embedding.

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Continuous outcome measurement in modern data-informed psychotherapies

Continuous outcome measurement in psychotherapies has become a central research topic only in the last two decades[1]. Here we provide a short introduction to the relevant concepts and discuss the opportunities and challenges of their implementation in clinical practice.

Most continuous outcome measurement systems comprise short self-report questionnaires which assess patient progress on a session-by-session basis. Feeding this psychometric information back to therapists enables them to evaluate whether their current approach is successful or adaptations are necessary. In order to help therapists judge whether a particular patient is improving or at risk for ultimate treatment failure, many routine outcome monitoring (ROM) systems include feedback and empirically-based decision rules.

Decision rules are generated based on datasets from clinical practice settings[1]. Based on such large archival datasets, expected recovery curves can be estimated and used to build thresholds indicating which scores are reflective of an increased risk for treatment failure. Having identified a patient as at risk, some ROM/feedback systems provide therapists with additional clinical support tools[2]. These support tools have incorporated process measures designed to assess specific change factors within and outside treatment that impact outcome.

Originally, these tools comprised two elements to help therapists adapt treatments specifically for patients at risk for treatment failure: a) an additional assessment of potential problem areas (e.g., suicidal ideation, motivation) to elucidate the patient's individual risk profile, and b) a decision tree directing therapists to specific interventions depending on the identified risk profile. New developments have built on these ideas and included multimedia instruction materials and machine learning prediction models in order to help therapists provide the specific interventions that are most promising for a particular patient[3].

Over 40 randomized clinical trials (RCTs) and several meta-analyses provide a compelling evidence base for ROM and feedback. Feedback-informed treatments have been shown to result in improved outcomes, reduced dropout, and higher efficiency than standard evidence-based treatments[2,4]. The most recent and comprehensive meta-analysis reported a significant effect size advantage of d=0.15 for progress feedback compared to treatment as usual[4]. This effect was slightly higher for the subgroup of patients showing an initial treatment non-response (d=0.17).

When evaluating the size of these effects, it is important to keep two issues in mind. First, these effects come on top of the effects of effective evidence-based treatments. Second, feedback is a minimal low-cost technological intervention that does not put much of a burden on either patients or therapists. Accordingly, the largest RCT to date (N=2,233) demonstrated the cost-effec-

tiveness of adding ROM and feedback to evidence-based psychotherapies within the UK Improving Access to Psychological Therapies (IAPT) system. While feedback was associated with a non-significant increase of costs per case (£15.17), it helped a significant amount of 8.01% more patients to be reliably improved at the end of the treatment[5]. A further enhancement of feedback effects has been repeatedly documented for additional clinical support tools[2,4].

However, not all therapists show improved outcomes when using psychometric feedback. The main reason for this seems to be the different extent to which therapists make use of the information provided by feedback systems. This usage determines the extent to which feedback is advantageous[3,4].

As a result of the above research, the use of progress feedback and empirical-based decision rules is now considered an important clinical competence and a significant component of training. As such, current challenges and research questions in this field mainly deal with the implementation of feedback systems in order to further increase uptake by mental health professionals.

The recent debate about the development and implementation of "personalized" or "precision" mental health care has also influenced research on measurement-based and data-informed psychotherapies[6,7]. This development includes data-informed recommendations and decision rules for treatment selection derived from statistical and/or machine learning algorithms[7]. These approaches aim to predict the optimal treatment package, module or strategy given a patient's characteristics.

Data-informed treatment selection and routine outcome monitoring have recently been combined in comprehensive decision support systems, which form the basis of modern data-informed therapies (DITs). Such DITs include (intensive) assessments before and during treatment, allowing the immediate application of empirical findings to clinical practice and enabling clinicians to develop individualized diagnoses, case conceptualizations, and treatment options, especially for patients at risk for treatment failure. The strength of such data-rich research has also been shown in other areas of public health, such as new treatment options for Parkinson's disease or patient-tailored tumor therapies.

An example of such a system is the Trier Treatment Navigator (TTN), which empirically supports clinical decisions that need to be made at the beginning of psychotherapy as well as during ongoing treatment. At the beginning of treatment, an algorithm is used to generate patient-specific treatment strategy and dropout risk predictions. Having decided on an initial treatment plan, the TTN further supports therapists with ongoing personalized feedback on their patients' progress over the course of treatment. In order to enable therapists to evaluate these changes, a dynamic threshold indicates whether these changes are as expected or whether they indicate an increased risk for treatment failure. If the patient's scores exceed the threshold, the TTN alerts the therapist and provides additional information on potential risk areas that might be impeding improvement. On the basis of this risk assessment, the therapist is supported with multimedia learning tools suggesting alternative clinical interventions (e.g., via video or text material).

A recently published study evaluated both components of this comprehensive navigation system in a sample of 538 patients[8]. Each patient-therapist dyad was randomized to either the therapist having access to the TTN (intervention group; N=335) or not (treatment as usual; N=203). Analyses revealed that patients who received their prospectively predicted optimal strategy had greater early improvements (d=0.3). The analyses regarding the personalized feedback during treatment showed that therapist variables significantly predicted or moderated the effects of the system. For example, therapists' symptom awareness and attitude towards and confidence using feedback had an impact on treatment outcome[8].

Thus, the technical implementation of DITs does not seem sufficient. Rather, quality standards for implementation as well as the scientific training of therapists are necessary, and these factors require further study. Furthermore, new methodological and technological advancements might further improve DITs (e.g., more intensive measures several times a day or digital phenotyping of stress markers).

In summary, DITs have the potential to broaden our understanding of clinical concepts and improve clinical practice. The integration of modern technologies in continuous outcome monitoring has become more sophisticated and builds a bridge to precision mental health care[9]. We think it is time to abandon the seemingly perpetual cycle of developing and testing new treatment packages for the average patient, which are seldom more effective than available treatment options. Instead, we encourage progress monitoring in daily practice and an increased focus on patients at risk for treatment failure.

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Reasons why people may refuse COVID-19 vaccination (and what can be done about it)

The Vaccination Act of 1853, which mandated smallpox vaccination for infants in England, prompted the emergence of the Anti-Vaccination League, widespread street protests, and the appearance of several anti-vaccination journals. Various criticisms were levelled: that vaccines were unsafe; that vaccinations were "unchristian"; that the mandate was a violation of personal liberties. Conspiracy theories and misinformation abounded.

When we reflect on vaccine hesitancy in the COVID-19 era, it is worth remembering that these sentiments are not new. What is relatively new is the systematic empirical exploration of the psychological mechanisms underpinning vaccine refusal: examination of Web of Science data suggests that 35% of the papers ever written on the psychology of vaccines were published since 2020. Also new are concerns that vaccine refusal presents a mental health challenge. Since the emergence of the pandemic and associated debates about mandating vaccination, there has been concern that vaccine hesitant people are being caught in a self-reinforcing cycle of mistrust, stigma, isolation, and psychological distress. Parallel to this, emerging data show that those with pre-existing mental disorders are disproportionately likely to die from COVID-19[1]. In this context, mental health professionals are asking: why would people refuse COVID-19 vaccination, and what can be done about it? Here I explore three factors implicated in vaccine refusal – flawed risk appraisal, conspiracy theorizing, and ideology – and reflect on their implications for informing communication strategies.

A curious aspect of the human mind is that we struggle to rationally appraise risk. Arguments such as "you have a one in a million chance of developing lethal blood clots if you take this vaccine" or "the risks of vaccinating are far lower than the risks of not vaccinating" require us to think analytically and dispassionately about risk. But our evolutionary history did not prepare us for a world of science, statistics and base rates. Rather, our minds are designed to appraise risk as a function of vivid events and narratives, processed emotionally[2]. Base rate statistics have surprisingly little impact in the face of dramatic "case rate" stories of otherwise healthy people whose lives have been ruined or lost because of adverse reactions to vaccines. These images and narratives are a stock strategy of the anti-vaccination movement, but also a common feature of mainstream news coverage of COVID-19 vaccines. In this context, it would be human nature to experience anxiety at the thought of taking COVID-19 vaccination, particularly among those of us who are predisposed to intuitive or experiential cognitive styles.

Overlaid on this basic tendency, it is possible that clinical or subclinical issues can complicate people's ability to objectively appraise risk. It has been speculated that certain mental health conditions – for example, blood-injection-injury phobia – might predispose people to feeling instinctive aversion to vaccinations[3]. Related to this, a large-scale survey found that participants' levels of disgust or repugnance at the sight of anaesthetic needles or blood was predictive of vaccine hesitancy across 25 nations, much more so than their levels of education[4].

Attempts to reassure the population that vaccines are safe are further complicated when people dispute the validity of scientific messaging. For some, scientists, governments and drug developers are part of a cabal of vested interests who exaggerate evidence that vaccines are helpful and cover up evidence that vaccines can be harmful. One of the most powerful predictors of vaccine hesitancy is the conspiracist worldview: the notion that it is commonplace for groups of elites to conduct elaborate hoaxes on the public in near-perfect secrecy. Particularly in the West, a surprisingly large amount of variance in vaccine hesitancy can be accounted for by merely knowing whether people think that Princess Diana was murdered, or that 9/11 was an inside job[4]. When people have this worldview, messages that would normally be persuasive – for example, government assurances of safety and scientific consensus around effectiveness – can be inverted to be *proof* of a conspiracy. Unable to trust official messaging, these people may place implicit faith in messengers that mirror their distrust, such as elements of the wellness industry and some populist politicians[5].

It should be noted that there may be some sensible foundation to the mistrust, although in this case it is over-generalized to embrace objectively implausible conspiracy theories. It is common sense to argue that we should be vigilant to signs that vested issues have a corrupting influence on health care (the thick layers of independent regulation around vaccine development are testament to the fact that the health system shares that concern). It is also worthwhile remembering that there are traumatic historical examples of medical racism, that are circulated widely within certain communities while they debate the safety of vaccines. For members of society who feel protected by the system, it is easier to communicate that the system can be trusted than for people who feel marginalized by the system, which may be a reason why in some countries culturally and linguistically diverse communities have been the slowest to vaccinate against COVID-19[6].

Finally, there is a convergence of evidence that ideological factors have shaped people's willingness to embrace COVID-19 vaccines. For people who are committed to small government, economic progress, and individual freedoms (as are many conservatives), the regulatory response to a pandemic can be perceived as ideologically noxious. Faced with an aversive solution to the pandemic, conservatives may be motivated to instead question the COVID-19 science. In some countries such as the US, this ideological divide is one of the most recognizable phenomena of the COVID-19 era: although there are small pockets of vaccination resistance among the far left, conservatives report less intention to vaccinate than liberals overall[7]. Having been drawn into the algorithm that defines one's political persuasion, the decision to vaccinate has become not just a reflection of what people believe, but also a way of signalling to others one's political and ideological identities.

Understanding the factors discussed above helps make sense of what, for many scientists and health professionals, is one of the most exasperating and difficult-to-understand features of the vaccination debate: facts are not enough. Merely repeating evidence has been a notoriously ineffective way of shifting attitudes among those who self-identify as anti-vaccination[8]. One reason for this is that people do not always behave like cognitive scientists, weighing up evidence before reaching a conclusion. Frequently, we behave more like cognitive lawyers, selectively exposing ourselves, critiquing, and remembering evidence that reinforces a conclusion that feels "right" for us. Successful communication requires deep listening and an attentiveness to the fears, worldviews and ideologies that might be motivating COVID-19 refusal[9]. Persuasion attempts that are responsive to these underlying "attitude roots" are more likely to be successful than those that sail above them with an exclusive focus on facts and data[3].

Finally, mental health professionals recognize as much as anyone the importance of communication that is non-stigmatizing and inclusive. Although the public face of the anti-vaccination movement sometimes seems strident and unworthy of empathy, community members who align with those views are frequently characterized by anxiety and uncertainty. There is the potential for negative feedback loops, where the vaccine hesitant feel misunderstood and stigmatized, reinforcing their worldview that the system is corrupted and lacking in humanity. Feeling socially isolated, vaccine refusers may be driven toward the online communities and misinformation echo chambers that reinforce their fears. Respectful and inclusive communication is not just the "nice" thing to do; on a pragmatic level, it is a pre-requisite for enabling positive change.

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DSM-5-TR: overview of what's new and what's changed

The DSM-5 Text Revision (DSM-5-TR)[1] is the first published revision of DSM-5 since its original publication in 2013. Like the previous text revision (DSM-IV-TR), the main goal of DSM-5-TR is to comprehensively update the descriptive text that is provided for each DSM disorder based on reviews of the literature since the release of the prior version. However, in contrast to DSM-IV-TR, in which updates were confined almost exclusively to the text[2], there are a number of significant changes and improvements in DSM-5-TR that are of interest to practicing clinicians and researchers. These changes include the addition of diagnostic entities, and modifications and updated terminology in diagnostic criteria and specifier definitions.

The updates to the diagnostic criteria and text in DSM-5-TR are the product of two separate but concurrent processes: the iterative revision process that allows the addition or deletion of disorders and specifiers as well as changes in diagnostic criteria to be made on an ongoing basis[3], which commenced soon after the publication of DSM-5, and a complementary text revision process which began in 2019.

While most of the changes instituted since publication of DSM-5 and included in this text revision involve relatively minor changes and serve to correct errors, clarify ambiguities, or resolve inconsistencies between the diagnostic criteria and text, some are significant enough to have an impact on clinical practice[4]. Here we outline the main changes in DSM-5-TR, subdivided into four categories: addition of diagnostic entities and symptom codes; changes in diagnostic criteria or specifier definitions; updated terminology; and comprehensive text updates.

Diagnostic entities added to DSM-5-TR include Prolonged Grief Disorder, Unspecified Mood Disorder, and Stimulant-Induced Mild Neurocognitive Disorder.

Prolonged Grief Disorder is characterized by the continued presence, for at least 12 months after the death of a loved one, of intense yearning for the deceased and/or persistent preoccupation with thoughts of the deceased, along with other grief-related symptoms such as emotional numbness, intense emotional pain and avoidance of reminders that the person is deceased, that are sufficiently severe to cause impairment in functioning[5,6].

Unspecified Mood Disorder is a residual category for presentations of mood symptoms which do not meet the full criteria for any of the disorders in either the bipolar or the depressive disorders diagnostic classes, and for which it is difficult to choose between Unspecified Bipolar and Related Disorder and Unspecified Depressive Disorder (e.g., acute agitation).

Stimulant-Induced Mild Neurocognitive Disorder has been added to the existing types of substance-induced mild neurocognitive disorders (alcohol, inhalants, and sedative, hypnotics or anxiolytic substances), in recognition of the fact that neurocognitive symptoms, such as difficulties with learning and memory and executive function, can be associated with stimulant use[7].

Free-standing symptom codes have been added to the chapter Other Conditions that May Be a Focus of Clinical Attention, to indicate the presence (or history of) suicidal behavior ("potentially self-injurious behavior with at least some intent to die")

and nonsuicidal self-injury ("intentional self-inflicted damage to the body likely to induce bleeding, bruising, or pain in the absence of suicidal intent")[1]. These codes will allow the clinician to record these clinically important behaviors independent of any particular psychiatric diagnosis.

Changes in diagnostic criteria or specifier definitions have been implemented for more than 70 disorders. While most of these changes are relatively minor, a number are more significant, and address identified problems that could lead to misdiagnosis. Diagnostic criteria sets or specifier definitions with more significant changes include those to criterion A for Autism Spectrum Disorder; changes in severity specifiers for Manic Episode; addition of course specifiers to Adjustment Disorder; and changes to criterion A for Delirium.

Autism Spectrum Disorder is defined by persistent difficulties in the social use of verbal and nonverbal communication (criterion A) along with restricted repetitive patterns of behavior (criterion B). While the minimum threshold for the restricted repetitive behavior component was straightforward (at least two of four), the minimum required number of types of deficits in social communication was ambiguous. Specifically, the criterion A phrase "as manifested by the following" could be interpreted to mean "*any* of the following" (one of three) or "*all* of the following" (three of three). Since the intention of the DSM-5 Work Group was always to maintain a high diagnostic threshold by requiring all three, criterion A was revised to be clearer: "as manifested by all of the following".

The "mild" severity specifier for Manic Episode (few, if any, symptoms in excess of required threshold; distressing but manageable symptoms, and the symptoms *result in minor impairment* in social or occupational functioning) was inconsistent with Manic Episode criterion C, which requires that the mood disturbance be sufficiently severe to cause marked impairment in social or occupational functioning, necessitate hospitalization, or include psychotic features. The severity specifiers from DSM-IV have now been adopted: "mild" if only minimum symptom criteria are met; "moderate" if there is a very significant increase in activity or impairment in judgment, and "severe" if almost continual supervision is required.

Specifiers indicating the duration of symptoms in Adjustment Disorder were inadvertently left out of DSM-5 and have now been reinstated: "acute" if symptoms have persisted for less than 6 months, and "persistent" if symptoms have persisted for 6 months or longer after the termination of the stressor or its consequences.

The essential cognitive features in Delirium are disturbances of attention and awareness of the environment. While the nature of the attentional disturbance – characterized in criterion A as a reduced ability to direct, focus, sustain, and shift attention – is clear, the characterization of the awareness component as "reduced orientation to the environment" is confusing, given that "disorientation" already appears as one of the "additional disturbances in cognition" listed in criterion C. Consequently, criterion A has been reformulated to avoid using "orientation", so that it now reads "A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) accompanied by reduced awareness of the environment".

DSM-5 terminology has been updated to conform to current preferred usage, and includes replacing "neuroleptic medications", which emphasize side effects, with "antipsychotic medications or other dopamine receptor blocking agents"; replacing "intellectual disability" with "intellectual developmental disorder"; and changing "conversion disorder" to "functional neurological syndrome". Reflecting the evolving terminology in the area of gender dysphoria, "desired gender" is replaced with "experienced gender"; "natal male/natal female" with "individual assigned male at birth" or "individual assigned female at birth"; and "cross-sex treatment regimen" with "gender-affirming treatment regimen".

The updates to the text were the result of a three-year process involving over 200 experts, most of whom had participated in the development of DSM-5. There were 20 Review Groups to cover the Section II chapters, each headed by a Section Editor. Experts were asked to review the text to identify material that was out-of-date. This was supplemented by literature reviews that covered the period of the prior 10 years.

Three cross-cutting Review Groups (Sex and Gender, Culture, Suicide) reviewed every chapter, focusing on material involving their specific expertise. Revisions to the text also underwent a forensic review. Finally, an Ethnoracial Equity and Inclusion Work Group reviewed the entire text to ensure among other things that explanations of ethno-racial and cultural differences in symptomatic presentations and prevalence took into consideration the impact of experiences such as racism and discrimination.

Most disorder texts had at least some revisions, with the overwhelming majority having significant revisions. Text sections most extensively updated were Prevalence, Risk and Prognostic Factors, Culture-Related Diagnostic Features, Sex- and Gender-Related Diagnostic Features, Association with Suicidal Thoughts and Behaviors, and Comorbidity. The text sections with the fewest updates were Diagnostic Features and Differential Diagnosis.

The American Psychiatric Association continues to welcome empirically-grounded proposals for change. Guidelines for submitting such proposals can be found at www.dsm5.org.

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Acute psychiatric care: approaches to increasing the range of services and improving access and quality of care

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Acute services for mental health crises are very important to service users and their supporters, and consume a substantial share of mental health resources in many countries. However, acute care is often unpopular and sometimes coercive, and the evidence on which models are best for patient experience and outcomes remains surprisingly limited, in part reflecting challenges in conducting studies with people in crisis. Evidence on best approaches to initial assessment and immediate management is particularly lacking, but some innovative models involving extended assessment, brief interventions, and diversifying settings and strategies for providing support are potentially helpful. Acute wards continue to be central in the intensive treatment phase following a crisis, but new approaches need to be developed, evaluated and implemented to reducing coercion, addressing trauma, diversifying treatments and the inpatient workforce, and making decision-making and care collaborative. Intensive home treatment services, acute day units, and community crisis services have supporting evidence in diverting some service users from hospital admission: a greater understanding of how best to implement them in a wide range of contexts and what works best for which service users would be valuable. Approaches to crisis management in the voluntary sector are more flexible and informal: such services have potential to complement and provide valuable learning for statutory sector services, especially for groups who tend to be underserved or disengaged. Such approaches often involve staff with personal experience of mental health crises, who have important potential roles in improving quality of acute care across sectors. Large gaps exist in many low- and middle-income countries, fuelled by poor access to quality mental health care. Responses need to build on a foundation of existing community responses and contextually relevant evidence. The necessity of moving outside formal systems in low-resource settings may lead to wider learning from locally embedded strategies.

Key words: Acute care, mental health crises, inpatient psychiatric wards, emergency departments, crisis houses, acute day units, crisis resolution and home treatment teams, intensive home treatment

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Acute mental health care, including acute inpatient wards and services that manage mental health crises in emergency departments and in the community, consumes a large proportion of the resources dedicated to mental health in many countries[1]. However, it continues to be often unpopular, is sometimes experienced as traumatic or coercive, and shows little evidence of resulting in sustained improvements in outcomes.

Nonetheless, ready access to crisis response remains of high importance in the eyes of many service users, carers, clinicians and referrers to mental health services. Thus, innovations that result in better experiences and outcomes and more efficient use of resources have high potential for overall impact. In this paper, we take stock of current service models and their evidence base and identify innovations with promise for the future.

We begin by considering initial response to the acute crisis, including assessment, triage and initial care planning. We then discuss the settings in which intensive intervention to resolve the crisis is delivered. Finally, we offer some cross-cutting perspectives on crisis care delivery, focusing on contributions from the voluntary sector; the role of service users and peer workers in designing, leading and delivering crisis services; remote delivery of crisis care; and crisis prevention.

Regarding geographical scope, it is not feasible to take a truly worldwide perspective on acute mental health care. However, while the majority of the authors of this paper are based in the UK, and thus tend to draw especially on examples from the National Health Service (NHS) of that country, we also include authors from several other countries, and conclude with a section that focuses on low- and middle-income countries (LMICs) where specialized forms of crisis service are not present.

We focus primarily on services for adults of working age rather than on specialized models for children and adolescents or older adults. Distinct crisis services for these latter groups are relatively uncommon in most countries, and the extent to which the services we discuss in this paper also serve them varies greatly.

Service design and development should be rooted in evidence, and we would have preferred to focus primarily on interventions and service models for which evidence is robust. However, practical and ethical challenges in recruiting participants who are experiencing a mental health crisis have hampered research in this field[2], so that the evidence base is far from proportionate to the importance of acute mental health care. We therefore include not only approaches and models that are root-

ed in evidence of reasonable quality, but also others that appear of sufficient potential value for robust evaluation to be needed.

ASSESSMENT AND IMMEDIATE MANAGEMENT OF THE CRISIS

Mental health presentations in the emergency department of the general hospital

For many people experiencing an acute mental health problem, attending the emergency department (ED) of a local general hospital is the default option in a crisis[3], and in some mental health systems primary care referrals may be directed to this setting. Despite efforts to develop alternatives, mental health presentations to the ED have been reported to be on the rise across the US[4], Australia[5] and England[6]. Attendances are reported to have risen again following a dip during the early phases of the COVID-19 pandemic[7,8].

A review of evidence from seven countries[9] found that the most common mental health presentations to EDs are self-harm, suicide attempt, suicide ideation, depression and schizophrenia, with mental health crises making up around 4% of all ED presentations.

Despite these high levels of use, EDs are often reported to be poor environments for mental health care. They tend to be hectic and may expose service users to long waiting times and distressing sights and sounds. Assessments take place in a very different and more institutional environment from service users' usual social context, and ED assessment has been reported to be more likely to result in hospital admission than when similar crises are assessed elsewhere[10].

ED staff may not have the training required for working effectively and empathically with people in mental health crisis[11]. Negative attitudes towards people with mental health presentations have frequently been reported[12], especially towards those who present on multiple occasions following self-harm and who may have a "personality disorder" diagnosis[13].

The quality and volume of research investigating the effectiveness of different approaches to improving mental health assessment and treatment at EDs does not match what is needed. Challenges include the highly diverse nature of tasks undertaken in EDs, and more widely in general hospitals where a liaison psychiatry model is employed; lack of high-quality routine data; difficulties with linking general hospital and mental health provider data sources; and difficulty selecting appropriate outcome measures to reflect brief contacts[14].

An international systematic review of models for mental health care in EDs found just 17 relevant studies, relating only to Australia, Canada, UK and US[15]. Mental health staff may be integrated into the ED team, supporting it with patient assessment and triage. A psychiatric liaison service may work across the ED and the general hospital as a whole. Agreements of various forms may be established between the ED and a psychiatric service within the same hospital, so that the latter can provide input to ED patients on referral. Finally, as discussed further below, mental health EDs may be located away from the general hospital. A variety of benefits have been reported for these models, mostly related to service use measures such as waiting times, restraints, or unplanned departures from the ED department. Most studies do not include clinical or patient-reported outcomes.

Whichever model is employed, a challenge in the ED is ensuring that, within the brief period of a crisis assessment, a warm and supportive therapeutic relationship is rapidly established, to avoid traumatic and coercive experiences of care and create a context for collaborative decision-making about next steps[16,17]. More research focused on clinical communication, therapeutic relationship, and approaches to assessment in mental health crises in the ED would be valuable.

Models offering extended assessment and diversion following ED attendance

An international data synthesis found that studies varied greatly regarding proportion of ED attenders admitted to hospital[9]. Efforts to reduce this and to improve the quality of initial assessment following an ED attendance have resulted in service models that extend the period of mental health assessment in an environment intended to be more calming and conducive to good quality mental health care than the ED.

A range of such approaches has been developed and described internationally. Psychiatric emergency services (PES; for which other names include comprehensive psychiatric emergency program, CPEP; and emergency psychiatric assessment, treatment and healing, EmPATH) are widespread in the US, where emergency psychiatry is a distinct subspecialty, and in Canada. They are linked to one or more EDs[18] and staffed by multidisciplinary psychiatric teams, including mental health nurses and psychiatrists (available on-call if not on-site), usually providing 24-hour access.

Unlike the standard ED approach of triage and transfer, PES have extra capability to observe and provide intensive treatment, typically for a period of up to 24 hours, aiming to stabilize the crisis within this time and reduce the need for admission. Routine data on the impact of a PES serving a large area of California and linked to several EDs indicated that it substantially reduced both ED waiting times and admission rates[19].

Similar models are reported in other countries. For example, in Australia, a behavioural assessment unit with six beds within an ED in Melbourne was designed to provide a calming environment, mental health assessment and observation, aiming to discharge home within 24 hours. A before-after comparison indicated reductions in ED delays and restrictive interventions[20].

Psychiatric decision units have been established in a small number of centres in the UK[21] and are accessed via psychiatric liaison teams in the ED. They offer a stay of between 12 and 72 hours, providing recliner chairs rather than beds (subject to some criticism[22]) and aiming to ensure a calming environment, psychosocial assessment, brief interventions, and onward referrals. In general, although there are promising reports of impacts on service use, substantial evaluations of extended assessment and triage services following ED attendance are so far lacking, and impacts on

patient experience need to be better understood.

A further model that may be linked to the ED is the brief admission ward where, rather than a full-scale hospital admission, initial admission is to a ward in which intensive assessment and treatment planning takes place within a strict time limit, characteristically a few days. Several early trials of this model suggested rather modest benefits[23], although they were conducted in contexts where intensive crisis alternatives were generally unavailable. A more recent UK version of this model did not find an impact on length of stay[24], and we are not aware of substantial recent evaluations of triage or short stay wards linked to EDs or of a recent comprehensive literature synthesis.

Assessment centres outside the general hospital

Crisis assessment services may also be situated away from the general hospital in freestanding centres, within community mental health service premises, or co-located with specialist psychiatric hospitals. Evidence is lacking regarding which locations are best and for whom. Notwithstanding the ED disadvantages discussed above, links between acute mental and physical health care are important (for example, following self-harm, and for people with both physical and mental health problems, or who present with functional somatic and neurological symptoms).

Thus, even in mental health systems where referrals from primary care and self-presentations are directed elsewhere, as in many European countries, mental health care is still needed in EDs. Integrating this with general hospital and mental health care systems effectively, and achieving continuity of care between acute and continuing care services, is a complex task presenting different challenges in each national system[25].

In the 1960s and 1970s, community mental health assessment centres, often called emergency clinics, were an important innovation in some countries, including the US and UK. These services provided walk-in assessment, triage and sometimes brief treatment, often informed by the crisis intervention theory[26], which regards a crisis not as a manifestation of mental health problems but as a general human response to severe psychosocial stressors, presenting challenges but also opportunities for growth. Similar models later emerged especially in the Netherlands, Italy[27], and German-speaking countries, although investigation of their activities suggested that they tended not to focus on people with severe mental health problems[28,29].

Today, there are numerous international examples of mental health crisis assessment centres, some of which employ conventional models of clinical assessment and intervention not dissimilar to ED services, while others are more innovative in offering alternative models. The PES discussed above may be located away from general hospital premises, even though they retain close links with EDs. Such services may also be established to prevent people in crisis being referred directly for assessment to psychiatric wards, which has been observed to be associated with high rates of admission. In Switzerland, for example, establishing a unit for clinical decision-making to assess referrals rather than referring directly to wards was reported to have reduced unnecessary admissions and costs[30].

Overcrowding in EDs and infection control considerations during the COVID-19 pandemic have resulted in some countries in further development of crisis assessment centres outside hospital. For example, a survey in England found that mental health providers in 80% of areas had established an alternative to their local EDs for mental health assessments, most often on a site where other mental health services were delivered[31]. Psychiatrists reported that these often provided a better environment than EDs for mental health care, but had very limited capacity for providing physical health interventions. Concerns were raised that removing mental health professionals from EDs may increase stigma among acute hospital staff and negatively affect care for the many people with both physical and mental health problems. An Italian service system has been described[32] in which the community mental health centre, already used as a setting for some crisis assessment, shifted its focus towards greater crisis care provision during the pandemic.

Crisis centres in the community may also aim to provide a more clearly distinct alternative to standard clinical approaches. For example, a model that has emerged in England over the past decade is the "crisis café", sometimes referred to as "safe havens" or "sanctuaries"[33]. These services provide walk-in assessment, support and triage for people experiencing a mental health crisis. They are designed to provide a less formal and clinical environment, and are usually delivered by the voluntary sector with staff who do not have formal mental health professional qualifications, although they often have considerable relevant experience. Some are also staffed by peer support workers and a few are led by people with lived experience of mental health problems (e.g., the Well-bean Crisis Café in Leeds, England). They are usually open outside typical working hours (evenings and weekends), when other forms of support may not be available, and are located separately from any other health service.

Crisis cafés provide a source of immediate support. People in crisis can usually access them without a referral, which may prevent a crisis escalating to a point where ED attendance or admission results. The potential of these services to improve access and choice is clear, but research evaluating their effectiveness and safety is still lacking.

Community crisis assessment

High anxiety, enervating depression or cognitive disorganization may all prevent some people in mental health crisis from actively seeking and accessing help. Perceived stigma of mental health services, or previous experience of unsatisfactory treatment following help-seeking or of an unsympathetic response at hospital EDs[34], may also create barriers.

Assessment at home may be more feasible and less frightening or distressing for many. It enables evaluation of someone's living situation, current coping, and potential risks in the home. It can help clinicians to consider social precipitants of a crisis, which may otherwise be overlooked[35]. Home-based assessment may engage the

family from an early stage, helping clinicians to understand and manage a crisis[36]. For these reasons, home-based crisis assessment services have been developed as part of the community psychiatry movement, with "psychiatric first aid" multidisciplinary teams in the Netherlands in the 1930s[37,38] being an early example.

Community teams providing longer-term care may be well placed to respond to crises for people on their caseload, allowing assessment by clinicians who already know the person in crisis. Indeed, providing a 24-hour crisis response is a fidelity criterion for high-intensity assertive community treatment (ACT) teams[39]. Flexible, stepped care models have been developed internationally and can offer a prompt crisis response to new referrals, as well as longer-term care of varying intensity, to meet people's current needs. Two examples (for both of which a robust evidence base has yet to be established) are the German RECOVER programme[40] and the FACT (flexible ACT) model developed in the Netherlands[41]. However, most community mental health services are not 24-hour, or resourced or organized to respond rapidly to needs for crisis assessment across a whole community, including people not previously known to services.

Dedicated crisis resolution and home treatment teams (CRHTTs) have therefore been developed, with the sole function of providing assessment and short-term, multi-disciplinary home treatment for people during a mental health crisis. Pioneered in the US[42] and Australia[43], CRHTTs are now provided nationally in England and Norway, and in many areas across Europe, North America and Australasia[44]. Established fidelity criteria for CRHTTs include standards for ease of referral, rapid response time, a 24/7 service, assertive engagement and comprehensive initial assessment[45].

Two key challenges for community crisis assessment relate to providing a rapid response, and managing safety and risks.

Regarding rapid response, in-person assessment within four hours from referral has been adopted as a nationally audited performance indicator in England. Yet, a 2016 survey of CRHTTs in England found that target response times varied from one hour to one week, with less than half of teams routinely providing a response within four hours. Less than a third of Norwegian CRHTTs achieve good fidelity for the rapid response criterion[46]. CRHTT staff highlight the competing pressures of responding rapidly to new referrals while reliably maintaining frequent, scheduled home treatment appointments with people being offered crisis support[47].

To address this issue, a recent trend in England has been to split crisis assessment and brief crisis home treatment functions into two different teams. This split model is now provided in over a third of English health care regions[33]. Crisis assessment teams, sometimes called "first response" teams, have achieved marked improvements in service accessibility and response times in local evaluations[48], and offer a "no wrong door" point of access for people in mental health crisis of any severity. However, they risk introducing new discontinuities between assessment and treatment, with opportunities for information to be lost or people in crisis being required to tell their story multiple times to different professionals. As yet, no robust evidence compares effectiveness or users' experience of integrated CRHTTs versus split assessment and treatment teams.

Regarding safety and risk, crisis assessment at home is not suitable when someone requires urgent medical tests or treatment (for example, following an overdose or other self-harm). Escalating risks to the person in crisis or others may be harder to manage by lone clinicians in an unfamiliar home environment than in a clinical setting. A Cochrane review cautions that people with the highest risks or using drugs and alcohol were typically excluded from studies that have provided positive evaluations of CRHTTs[49].

Thorough information gathering and careful triage are therefore essential before home-based assessment is offered. 24-hour crisis phone lines staffed by trained clinicians, with links to other local or national health service helplines, may help to achieve this, and improve the accessibility of crisis support[33]. Effective system integration with police and ambulance services is required for circumstances where the need for immediate access to hospital or clinic-based care becomes apparent during a home assessment, and help from emergency services is necessary to ensure safe conveyance of the person. This is further discussed in the next section of this paper.

Practical measures to help ensure the safety of staff, such as a lone working policy with check-in and follow-up processes, alarms for staff, and team capacity to visit in pairs when indicated, are also recommended[44]. Challenges are compounded in remote areas, and the role of telepsychiatry in crises is discussed further below.

Initiatives to facilitate prompt assessment following police contact

A 2016 literature review estimated that, for around one in ten individuals, the police were involved in their pathway to mental health care[50], although, while the author searched for all English language studies, only studies from North America were found. In a Canadian city, around half of mental health-related police contacts resulted in apprehension using mental health legislation, and half of these led to a hospital admission[51]. Concerns have been reported around the world that police officers, without adequate training or support, are often acting as frontline mental health workers, potentially resulting in worse outcomes for people in mental health crisis, increased trauma and coercion, and higher numbers of unnecessary arrests[52] and escorts to hospital[53].

Various service models have been developed to improve outcomes for people in mental health crisis following contact with the police. They usually consist of police and mental health staff responding to mental health-related emergency calls together. Some successes have been reported in reducing unnecessary use of mental health legislation. For example, in Toronto, Canada, a model involving additional training and a joint response by mental health nurses and police officers was found to result in lower rates of involuntary escorts to hospital and of arrest and injury, although total numbers of escorts to hospital increased[54].

In the UK, around 70% of NHS providers now have a street triage service involving various models of joint response by police and mental health professionals, ranging from telephone liaison to (in a

few cases) 24-hour joint response[47,55]. A systematic review of co-response models found studies carried out in Australia, Canada, UK, and US[56]. There were indications that these services reduced the use of police powers to detain people under mental health legislation, and of police custody.

Feedback from both police officers and health staff working in street triage teams or similar models is generally positive[55,57], but there has been a lack of research investigating service user experiences and outcomes[56]. The research that does exist suggests that service users value responders with expertise in mental health and skills in de-escalation[54].

There are many challenges in delivering joined-up responses across different organizations with very different roles, and models which may lead to greater police involvement in management of mental health crises may prove unacceptable or have unintended negative consequences. For example, the Serenity Integrated Mentoring model (SIM), deployed in England by around half of NHS Trusts, is designed to be a concerted approach by mental health care services and the police to better supporting people who frequently use emergency services. Reports that it resulted in inappropriate diversion from health services and in approaches mainly based on enforcing boundaries have led to the #StopSIM coalition of service users campaigning against the model's deployment, supported by allies across the mental health sector [58-60], following which policy makers have required Trusts urgently to review its further use. Much of the debate has focused on the ethics of police involvement and on its lack of underpinning evidence base, exemplifying the risks of rolling out models that are not supported by robust evidence.

INTENSIVE TREATMENT FOLLOWING CRISIS

Management of crises in hospital

Despite their ubiquity in mental health care systems, there has been surprisingly little definition or discussion of the role, function and design of acute inpatient mental health wards. Bowers et al[61] provide a conceptual model of inpatient treatment. The primary admission tasks for inpatient care may include any or all of: assessment, treatment of acute illness, providing safe and highly tolerant accommodation, rehabilitation, and the resolution of personal stress.

Inpatient wards are uniquely able to enforce treatment, provide constant observation to contain risks, and tolerate behaviour which would be unmanageable or unacceptable in the community. Inpatient admission also offers respite from and space to address stressors in the person's home environment, and the potential, through 24-hour care, for providing high levels of interpersonal contact and therapeutic engagement[61].

Thus, there is clearly a role for inpatient wards in managing and supporting those who are most acutely unwell at times when community services are unable to offer a safe alternative. Nonetheless, in the context of the narrative of deinstitutionalization, acute inpatient wards tend to be seen as an expensive legacy of a past institutionalized system of care, with admission reflecting a failure of care, rather than as unique and specialist clinical services playing an important role within a balanced mental health system[62].

Internationally, bed provision is inevitably influenced by the national and regional configuration of mental health care systems[63]. In general, across Europe, there are mental health care systems with predominantly community-oriented approaches, such as those in the UK, Italy and Spain; areas with a high availability of community, residential and hospital services (mainly in Scandinavian countries); and areas where the deinstitutionalization process is still incomplete and inpatient services are the main source of care, such as in rural France, or where it is still in its very early stages, as in several Eastern European countries[64].

A recent study involving 22 high-income countries in Europe, North America and Australasia found wide variation in the extent of inpatient provision: the mean number of beds per 100,000 population was 64, with an interquartile range of 46-93[65]. Throughout Europe and elsewhere, psychiatric inpatient bed numbers have tended to decrease in recent decades, and this trend has been marked in some countries: for instance, bed numbers fell by 62% in England between 1988 and 2008[66].

Much literature on inpatient care focuses on negative patient experiences and risks. Potential iatrogenic harms include institutionalization, exacerbation of psychotic symptoms from intense social contact with others, injury or victimization from other patients, loneliness due to separation from their home environment and social network, despair and depression arising from the environment and seeing other very unwell patients, and stigmatization[61]. Women are vulnerable to sexual harassment or assault, especially in mixed-gender inpatient wards[67].

Evidence suggests that acute inpatient mental health wards are often unsafe, with high levels of intra- and international variation in levels of conflict and containment [68,69]. During inpatient care, patients may experience high levels of restrictive practices (physical and mechanical restraint, forced medication); discrimination based on ethnicity, gender or diagnosis; crime (physical or sexual assault, criminal activity, drug taking); and blanket restrictions and rules. In England, the most frequently occurring incidents in this setting involve aggression and self-harm[70].

Safety incidents are often associated with high physical, emotional and financial costs. The physical and psychological harm to the patient, which may increase length of stay as well as having a negative impact on health-related quality of life[71], is often underestimated even in those services which aspire to operate trauma-informed models, in which an aim is to avoid retraumatizing the many patients who have previously experienced significant trauma[72]. In some cases, injuries to staff may also occur, leading to costs of replacement and impacts on burnout, stress and morale[73]. The financial cost of restraint, seclusion, rapid tranquilization, and one-to-one nursing have not been examined in any depth. One incident on a ward may increase the likelihood of further incidents via a disturbed ward milieu and social contagion[74].

Negative service user and carer experiences of involuntary detention are frequently reported and are of particular concern, given the contrast between such detentions and the principles of collaboration and consent usually advocated as central underpinning values for mental health treatment[75,76].

Rates of involuntary detention in psychiatric hospitals under mental health legislation have risen in some high-income countries and fallen in others in recent decades[65]. Explanations of why this is occurring remain confused. A complex combination of societal, service-related and legal factors is probably implicated[65]. Evidence regarding the relationship of bed numbers and availability to detention rates is mixed and inconclusive[77]; however, in countries where the drive to cut inpatient beds has been strong, there are widespread concerns and perceptions that lack of bed availability has resulted in higher thresholds for admission to hospital, a greater likelihood that those who are admitted will be involuntarily detained, a higher concentration on wards of people who are very acutely unwell and whose needs are complex, and a disturbed ward milieu. These factors combine to create high risks of iatrogenic harm. Detention also tends to establish a pattern of increased risk of future detentions[78].

Inpatient admission offers rapid access to needed medication, intensive monitoring and assessment to inform medication review, and enforcement of treatment if required – all of which may be problematic in community care[61]. However, prescribing practices are reported in many settings as relying too heavily on high-dose medications, polypharmacy and supplementary as-required doses[79], and there is a dearth of evidence on effective non-pharmacological approaches to managing acute illness and violent behaviour[80]. A literature on cognitive-behavioural interventions for psychosis adapted to inpatient settings is beginning to develop and provides examples of feasible approaches for people with complex needs, but does not yet offer conclusive evidence to underpin a large scale transformation[81]. Moreover, there is a striking lack of good quality evidence to underpin inpatient care for people with a "personality disorder" diagnosis.

Recent years have seen the development of interventions designed specifically to reduce conflict and use of restrictive practices in inpatient wards. A recent systematic review[82] identified two programmes with trial evidence of effectiveness, *Safewards*[83] and *Six Core Strategies*[84], both of which now commonly inform practice[85]. These are multi-component team-level interventions, which target avoiding or mitigating potential flashpoint situations resulting from interactions between patients, staff-patient interactions, or the ward regulatory or physical environment. The need to improve therapeutic engagement and the culture of care on wards more generally has also been emphasized[86].

An umbrella review of interventions to reduce coercion in mental health services concluded that there is supporting evidence for staff training interventions[87]. However, evidence for initiatives which have tried to improve the therapeutic quality of wards, such as scheduling protected time for ward staff to engage with patients, has tended to be inconclusive. Boredom is identified as a common problem for patients on inpatient wards, but further empirical evidence is needed about its impacts and the best ways to address it[88].

Another area where practice varies internationally and where evidence to support best solutions is lacking is the location of wards. In some countries, embedding acute wards in general hospitals is seen as advantageous, offering close links with physical health care services, normalization of mental health and accessibility to local communities[89]. However, potential drawbacks include wards that have not been specifically designed for mental health patients, and lack of access to safe open space.

There is a need for better understanding of how to design healing environments that offer private space, light, access to fresh air, and attention to details relevant to recovery (e.g., making the environments autism-friendly)[90]. The identification and international dissemination of examples of good practice would be very valuable, as the nature and probably the quality of ward environments varies greatly between countries. Other questions that have yet to be fully addressed include the value of specialized wards based on diagnosis or other indicators of need, and separation by gender[91].

Staffing is a further area in which there is scope for innovation to improve care. The staffing of wards remains a nurse's domain, largely providing the 24/7 care for inpatients. The approach to staffing is often constrained by budgets and custom rather than evidence, and we lack high quality research regarding safe staffing levels or optimal skill mix on inpatient wards. Clinical decision-making still tends to be dominated in most settings by psychiatrists, often via a traditional ward round model. More extensive involvement of other multidisciplinary team members such as psychologists and occupational therapists has great potential to enrich both decision-making and therapeutic environments and activities, though limited size of the specialist health professional workforce may constrain this[92]. The opportunity to further enrich the skill mix by enabling the roles of peer support workers, mental health advocates, housing officers and social workers could help heal disconnections from the community and address those key issues which precipitate and prolong admissions, such as social isolation, poverty and poor housing.

The future of acute inpatient provision requires serious attention. Services can improve, and listening to the patient voice is key to this[86,93]. There is a broader need to listen to those voices marginalized as a result of gender, ethnicity or diagnosis, including those labelled with "borderline personality disorder", who may be at most risk of receiving a poor service[94]. Achieving high quality community care and supporting people outside hospital is rightly a policy priority internationally, but it is vital that this is accompanied by sustained efforts to re-design and improve the provision of care in acute inpatient settings, rebalancing multidisciplinary teams, listening to service user voices and investing in interventions that demonstrate improvements in patient outcomes.

Home treatment

Early crisis home treatment programmes formed part of a broader deinstitutionalization movement, seeking to minimize stigma

and normalize mental health crises. In this section we discuss intensive treatment at home. We note that in many systems the same teams are offering both crisis home assessment (discussed above) and intensive home treatment.

Treatment at home from CRHTTs may reduce the perceived stigma and coercion associated with hospitalization. Because it requires negotiation and takes place on the territory of the person in crisis, it potentially reduces power imbalances and respects people's autonomy[95]. It may encourage a greater focus on interpersonal issues and involvement of the family and wider support system[34,96]. It may also avoid difficulties of transferring coping strategies and skills learnt in a hospital setting to a home environment[41].

A Cochrane Collaboration review of community crisis intervention for people with severe mental illness[49] included six trials of CRHTT-style services (and two residential community crisis services). It found evidence that CRHTTs can reduce inpatient service use, improve clinical outcomes and patients' experience of care, and reduce costs. Observational studies similarly suggest that the introduction of CRHTTs in a local area can help reduce overall mental health inpatient admissions when well-implemented[97]. A qualification to this promising evidence base is that crisis home treatment will not be suitable for people with the highest risks to self or others, and CRHTTs have not demonstrated effectiveness in averting involuntary hospital admissions[98].

CRHTTs do not originate from a highly specified theoretical model. Key characteristics of model services have included: a multi-disciplinary team; 24/7 availability and a rapid response to crises; intensive short-term home-based treatment (typically of less than six-week duration and with visits more than once a day); collaboration with families and other involved services; working with people in crisis who would otherwise be admitted to hospital, and facilitating early discharge from hospital for those who are admitted[43]. There is some empirical evidence that having a psychiatrist in the team and extended opening hours are related to CRHTT effectiveness[99]. A more highly specified CRHTT model and an accompanying fidelity scale have been developed[44], with fidelity scores shown to relate to inpatient admission rates and satisfaction with care[100], but the relative importance of individual fidelity criteria and the critical ingredients of CRHTTs have yet to be established.

Implementation of the CRHTT model has proved challenging. Model fidelity is typically low or moderate in CRHTTs in England and Norway – the two countries where it has been scaled up nationally[45,101]. Criticisms from service users and families have included poor continuity of care within CRHTT team-working, a narrow therapeutic focus on risk and medication (with a corresponding lack of other meaningful therapeutic interventions), and lack of support for or involvement of families[33,99,102,103]. CRHTT staff have highlighted difficulties in establishing role clarity for CRHTTs across the mental health system, and in joint working with inpatient services and longer-term community care teams[46].

Three initiatives may offer helpful ways to address some of these difficulties and improve the effectiveness of CRHTTs. First, a UK trial[104] showed that a service improvement programme for CRHTTs over one year, involving coaching from a senior clinician, regular fidelity assessment, and access to an online bank of practice resources, increased model fidelity and led to reductions in inpatient admissions and bed use. Second, a recent Swiss trial[105] reported that a CRHTT was able to reduce inpatient bed use, despite focusing almost exclusively on facilitating prompt hospital discharge rather than preventing admissions, which shows the importance of working closely with inpatient wards to end inpatient stays as soon as home treatment becomes a viable alternative. Third, a number of models for enhancing the involvement of families in acute mental health care have been developed, which typically include a focus on communication, language use and joint decision making[106].

Most attention internationally has been given to the open dialogue approach (ODA). ODA is a model of crisis and continuing care characterized by a rapid response to a crisis presentation, care centred around regular meetings of the whole support network of the person in crisis; and a psychologically informed approach to care facilitated by clinicians trained in family therapy. Three evaluations of ODA in Finland have reported promising findings[107], although robust trial evidence for effectiveness and transferability to other health care contexts has yet to be provided. A randomized controlled trial of an adapted ODA approach within a contemporary CRHTT context is currently in progress in England[108].

Both crisis assessment and intensive home treatment are in some service systems undertaken as functions within community mental health teams that also provide longer-term care[109,110]. This has advantages for continuity of care and therapeutic relationships. However, community teams also providing a range of other functions may struggle to deliver sufficiently intensive support and may not be well-placed to work with people not already on their caseloads.

Treatment at home may not be helpful for people who are extremely socially isolated, or for whom tensions or abusive relationships with others in the household are contributing to the crisis, or when other household members require respite from their caring roles. "Family sponsor homes" – short-term crisis placements with host families, who are trained and supported by mental health teams – have been established in the US and England[33], although practical and legal challenges have limited the implementation of this model internationally.

Acute day units

Acute day units (ADUs) typically offer programmes combining therapies, activities and social contact to people experiencing mental health crises who are close to the threshold for admission and attend several times a week for a number of weeks. Traditional names include day hospital or partial hospitalization service, but the more recent use of terms such as ADU or recovery centre reflects a concern that the term "day hospital" may have unduly institutional connotations[111].

The history of ADUs extends over most of the last century, with Moscow in the

early 1930s sometimes identified as their birthplace, prominent models established around Europe and the US before and after the Second World War, and provision expanding rapidly in many countries between the 1950s and the 1980s[112].

The evidence base for ADUs is arguably the most robust for any admission alternative. The authors of a Cochrane review concluded that around one in five of those otherwise admitted to an acute psychiatric ward could successfully be treated in an ADU setting, with similar clinical and social outcomes[113]. The most recent UK trial showed greater service satisfaction and symptom improvement for ADU service users[114], but new trial evidence has been lacking worldwide over the past 15 years, so that it cannot be assumed that such findings would be replicated in contemporary service systems which tend to have high thresholds for hospital admission and other approaches, such as CRHTTs, providing alternatives to admission. However, a recent naturalistic study compared outcomes for ADU and CRHTT care, finding greater service satisfaction and better outcomes for depression and well-being for the ADUs[115].

Despite the robust underpinning evidence, a decline of ADU provision has been documented in the UK[116], and may have accelerated during the COVID-19 pandemic, while little new evidence has been published elsewhere in the world. Reasons for this may include a perception that the model is unduly institutional, the substantial premises required to support a comparatively small number of service users, and the rise of other admission alternatives.

Care of an ADU form may also be integrated into community mental health centres, where these are central to service provision. However, qualitative work as well as trial evidence suggests some specific advantages which may not be shared by other admission alternatives: ADUs have important potential to address loneliness, social isolation, and lack of purposeful activity, and are also a potential environment for fostering both formal and informal peer support[117]. Evidence for the importance of social connection, sense of belonging and peer support in mental health recovery is growing, and purposeful activity also has established significance for recovery. A resurgence of the ADU as the principal acute service in which these elements are a central focus would thus be timely.

Residential community crisis services

Like ADUs, crisis houses and other community residential alternatives to hospital admission have a history spanning many decades. They are characteristically services allowing a short stay of a few days to a few weeks, with 24-hour staffing and therapeutic programmes that range from relatively clinical services aiming to replicate the interventions delivered in hospital in a less coercive and institutional setting, to more radical alternatives aiming to support different ways of resolving crises and to enhance service user choice[118].

An early US example was Soteria House in California, which from 1971 to 1983 aimed to manage first and second episodes of psychosis with minimal medication in a community setting, with some reported evidence of success[119]. Subsequently, crisis houses have been described around the world in a variety of formats. In the UK, provision has been growing in recent years, with just over half of catchment areas having some access to crisis house provision in 2019[33].

The evidence underpinning the crisis house model is substantial, though not conclusive. Relatively few randomized controlled trials have been reported, reflecting the challenges of conducting such trials with people in crisis[2]. A systematic review[23] included five randomized trials and 11 non-randomized studies of community residential alternatives to admission. Services were diverse in theoretical model, content and workforce, and included 11 US, two UK and two Swiss studies. Summary conclusions were that, according to the limited available evidence, community residential alternatives show similar, or in a few cases better, clinical outcomes to hospitals, with similar or lower costs and greater service user satisfaction.

A subsequent US review[120] included "subacute" services, not necessarily 24-hour staffed but available for urgent admission with the aim of averting crisis. Equivalent or better clinical outcomes and greater user satisfaction were reported compared to acute wards, with lower costs also found in some studies.

Throughout this literature, the authors note that community acute residential services support a population overlapping with, but not the same as, acute wards, often excluding people who are assessed as posing a substantial risk of violence or who have been compulsorily detained[118]. We are aware of no randomized controlled trial of community residential alternatives to hospital in the past 10 years.

Positive reports regarding service user experiences, therapeutic relationships, and the availability of non-standard therapeutic models are prominent in the literature on crisis houses[121-124]. This, together with evidence of satisfactory outcomes and similar or lower costs compared to inpatient care, provides a justification for including community residential alternatives to inpatient acute care as a standard part of the range of services in any mental health system where choice, flexibility and cost-effectiveness are prioritized. Despite this, we are not aware of any countries where inclusion of crisis houses is a standard element in acute care, although the model is found in many countries.

The literature on residential community crisis services suggests that the models implemented are diverse[118]. While this is an impediment to drawing generalizable conclusions about their outcomes, it is a potential strength in developing a flexible crisis care system in which a range of needs are met. Needs vary greatly at the time of a mental health crisis: for example, a service user beginning to take medication following a relapse of psychosis or bipolar disorder may benefit from a crisis house that incorporates some clinical professionals and approaches, while someone experiencing escalating distress and risk of self-harm in the context of complex trauma and/or a "personality disorder" diagnosis may benefit more from a less clinical approach, in which relational care, psychotherapeutic approaches to trauma and complex emotional needs, and the support of peers might be the main elements. An optimized crisis care system might thus include multiple residential al-

ternatives offering a choice of approaches to service users and referring clinicians.

FURTHER PERSPECTIVES ON CRISIS CARE

Crisis prevention

Our primary focus in this paper is on the management of mental health crises. However, the best option is clearly to prevent such crises if at all possible, investing instead on maintaining good mental health and supporting recovery in the community[125]. A rapid evidence synthesis found that several interventions recommended by the UK National Institute for Health and Care Excellence (NICE) guidelines have some supporting evidence regarding prevention of crises and/or relapses of illness[126]. These include early intervention services for psychosis, intensive case management models, and a range of pharmacological and psychological interventions for psychosis and bipolar disorder. Investing in full implementation of such models has potential to reduce crisis care use. Beyond such clinical models, social stressors and adverse social circumstances are contributors to crises, and a comprehensive programme to reduce adversity and inequality, as well as to implement interventions for severe mental illness that are clearly evidence-based, is arguably the optimal approach to crisis prevention[125].

A wide range of approaches focus directly on preventing crises, including early warning signs monitoring and relapse prevention programmes, some in digital form, collaborative crisis plans, and advance statements or directives. Supported self-management, often incorporating relapse prevention, is a straightforward intervention that shows evidence of effects on a range of clinical and social outcomes[127], so that wide implementation appears desirable in an optimized mental health system. The time following a crisis is an obvious target for delivery of interventions to prevent further crises: a large trial of a supported self-management intervention delivered by peer support workers in sites around England found that it reduced repeat use of acute services[128].

Collaborative planning for what should happen at the time of a crisis is currently the intervention that appears most effective in preventing compulsory hospital admission, the form of acute care that it is most desirable to avoid[98]. Ideally, as advocated in the Independent Review of the Mental Health Act in England, this should include advance statements that have legal force regarding what should happen when compulsory admission is contemplated[129].

The role of the voluntary sector

In many high-income countries, the voluntary sector (including charities and community and service user groups) is increasingly playing a role in the provision of mental health support, valued for the distinctive approaches it offers and its greater focus on equalities.

Factors accelerating the contribution of the voluntary sector to crisis support include: a) recognition that the restricted focus of statutory acute mental health care results in people falling through the gaps in provision[130]; b) service user dissatisfaction with crisis support provided by secondary mental health services[131,132]; and c) disproportionately high rates of involuntary detention for people from some minority communities, and concern that their needs are not well addressed by statutory services[133].

The distinctive contribution of voluntary sector services results from the way they work, whom they work with, and their roles within local communities[134-136]. Their foundations are often in grassroots organizations and activism, and they tend to be "underpinned by an ethos of informality, promoting accessibility, using relational-based approaches, and valuing self-organization and service-user-defined outcomes"[130]. Hierarchies are often flat, and service user, volunteer and staff roles may overlap. They are thus potentially better placed to meet the needs of marginalized groups, and of those who are either unable to access or mistrust mainstream health services, such as people from racialized communities[137], homeless people, or those excluded because of complexity of difficulties or diagnoses such as "borderline personality disorder" (although coverage of marginalized communities may be uneven).

For example, Hutchinson et al[138] found that men using not-for-profit mental health services in London were more often unemployed and had more unmet needs than local users of public mental health services. Those using the voluntary sector service cited wanting to escape "the system", with levels of dissatisfaction with public sector mental health services reported to be particularly high among Black Caribbean participants.

Among the models discussed above, crisis cafés/safe havens and crisis houses have developed predominantly in the not-for-profit sector. Distinctive characteristics of their intended approaches[130,139] can include: a positive stance on mental health; a holistic understanding of crises that locates them in the biographical, social and relational context of people's lives; space and time for people to speak about their distress; a safe, calm and welcoming environment and relational safety; informality and a light touch in terms of assessment and note-keeping; greater autonomy, choice and responsibility for clients; strong therapeutic and peer relationships; enabling people to maintain their connections to "normal life" and the community; and a less stigmatizing and less clinical approach, with providers of care including peer support workers and volunteers embedded in local communities.

Types of help offered by such crisis services include emotional support and individual and group therapy; peer support and mentoring; social and therapeutic activities; programmes to better manage mental health; advocacy; and liaison with and signposting to both public sector and other not-for-profit organizations. Thus, mental health crisis management often sits alongside services that can support recovery and enable people to deal with financial, housing and social issues.

As well as these specific crisis support services, many other not-for-profit organizations play a role in crisis support, crisis prevention, recovery, and addressing inequalities in access and support. These include those supporting particular groups at risk of poor mental health – for example, members

of the lesbian, gay, bisexual, transgender and queer (LGBTQ) community, those who are deaf, communities from specific ethnic or refugee backgrounds – and those responding to life crises such as bereavement, rape or homelessness[130].

The research literature on the contribution of not-for-profit and community organizations remains relatively scant internationally, and stronger evidence regarding their roles in local systems, experiences and outcomes would be very valuable. Reported advantages suggest that approaches developed in some not-for-profit crisis services have potential to address the problems with accessibility, acceptability, equality, and appropriateness to specific communities often reported in public mental health services[33,125]. A case can thus be made both that this sector should be recognized and incorporated within a comprehensive crisis system, and that it provides a model for rethinking dominant models of crisis care to ensure a response that is accessible, acceptable and appropriate for all members of the local population[130].

The contribution of service user-led and co-produced initiatives, and of peer support

Change to crisis and acute services has been a consistent focus for action in the mental health service user (or consumer) movement for many decades[140]. In the 1970s, activists in the UK demanded rights-based reform of the conditions and treatment in psychiatric hospitals[141]. Later, in the context of "community care", user-led organizations established themselves as sources of mutual support, patient advocacy and forums for campaigning and involvement work[142]. Informal peer support naturally occurred when people with mental health problems came together, and mental health service user groups went on to develop more organized forms of peer support, including for people experiencing mental health crises and acute distress[143].

Since their inception in grassroots service user groups, organized versions of one-to-one and group peer support have become influential for crisis and acute services across the UK, US, Canada, New Zealand and Australia[144]. For example, "intentional peer support" defines crisis as "emotional and psychological pain" and peer support as being with another who has experienced similar pain in a relationship of trust and "mutual empowerment"[145]. This model has been introduced into acute inpatient environments in the UK[146], and small-scale qualitative studies show that patients can find it helpful in providing person-centred emotional and practical support and in modelling hope[147]. Research into the implementation and effectiveness of peer support in crisis and acute services is ongoing globally[148] and, while some study findings on discharge and readmission to acute care seem promising[128], a robust evidence base is still needed[149,150].

As originally conceived, peer support is rooted in a set of values and principles[144] which can sometimes conflict with clinical environments and treatments associated with acute services, such as seclusion and restraint[151]. Mental health service users, their organizations and allies have worked to establish a set of principles and principles-based approaches for delivering peer support services in mainstream mental health services, including inpatient and crisis care[152]. Recent research into the formalization of peer support in UK mental health services suggests that "we need to pay attention to the values underpinning peer support… [and] to resist the replication… of a para-clinical model of peer support"[153], whereby peer support workers become just another kind of non-professional staff making up numbers in clinical teams. Some are concerned that the professionalization of peer support could undermine its values and authentic practice, and might negatively affect user-led and community groups that have established their own forms of crisis peer support outside the psychiatric system[154].

An international consortium of peer support leaders agreed that present and future peer support innovations should adhere to values and principles rooted in maintaining "role integrity", and in civil rights, social justice, and responsiveness to local cultural world views[155]. These principles should apply whether crisis services are located within public mental health systems (such as Open Dialogue[156]) or beyond them in independent user-led projects, such as the Leeds Survivor Led Crisis Service (LSLCS).

LSLCS is notable as an independent organization offering an alternative to hospitalization and statutory crisis care underpinned by principles and values of peer support[157]. A social return on investment (SROI) analysis for the service estimated that the "SROI ratio for LSLCS lies within the range of £4.00 to £6.50 of social value generated for every £1 invested"[158].

The future challenge is to sustain and develop a diversity of values-based, innovative and responsive peer support services for people in crisis and acute states. This is likely to expand further into the digital and online space for crisis prevention and recovery support[159]. Research into implementation, development and effectiveness using a range of methodologies is needed to ensure that a robust evidence base is built on current and emerging forms of peer support, both within and beyond mainstream services.

Other essential considerations for service planning in the future include the benefits of a co-production approach and of service user leadership. Given frequently negative service user views regarding mainstream acute services, such approaches have potentially much to offer across the acute care system.

Remote acute care delivery

Most literature on telepsychiatry focuses on videoconferencing, seen as the preferred substitute for in-person interactions, but rapid and wide accessibility suggests that there is a significant role for telephone support in crises. Voluntary sector organizations have a long history of providing such mental health support, and have been found to deal with suicidal callers as effectively as professionals[160]. The use of mental health hotlines has increased greatly in the early stages of the COVID-19 pandemic[161]. Telephone services may also be used in secondary mental health care as an initial contact, support and triage point: for example, all NHS Trusts in England are now required to provide a local helpline[162].

Telepsychiatry, predominantly using videoconferencing tools, has been used for decades to overcome geographical barriers to specialized care, particularly in rural parts of Australia and Canada, and some parts of the US[163-165]. The adoption of these services has expanded to the crisis setting to provide urgent and emergent consultation, informing care management and decisions regarding transfer to hospital[166]. For example, the Mental Health Emergency Care - Rural Access Program provides telephone and video triage and assessment for emergent psychiatric presentations across Western Australia[167,168].

Urban emergency settings characterized by variations in psychiatric coverage can also be served by a telepsychiatry liaison model. Such models have shown promise in the US and Canada to increase access to consultation, reduce wait times, decrease system costs, and improve post-ED visit outcomes[169-171]. Evidence indicates that a trained team following comprehensive safety protocols can reliably assess a wide range of presentations remotely[172,173]. This includes the assessment of suicidal behaviour, psychosis, affective symptoms, and substance use.

Virtual care is expanding rapidly, including web-based programmes and apps with potential usefulness in crisis settings. Patient-directed apps designed to help individuals cope during crises can be provided at the point of care to support post-crisis self-management and safety planning[174]. Personal videoconferencing is now emerging as a viable modality of direct care delivery, removing the need for a traditional telehealth suite and allowing assessments to take place with individuals remaining in their homes or other accessible settings. As a result, some centres are innovating and pushing the usual boundaries for crisis care delivery[175], and virtual hospital-at-home models may become a significant format for acute care in the future[176].

However, significant barriers to scaling up telemental health effectively include remuneration models, digital exclusion, inadequate privacy in many service users' homes, and perceptions that quality of care and therapeutic relationships are impaired[177]. Rigorous research is thus needed to inform future development of remote crisis care within specific health care systems[178-180].

Crisis care in low- and middle-income countries (LMICs)

In many LMICs, as well as in underserved areas of high-income countries, health services are often not the first port of call for individuals in crisis and their families. This is partly due to the limited availability and poor accessibility of mental health care. The average number of psychiatrists per one million population ranges between 0.6 in low-income countries to 20 in upper middle-income countries[1]. Even with efforts to expand access to care through integration in primary health care[1], service coverage in LMICs remains low, with only 14-22% of individuals who meet the criteria for a mental disorder receiving treatment[181]. Past experiences of poor-quality or coercive care that fails to meet prioritized needs may also deter help-seeking[182]. Only 44-50% of countries in Africa and Southeast Asia have legal protections for people requiring crisis mental health care[1], and there may be minimal enforcement.

Low community awareness about mental health, high levels of mental health stigma and, in some countries, a preference for religious and traditional healers contribute further to low levels of help-seeking from formal services[183]. In this section, we focus principally on those countries where specialized mental health services other than large psychiatric hospitals are not available, applicable to most low-income and some middle-income countries.

Crisis presentations are often not framed as mental health problems in LMICs. Community responses to mental health crises may focus on overt manifestations of a problem, including acute behavioural disturbance or distress, suicidal behaviour and self-harm, severe physical consequences (e.g., dehydration in severe depression or exhaustion linked to mania), and sudden loss of sensory or motor functions as part of conversion disorder[184]. Non-overt indicators of a mental health crisis, such as suicidal ideation, may not be prioritized for intervention.

An individual's family often drives the response to a mental health crisis, drawing on informal support from communities. Responses to acute behavioural disturbance could include involvement of the police or religious or traditional healers [185], complementary or homeopathic remedies, abandonment of the individual to the streets[186], some form of restraint[187], or emergency presentation to psychiatric services. Involvement of the police places the individual at risk of exposure to physical abuse, excessive force, restraints and detention[188]. Restraint in the context of families is often seen as a last resort in the absence of accessible and effective care[189].

Stigma and taboos associated with self-harm and suicidal behaviour may result in family concealment or punishment of the individual. Physical treatment for consequences of self-harm or suicide attempts is not usually accompanied by any form of mental health assessment or treatment.

Community responses may frame acute distress in terms of a spiritual crisis or as the understandable consequence of severe social adversities (e.g., intimate partner violence, an acute life stressor) and mobilize resources accordingly. These responses may include mediation of relationship difficulties, material supports, or providing meaning to adversity[190].

A 2015 systematic review of mental health interventions for crises in non-specialist settings in LMICs found a lack of evidence-based guidelines for crisis care[184]. Only one intervention study was identified. In a recently published guidance, the World Health Organization (WHO) set out recommendations for rights-based, recovery-oriented responses to mental health crises[191]. In developing the guidance, the WHO sought to identify case studies of good practice that were compliant with the 2006 United Nations Convention on the Rights of Persons with Disabilities, meeting five criteria (use of non-coercive practices, community inclusion, participation in care, recovery approach, respect for legal capacity). Identifying good practice case studies from LMICs was a priority, but none was found.

An integrated mental health response to crisis presentations is rare in many LMICs. Referral to specialist mental health services

may occur, but cost, inaccessibility and non-acceptability are potent barriers to uptake. Involvement of people with mental health conditions in decisions about crisis care is very limited[182]. Consequences of the existing responses include violations of human rights, prolongation of severe mental illness linked to heightened vulnerability and poorer prognosis, risk of acute physical ill-health and premature mortality, and more coercive mental health care (if accessed at all).

The WHO mental health Gap Action Programme (mhGAP) includes an intervention guide (mhGAP-IG) comprising evidence-informed algorithms for the provision of crisis care for acute psychosis or mania, suicidal behaviour or self-harm, as well as acute behavioural disturbance in the context of dementia or developmental disorders[192]. However, it does not provide clear guidance on key components of rights-based care (including supported decision-making, informed consent for treatment, and non-coercive practices) and evaluation for people with crisis presentations has been limited[193].

There have been small-scale efforts to provide alternatives to hospitalization for people in acute crisis in Somaliland[194] and Jamaica[195], but these models of care have not been rigorously evaluated and have limited potential for scalability, due to reliance on specialist mental health professionals. An adapted form of the crisis intervention team model, used widely in the US, has been piloted with law enforcement officers in Liberia, with preliminary evidence of beneficial impacts on knowledge, stigmatizing attitudes, and engagement with mental health clinicians[188].

To date, there have been two randomized controlled trials of crisis interventions for people presenting to non-specialist services after suicide attempts in LMICs[196,197]. Both trials evaluated the brief intervention and contact model, comprising an initial one-hour psychoeducation session at the time of the attempt, followed by nine phone calls over the next 18 months which assessed suicidality and support needs. The larger, multi-country trial (Brazil, China, India, Iran and Sri Lanka) demonstrated an impact of the intervention on repeat self-harm attempts and suicide, whereas the single country study (French Polynesia) showed no impact[197].

For the future, improving crisis response in LMICs will require the development and evaluation of contextually appropriate interventions, building on existing community resources and enabling community members to identify and support those in acute crisis, alongside strengthened access to mental health care and changes to policy and legislation. Building on community resources and equipping accessible individuals (e.g., peers, family members, community health workers, traditional and religious leaders, community leaders, teachers, police) to deliver psychological first aid in response to a mental health crisis is an important step to improving care[198]. The crisis intervention team approach that has been used with law enforcement officers[188] may also be relevant for traditional and religious healers or community leaders, who play an important role in determining community responses to an individual with acutely disturbed behaviour.

The COVID-19 pandemic has had a significant impact on the availability and accessibility of mental health care globally, including in LMICs[199]. Use of hotlines and digital technology creates new opportunities to provide crisis support and to identify and respond to those at risk of suicide, although as elsewhere the most vulnerable may also be at high risk of digital exclusion. Ensuring that crisis care is available in local primary and general health care settings is essential. Competency-based assessments of health workers delivering WHO's mhGAP-IG[200] in non-specialist settings should incorporate de-escalation techniques, and programmes should be informed by the WHO recommendations for crisis care[191] and ensure supported decision-making and provision of alternatives to coercive care.

Formal mental health crisis services also need to be able to move outside of facilities – for example, providing outreach to those in crisis who are homeless or restrained at home and unable to access care. The potential contribution of peer support to many aspects of mental health care, including crisis response, is gaining traction in LMICs[201,202], but starts from a low base of involvement and empowerment of people with lived experience of mental health conditions[203].

Policies and legislation upholding the human rights of individuals experiencing a mental disorder are necessary to the implementation and sustainability of effective and appropriate interventions. The WHO has specified what legislation and regulations need to include, as well as how these might be implemented. For example, current efforts in India to implement these principles through new mental health legislation include strategies to support decision-making for people experiencing a mental health crisis through advanced directives and nominated representatives[204].

Much more robust evaluation needs to accompany programmes to improve crisis response within communities, ensuring that unintended adverse consequences do not result, for example, where law enforcement agencies or traditional healers become involved in crisis response. Before adapting existing or developing new interventions, we need greater understanding of what happens at the point of crisis, to identify ways to move towards more rights-based and person-centred care. Interventions should be co-developed with service users, their families, service providers and other key members of the community to increase their appropriateness, acceptability and sustainability.

For the future, while the transfer of high-intensity, high-resource, specialist models from high-income countries to LMICs is likely to be undesirable and ineffective at meeting need, reverse innovation is possible. Where crisis responses are developed that are embedded in communities and service user involvement, as in the voluntary sector responses discussed earlier, they have the potential to serve as a template for collaborative crisis care in high-income countries.

CONCLUSIONS

Much of the focus in this paper has been on specific acute care models and the potential they hold for improving care and widening the range of options available in a crisis. However, this reflects a clinician rather than a patient perspective. During

a crisis, a service user may seek help from and be supported by a range of local agencies and will be affected not so much by the quality of individual services as by the overall accessibility of appropriate types of help and the extent to which an integrated and flexible crisis response is available from helpful and empathic staff[205].

So far, very little research has focused on the overall patient journey and on crisis care systems[47]. A flexible and accessible local area crisis care system that offers a variety of crisis options to meet service user needs and preferences and that integrates sectors appears optimal. However, a relatively complex service system involving multiple crisis service models may also lead to fragmentation and service gaps. We therefore suggest that how best to design integrated local crisis care systems should be a research and policy priority. Co-production with people who use services and their communities, as well as staff in all relevant sectors, is essential for such redesign to address diverse needs in crisis effectively and acceptably.

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No service is an island: towards an ecosystem approach to mental health service evaluation

Johnson et al[1] provide an overview of the huge transformation occurring in acute mental health care during the last two decades. The authors enumerate and discuss an extensive array of novel alternatives, while underscoring the lack of robust evidence to support their implementation. We provide here some complementary information to further understand the context of this reform and the current challenges related to its evaluation.

The accelerated reform of acute mental health care should be framed within the broader shift from hospital to community care occurring in the health sector as a whole. The development of vanguard services include enhanced health care at home, multispecialty community providers, integrated primary and acute care systems, and blended systems encompassing real world and digital health care[2]. The combined effect of these innovations is inexorably displacing care from hospitals to community in general health care and not only in the mental health field.

Awareness is increasing that acute health care improvement cannot be attained without adopting a whole system approach to the design, implementation and evaluation of new models of care. A health care ecosystem includes four main domains: the places and communities in which we live; the wider social and demographic characteristics; health lifestyles; and the health care provision at the different levels of the ecosystem: nano (patient-professional level), micro (service level), meso (local area level) and macro (region/country level)[3]. This whole system perspective is particularly relevant in the mental health field.

Johnson et al's paper describes how integrated community care models, including acute care, started in the mental health field decades before being adopted by general health care. Note that most general Hospital in the Home research was preceded by several generations of randomized controlled trials of integrated home-delivered mental health care[4]. Breakthrough innovations in mental health included the first integrated models of care such as the community/hospital care systems[5], and the "balance of care" across hospital and community, and across different sectors (health and social care)[3].

The mental health field also contributed the first ecological model for the assessment of the production of care (the Care Matrix[3]), the first integrated standards defining all sites of acute mental health care (Area Integrated Mental Health Service Standards - AIMHS[3]), and the instruments for assessing mental health care in catchment areas developed by the European Psychiatric Care Assessment Team (EPCAT) in 2000[6].

However, the pioneering contribution made by the mental health field may drop behind advances in other areas of medicine due to a restrictive focus on acute care and the methodological challenges of its evaluation in real world conditions. Acute mental health services are typically analyzed in isolation, disregarding a whole system's perspective. For example, demands for more emergency rooms and hospital beds in Australia are made without even considering a system perspective to mental health crises[4]. We need to emphasize that continuity of care (e.g., in continuing day centres, rehabilitation programmes, assertive community treatment teams, community respite and supported accommodation, often with their own internal crisis response capabilities) may prevent relapses, provide early intervention, and avoid need for acute care.

The lack of current evidence on new services and interventions in acute mental health care is attributed to the practical and ethical challenges in recruiting participants experiencing a crisis, but it is not only this. The evidence-based medicine approach may not suffice to generate evidence on the efficiency of new models of acute care. These complex systems are nonlinear, and operate under conditions of uncertainty. Therefore, realistic priority-setting requires the incorporation of systems thinking, standard classification of services, new data analytics techniques, modelling tools, and decision-support systems that incorporate domain expertise[3].

Terminological ambiguity and lack of comparability are key problems in mental health service research. As first reported by Leginski et al[5] and widely corroborated by our service mapping research[6], the nominal definition of a service does not correspond to its function. For example, the variation in target response times of crisis resolution and home treatment teams (CRHTTs) described in England and in Norway[1] may indicate that very different services are grouped under this heading.

"Service" is an umbrella term and not an operational unit of analysis. The European Service Mapping Schedule (ESMS) and its extension beyond mental health, called the European Description and Evaluation of Services and DirectoriEs (DESDE), have been extensively used for mapping services across health conditions (mental health, chronic care, disability, ageing) and care sectors (health, social, employment, education) in over 34 countries[6].

The disambiguation process facilitated by ESMS/DESDE is not limited to service types. It provides an operational definition of acute care: assessment and initial treatment in response to a crisis – deterioration in physical or mental state, behaviour or social functioning – which is related to a health condition, that can usually be provided on the same day or at least within 72 hours after the care demand. Standard definitions of related services and acute care categories such as crisis, emergency, disaster and catastrophe are also needed as part of a common terminology in this field[7].

The comparable description of services in catchment areas is critical to establish the local availability of services, their capacity (e.g., in individual "places" or in bed occupancy) and workforce provided. Once collected, this information can be used to assess the evolution of a care system, for gap and equality analysis, quality assessment, and modelling the effect of the implementation of new services or the needs of staff. Thereby, mapping of a

care system has been used to estimate the optimal workforce in full time equivalents in acute wards and acute day care in the Basque Country (Spain), and the relative technical efficiency of service provision in catchment areas, including both acute and non-acute services[6].

Impact analysis is another key component of the evaluation in mental health care. This should not be limited to end-point results on individuals. Major attention should be paid to the process of implementation and the analysis of the readiness, usability, adoption and penetration of a new service in real world environments[8]. The emphasis on fidelity should be balanced with the need for adaptation to local contexts[9].

Additional mention should be made of the role of international networks in promoting new models of care and implementation. Relevant examples are the Crisis Now/Recovery International globally growing network of facilities, which provides welcoming, peer-partnership and firmly community-based service facilities, not backed as yet by published rigorous research; the I-CIRCLE consortium, that promotes community models in urban environments; and the EUCOM model of community care in Europe.

The broader bio-psycho-socio-cultural innovations have evolved with an emphasis on complexity science, co-design with lived experience and family expertise, human rights facilitation and community-based recovery approaches. Attempts to fragment and undo cost-effective community-based reforms are often accompanied by demands for ever-more hospital beds[4]. These hospital-centric views should no longer prevail over responsive, wholistic ecosystems, integrating community and hospital components.

Transforming acute mental health care towards community models exceeds mental health systems, heralding broader reform of general acute health care and support systems towards community care. To keep on-track with previous advances, the evaluation of the mental health sector acute care should adopt a health care ecosystem perspective, including systematic assessment of the service delivery systems, their impact on processes, outcomes, workforce, and especially service users and families, valorizing lived experiences.

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Acute psychiatric care: the need for contextual understanding and tailored solutions

Johnson et al[1] review different aspects of acute psychiatric care, with the aim to identify evidence-based practices in order to increase the range of services and improve access and quality of care. They acknowledge the assortment of services involved as well as the divergent settings across health systems and countries.

Crises are multidimensional phenomena and result from complex interactions between mental illness, substance use, emotional reserves and social supports. They present complex challenges for assessment of their multiple dimensions and require a multifaceted response.

The quality of evidence for current crisis interventions and models for acute psychiatric care is, at best, moderate. The availability of only few studies, many of which marked by small samples, selective inclusion criteria, narrow focus of assessment of outcomes, and the lack of a comprehensive map of caregiver inputs and medication compliance, argues for the lack of robust evidence base for many interventions[2,3].

Different fidelity scores for implementation of the various intervention models and programs across regions suggest variations in the translation of crisis care packages[4]. The unpredictability of crisis presentations and the need for urgent care complicate the evaluation of interventions. Randomization of participants in crisis raise difficult ethical issues.

Most appraisals have examined issues from health provider perspectives, with limited user involvement in the evaluation of health care delivery. Consumer-led movements rooted in civil rights, social justice and cultural responsiveness appear promising in crisis resolution and even in prevention, and need to be included in future evaluations. The voluntary sector's involvement in providing peer support, particularly for marginalized communities, while invaluable, needs to be systematically investigated.

The delivery of acute psychiatric care has more recently focused on telepsychiatry and substitutes to in-person interactions. While telephone, videoconferencing facilities and smartphone apps have increased resources, reduced wait times, decreased cost and improved access to care,

they have not resolved issues related to digital exclusion, privacy in users' homes, therapeutic relationships, quality of care and renumeration models. These technologies await evidence for their use in routine clinical practice.

Much of the evidence for acute psychiatric care is from high-income countries. Mental health care in low- and middle-income countries, with their financial and human resource constraints, urban-rural divide, and diverse mental illness perspectives (e.g., religious and traditional healer explanatory models, complementary remedies, stigma, taboo) is often marked by inadequate provision of health services, lack of evidence-based intervention guidelines and large treatment gaps. The absence of a rights-based approach, recovery-oriented responses and inclusive community practices in addressing mental health crises, and the high cost, inaccessibility and non-acceptability of specialist mental health services complicate the scenario.

Notwithstanding the success of some programs, the issues related to efficacy, effectiveness and cost-benefit of interventions in acute psychiatric care need to be examined[5]. While randomized controlled trials are the cornerstone of evidence-based medicine, the results of a single trial or a systematic review of a few such investigations, while providing evidence about the efficacy of a treatment (i.e., "The treatment works somewhere"), do not necessarily provide evidence of effectiveness in clinical practice (i.e., "The treatment works widely").

Extrapolating knowledge gained from randomized controlled trials to other patient populations is problematic. The evidence for efficacy ("Can it work?"), effectiveness ("Does it work in practice?") and efficiency ("Is it worth it?") will need to be addressed before widespread implementation of models and programs[6]. The Hawthorne effect also confounds comparisons between innovative interventions with "standard care control arms". The motivational response of the subjects may be secondary to the interest, care and attention received through observation and assessment rather than due to the specific intervention.

Changes in clinical practice patterns over time, differences between health systems, and variations in patient demographic and clinical characteristics and in social determinants of health[7] and mental health[8], also impact generalizability of clinical research. Many crisis presentations are shaped to a great extent by the social, economic and physical environments in which people live. While targeted mental health interventions will help people in crisis, structural, public health and population-wide interventions are needed to level the social gradient in health outcomes[8].

Divergent disciplinary perspectives (e.g., crisis intervention theory, psychiatric points of view), different levels of community supports (e.g., caregiver, peer, professional), task splitting (e.g., triage, assessment and treatment), dissimilar modes of assessments (e.g., face to face, telephone, videoconferencing), varied pathways to care (e.g., health, police), multiagency integration (e.g., police, ambulance, health professionals), distinctive legal status (e.g., voluntary, compulsory, arrest), diverse location of crisis services (e.g., provision at home, within emergency departments, colocation within mental health facilities), wide spectrum of presentations (e.g., situational crisis, personality disorder, substance use/intoxication, psychosis) and the range of harm (e.g., suicidal ideation, deliberate self-harm, suicidal attempt, violence) make comparisons across services and regions difficult. Similarly, diverse therapeutic interventions (e.g., psychological, pharmacological, physical restrictive practices) and differences between stepped care models make generalizations problematic.

In addition, variation in population prevalence of crisis presentations, differences in help-seeking behavior, and variation in thresholds for different types of clinical interventions further complicate generalizability. Disparities in budgets, community and hospital infrastructure, and human resources add complexity to comparisons. Despite the success of some models, and calls for innovative approaches, the dissimilar reality across regions makes the task of identifying universally applicable models challenging.

While the evaluation of interventions is mandatory, their success will not automatically imply their generalizability to other settings. In fact, many complex programs, which often operate in project mode, succeed due to their high levels of financial, administrative and political support, but are difficult to scale up even across similar settings. Their implementation across different regions, health systems and countries can be extremely challenging.

The heterogeneity of acute psychiatric presentations, variety of interventions and diversity of settings demand the need to understand contexts. The reality of local environments and their distinctive issues demand tailored solutions. Transplanting knowledge structures, formations and practice across different contexts may result in the lack of goodness of fit[9]. Standardized protocols may not recognize locally relevant issues, demanding contextual analysis and interpretations grounded in regional reality. This is particularly true for multifaceted and multi-disciplinary intervention packages for acute psychiatric and crisis presentations.

Decisions in clinical practice should consider the broader biopsychosocial context, including clinical, psychological, social and economic problems, medical morbidity and risks, and patient and caregiver perspectives. The challenge, while attempting to replicate successful projects, is the need to understand local contexts, incorporate provincial knowledge and attempt to implement regionally tailored solutions.

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The need for a rights-based approach to acute models of care

Johnson et al[1] provide a comprehensive overview of the range of acute services and models of care currently considered and utilized by mental health systems, primarily in high-income countries. Their paper represents an excellent starting point for the evaluation of the range, access and quality of support available to those who experience acute psychosocial distress[2]. The authors make clear that there are multiple possible pathways into care, numerous modalities of assessment that can be applied, and an equally diverse set of potential options for support following assessment.

The breadth and depth of all this is nothing short of remarkable. What is equally remarkable, however, is the lack of a clear evidence-based direction provided by research. This is contrary to the widespread belief that an evidence base exists underpinning the predominantly biomedical approaches found in most high-income countries. As Johnson et al point out, most studies are negative in their findings or do not find benefit for the care model proposed. This results in making approaches to the planning, implementation and evaluation of acute care a wicked problem[3]. The "scope" and "status" of acute services currently generates a very real conundrum for service planners and individual clinicians: what are the best approaches to improving access and quality of care?

Actually, it is unlikely that there will be "best approaches" that are generalizable to individuals in terms of their presentation, time, culture or health care model. What is required is a contextually relevant model of care with adequate evidence. We would suggest that judgements as to whether the acute care approaches available in a society are sufficient and appropriate mostly belong to the patients that receive them and their support networks[4]. In order to make this evaluation, it seems likely that an understanding of acute psychosocial distress from the patient perspective is a prerequisite and that this should include an understanding of patient rights.

Taken as a whole, the existing evidence suggests that biomedical models for assessment (such as assessment in the emergency department) are largely unhelpful from a patient perspective and may increase the likelihood of inpatient care. This care is often implemented on the basis of a poorly specified "risk" that many wards are not designed to mitigate. Alternatives are therefore needed to develop more effective acute assessment and care.

It is interesting to see that home crisis teams, that are not based in a theoretical model, are more positively received by patients, as are residential community crisis homes. These exist throughout New Zealand and anecdotally reflect the positive experiences reported in the literature. Both of these models are less clinical in orientation, with a focus on the needs of the person in distress and approaches to meet them, as opposed to a focus on risk. The implication is that the biomedical models outlined as the "tip of the spear" may be insufficient or even outdated, and that co-produced acute care models are needed to adequately supplement them in meeting the needs of patients and their support networks.

We note the differentiation between the overview pertaining to high-income countries and that regarding low- and middle-income countries (LMICs) in Johnson et al's paper. What is somewhat of concern is the critical lens applied to the issues and approaches that exist in those LMICs. The identified systematic review of mental health interventions for crises in non-specialist settings in LMICs[5], which found a lack of evidence-based guidelines for crisis care, is consistent with the findings of Johnson et al's overview generally. As the United Nations (UN) Special Rapporteur pointed out in 2020, "globally, almost all contexts share the need for a paradigm shift in mental health, although what that shift looks like in practice is a matter of much debate… while a dominant global status quo in mental health exists, it is fracturing under the pressure of these divergent and powerful movements and experiences"[6]. Similarly, the World Health Organization (WHO) reports that "sector-wide solutions are required not only in low-income countries, but also in middle- and high-income countries"[7]. The issues identified in LMICs extend, we would suggest, their reach also into high-income countries.

One of the powerful movements to which the UN Special Rapporteur refers is represented by the expectations of countries that have signed and ratified the 2006 UN Convention on the Rights of Persons with Disabilities. This includes particularly the right of persons with experience of disability (including psychosocial disability) to legal capacity, which encompasses both legal standing (the ability to hold rights) and legal agency (the ability to exercise those rights).

A common assumption to counter this approach is the perceived need to substitute the choices of a person with acute psychosocial distress in order to meet his/her needs, for example by using mental health legislation. Arguably these concerns rest on poorly defined concepts, such as "insight", and there is increasing debate around appropriate capacity assessments[8], even in acute circumstances[9]. In response, the Convention requires that people are provided with support to make decisions in accord with their own will and preferences even in situations where they may have impaired decision-making skills.

As identified by Johnson et al, the recently published WHO guidance[7] sets out the core principles of rights-based, recovery-oriented approaches to community mental health services, including crisis services, as being a commitment to respect for legal capacity, non-coercive practices, community inclusion, participation, and the recovery approach. Fundamentally, the needs and rights of the person in distress should be the guide to the model of care delivered.

In sum, Johnson et al provide an excellent overview of the current range of services and quality considerations involved in acute psychiatric care. They point out that the literature is fractured or does not support many of the day-to-day interven-

tions offered. The changing global context, with an ever increasing recognition of the rights of people experiencing acute psychosocial distress, also challenges the status quo.

We would echo the authors' conclusion that new approaches need to be developed, evaluated and implemented, and we would suggest that rights-based, recovery-oriented approaches should inform any increase in the range, and improved access and quality of, acute psychiatric care. Co-production with people with lived experience and their support networks is likely to best facilitate this change.

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Continuity of care and therapeutic relationships as critical elements in acute psychiatric care

In their comprehensive review, Johnson et al[1] emphasize that acute psychiatric care consumes a substantial part of the resources available for mental health services, but that evidence on which models are associated with the most positive patient experiences and outcomes remains surprisingly limited.

It is well documented that continuity of care and therapeutic relationships are regarded as important factors by patients in mental health services[2,3]. There is also evidence that these factors are important in acute psychiatric care. Continuity of care has been shown to be positively associated with outcomes in acute psychiatric services[4]. Regarding therapeutic relationships, the majority of service users identify emotional support as a core component of crisis resolution team care, and emphasize the need to be given enough time and opportunity to tell their story and talk about their feelings and difficulties[5].

Building and maintaining a therapeutic relationship is difficult in inpatient acute psychiatric care, but has been shown to be possible and to contribute to lower use of coercion, higher patient satisfaction and better adherence to medication[6]. There is a need to adapt professional training in building and maintaining therapeutic relationships to the typical acute care setting, with limited time available and other restrictions. Research methods assessing therapeutic relationships also need to be adapted to acute psychiatric care, where the patients have personal contact with their responsible clinician as well as with other staff members.

Organization of acute care tends to focus on ready access to the services during a mental health crisis. Less attention is often given to building a therapeutic relationship during the acute care and to securing continuity of care in the transfer of contact to further services. In psychiatric inpatient units, this may result in short inpatient stays, with emphasis on medication and little time available to develop a therapeutic alliance and interacting with the patient as a person, as well as lack of securing adequate personal contact in the process of transfer to the following services. Too short length of stay or a discharge without appropriate follow-up may lead to repetitive short-term stays in acute psychiatric wards. Both length of stays and securing follow-up by health services in the community after discharge have been shown to be positively associated with reduction in readmissions[7].

Patients with serious psychiatric disorders may be more likely to keep a stability in their condition when they are allowed a long-term contact with clinicians with whom they have developed a trusting relationship, and they may need time to develop a similar relationship to a general practitioner or someone else in primary care. An additional problem is that many general practitioners are over-burdened and have limited capacity to follow up patients with mental illnesses.

It should also be considered that mental health crises often reflect problems that have developed over time and become gradually more serious. Early interventions may address problems when they are less serious and require less efforts for improvement, and low-threshold services may be provided as part of mental health care or primary care. Brief patient-controlled admission (PCA) to a mental health ward in a community center represents such a low-threshold model, which has been innovated in Norway, and is found useful by patients. PCA stays are typically a maximum of 5 days[8].

The crisis resolution teams in Norway have emphasized early intervention and low-threshold services in addition to community-based crisis interventions for patients who would otherwise be admitted to an inpatient unit. Compared to those in the UK, the Norwegian teams provide crisis care to a broader patient group, with more psychological interventions and less psychotropic medication management[9]. This practice also includes longer visits or sessions with more time for psychological help and for developing a therapeutic relationship.

Like several other team-based health services, crisis resolution team care is a complex model in which several persons

provide a wide range of interventions. Variations among team practices suggest that it is hard to practice all elements or components well, and that sometimes different components can compete, e.g., ensuring rapid response to new referrals vs. providing intensive care with frequent visits to current service users. Local adaptations are often necessary, and this may add to challenges in comparing complex interventions across sites and countries.

Johnson et al's overview describes a wide range of acute psychiatric care models used in various stages and contexts. For most of these models, there is a lack of research-based evidence, and achieving evidence for all these models may not be possible. However, a possible path may be to use research models currently under development for complex interventions to study individual elements of acute psychiatric care. If such research could identify which elements are critical for what types of clinical effect, these elements could be applied and studied within various models and contexts.

One dilemma of the increasing specialization and differentiation in mental health services, including acute psychiatric care, is the increasing discontinuity of care for service users who need services through several phases of illness. Models with more generic or integrated teams may secure more continuity in the personal relationships between the service user and the service provider. Efficiency requirements focus on management of disorders, but often leave little room for the interaction of providers with persons with these disorders.

We need to know more about which outcomes are most important for service users and what elements of acute psychiatric care contribute to the various outcomes. As a part of this, it is important to better understand how continuity of care and therapeutic relationships contribute to positive patient experiences and outcomes in acute psychiatric care, and how these two critical elements may be provided.

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Activities and technologies: developing safer acute inpatient mental health care

Johnson et al[1] provide a comprehensive and illuminating review of the evidence and key issues in relation to acute and crisis mental health care. As they suggest, psychiatric inpatient care is most often unpopular – with both patients and many staff – and can be traumatizing, re-traumatizing and coercive.

Huge tensions exist around keeping severely mentally distressed people safe whilst trying to build and sustain engaging, accepting, therapeutic relationships and milieu, often within health care systems and organizations that are inadequately funded and woefully understaffed.

Those staff that commit their time and energies to providing inpatient care often do so with great skill and humanity. A cross-national comparative case study[2] reported positive practice within acute inpatient wards, with evidence of safe, respectful, compassionate care. Patients were aware of efforts taken to keep them safe, but did not feel routinely involved in care planning or risk management decisions. Research on increasing therapeutic contact time, shared decision making in risk assessment, and using recovery-focused tools could further promote personalized care planning.

The ever-present issue of boredom on psychiatric wards is also highlighted in Johnson et al's paper. Freely available initiatives such as *Star Wards* (www.starwards.org.uk) provide multiple creative suggestions for increasing interactions on busy mental health wards, and can create opportunities for staff and patients to engage in conversations and collaboration to design and implement constructive activities.

There is a pressing need for research to investigate the organizational factors that need to be put in place to support more interactive, productive environments in acute mental health care[3]. Whether such solutions are possible within restrictive and risk-averse contexts remains to be seen. Activities to be considered, in addition to relief of boredom, include encouraging engagement, appraising the ability to undertake activities of daily living, preparing for discharge, and supporting tentative steps towards recovery.

It may be unlikely that all these needs can be adequately met in the typically short time spent on a ward, whilst also considering the varying demographic and diagnostic profiles. This applies in particular to the development of the necessary skills and confidence to build and maintain recovery while engaging with an often threatening outside world. Multidisciplinary approaches involving occupational therapists and peer workers may offer a way forward.

Johnson et al[1] highlight evidence supporting the use of *Six Core Strategies* and *Safewards* to reduce conflict and the use of containment measures on inpatient wards. A recent review acknowledged the increased evidence base for the efficacy of *Safewards* on acute wards in various countries[4]. More research is required to evalu-

ate adaptations in psychiatric intensive care units, secure mental health services, emergency departments, and wards for other age groups. However, the staff shortages and considerable pressures faced by those working in mental health care also create considerable barriers for those implementing interventions[5] and undertaking related research[6].

A narrative review of the literature[7] found a relatively small body of research on the use of closed circuits television (CCTV) to increase security for patients and staff in acute psychiatric units, but recognized the trade-off with privacy. CCTV increased subjective feelings of safety amongst patient and staff, but there was no evidence that it increased objective security or reduced violence.

CCTV and, more recently, infrared cameras have also been used to conduct close observations and monitoring of vital signs in patients, including in seclusion. Such technology can be less invasive for patients, reduce sleep disruption when making checks, and can be preferred by some patients as it avoids staff entering a person's private space. This may reduce triggers for conflict and aggression, and subsequent psychological harm associated with containment measures. Video monitoring can also allow over-stimulated patients to be left alone, while enabling staff to carry out their observations.

On the other hand, the use of electronic surveillance can be seen as distancing and dehumanizing. Studies suggest that the main factor in comforting patients and reducing trauma during an episode of seclusion or restraint is contact and communication with staff[8]. Symptoms of fear, distrust or delusions can be worsened in some patients, and there are concerns that CCTV might increase paranoid thoughts or trigger distressing memories of prior abuse involving videos. Video cameras might directly contribute to an atmosphere of detachment, control and fear, which could promote occurrence of the very events that surveillance is supposed to reduce. Videoing patients, especially in distress, can fuel feelings of shame and touches the right to privacy.

These concerns and the need for more research are important, as the increasing availability and affordability of digital technologies has seen body worn cameras (BWC) being introduced to inpatient units, in emergency departments and for paramedics in ambulances. BWCs are small devices that can be worn on clothing, which record sights and sounds in the vicinity of the wearer. Mental health staff are being asked to wear BWCs and to switch them on during incidents, or sometimes at the request of a patient. It is hoped that the use of BWCs will defuse situations, reduce aggression, and increase accountability and evidence-gathering around serious incidents. However, a recent systematic review of the literature identified only two low-quality evaluations of BWC use in mental health wards, with mixed results though some indication of reductions in more serious incidents[9].

In conclusion, addressing the activity and engagement needs of patients on busy pressured wards can be regarded today as a priority, whereas the idea of using electronic surveillance in acute mental health settings is not supported at the moment by convincing research evidence and is generating significant concerns.

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Centering equity in mental health crisis services

The review by Johnson et al[1] tells a compelling story: the evidence is significantly lacking in major domains regarding acute and crisis mental health services. We address here the major gaps in this area that relate to research on existing inequities in access to and quality of crisis services, as well as the degree to which new models and interventions are able to advance equity.

In the US, calls for diversion from overcrowded and under-resourced emergency departments, psychiatric hospitals and carceral settings have been long standing[2], with increased attention in the aftermath of the death of D. Prude, an African American man in mental health crisis who died while in police custody. Both consumer advocacy organizations and racial justice movements such as Black Lives Matter have advocated for alternatives to police response to people in mental health crisis. This momentum has been carried further by the increased burden of mental illness in the setting of the COVID-19 pandemic, as well as the highly anticipated rollout of 988 (a three-digit number specifically for mental health emergencies) across the US[3].

Diversion to mental health services is often put forward as a remedy for addressing the problems occurring at the intersection of mental health access and criminal-legal systems[4]. However, data about crisis programs resulting in meaningful diversion and reducing disparities have been equivocal. Unlike the criminal-legal system, the manifestations of racial inequity and structural harms in the mental health care system seldom go viral. But they most certainly exist, and are well documented as it relates to access, engagement, coercive practices and reception of evidence-based services[5].

A recent evaluation of a co-responder team composed of a mental health clinician and a police officer found that short-term incarceration risk was reduced, but not long-term risk of justice involvement; initial findings suggested that incarcera-

tion was significantly reduced among recipients of the co-responder services who identified as Black[6]. Also, unpublished data from Arizona suggest that Medicaid beneficiaries seen by mobile crisis teams and crisis facilities were actually more likely to be booked into jail within 30 days of a crisis episode.

To improve the evidence base for crisis services as a mitigator of mental health inequities, multiple challenges must be addressed. Major deficiencies in socio-demographic data infrastructure make it difficult to consistently measure baseline or changes in inequities by race, ethnicity, sexual orientation, indigenous groups (typically referred to as Native-American or American-Indian in the US, but also including other groups internationally), immigration status, socioeconomic status, education level, homelessness, disability, and language preference.

Notably, relevant socio-demographic hierarchies vary regionally and internationally, especially in low- and middle-income countries, where other factors (e.g., caste or last name) may manifest in inequities more so than the issue of race that is often highlighted in the US. While all of these socio-demographic factors should be studied for disparities, we focus here on racial equity with the understanding that learnings from this area will help advance equity more broadly.

One reason for the lack of socio-demographic data is the lack of incentives to collect this important information. Neither quality measures nor payors (public or private) routinely require measurement of these attributes. Although US organizations such as the National Quality Forum are developing risk adjustment methods that would incorporate relevant data on socio-economic status and other factors, widespread adoption is a long way off.

Another challenge to measuring equity in crisis intervention services is diagnostic overshadowing, which refers to assessments resulting in diagnoses at different rates for certain subgroups based on non-clinical factors (e.g., over-diagnosis of schizophrenia in African American men). Such biases at baseline can reduce the validity of control groups and confound outcome data. This issue is of particular concern in the measurement of coercive interventions such as involuntary hospitalization and forced medication administration, that have been shown to be administered in a racially inequitable manner[7].

As crisis programs are implemented globally, system administrators, policy makers and providers must commit to utilizing an equity framework in both the design and evaluation of crisis response systems. A crucial first step is to engage communities directly in crisis system design in a meaningful, ongoing collaboration, with mechanisms in place to measure progress and ensure accountability.

Leaders must make an explicit commitment to first account for extant inequities and then be held accountable to address them. Relevant activities include trainings, education, and intentional design related to structural inequities. Programs can utilize resources such as the Racial Equity Toolkit from the Government Alliance on Racial Equity[8] as well as the Self-Assessment for Modification of Anti-Racism Tool (SMART)[9]. Programs can support investments in the behavioral health workforce pipeline by hosting internships and other training opportunities aimed at diversifying the workforce to reflect communities served. Inclusion of peer specialists can also benefit the socio-economic and racial/ethnic diversity of the workforce, with the additional benefit of reducing stigma.

With regard to design and evaluation of crisis services, resources are needed to support rigorous, outcomes-driven strategies to measure a program's impact on perpetuating, worsening or dismantling inequity. Programs can draw on community-based participatory research models and implementation science methods to invite input from community stakeholders and advisory boards in the research process, to facilitate the identification and inclusion of outcome data that is meaningful to key stakeholders.

To improve data quality, evaluators can provide specialized training to clinical staff on how to collect the socio-demographic data that are needed to inform equity analyses. Similar to the need for diversification of the clinical workforce, supporting researchers of diverse backgrounds is an essential way to promote equity. Finally, increased funding of mental health crisis services research is needed to advance these goals, and equity-focused analyses should be part of every research project that is funded.

Facilitating proactive approaches to measuring and studying disparities can help advance the goal of truly achieving equity in how systems respond to people in crisis. Metrics must go beyond simple descriptive measures such as capacity and response times, and focus on more meaningful process and outcome measures, such as linkage to outpatient care and symptom improvement. So as not to perpetuate inadequate insurance payments for outpatient mental health services, it is essential that evaluations of crisis systems examine treatment outcomes as well as disparities between important subgroups.

The lack of hard data on the role for crisis services in advancing equity is deeply problematic. The increased attention to this key component of the mental health care system is a tremendous opportunity for addressing disparities in the mental health field.

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Crisis within a crisis – the fragility of acute psychiatric care delivery

Johnson et al[1] provide a comprehensive account of the different service models aimed to address mental health crises, focusing on assessment and immediate management of the crisis, intensive treatment following crisis, further perspectives on crisis care including prevention, and crisis care in low- and middle-income countries. They conclude that a variety of options exist, but also that the evidence based on robust studies is scarce, and that most studies and policies reflect a clinician rather than a patient or consumer perspective.

Generations of mental health care providers and consumers have strived to improve management of mental health crises, and the extensive synopsis of these efforts is striking in many ways. On the one hand, it illustrates the complexity of the issue; on the other, it shows the creativity needed in trying to address it. However, the plethora of models that the authors describe also reflects the general inadequacy of the services available and the failure of experts and service users alike to identify effective solutions. In addition, complex systems tend to be ineffective, complicating the pathways to care, increasing the time for a patient to receive adequate support, and increasing direct and indirect mental health costs.

The COVID-19 pandemic has introduced many new challenges to our societies, especially affecting the most vulnerable populations, including people with mental illness. While the united efforts of scientists worldwide have yielded the unprecedentedly rapid development of immunization strategies, health care service delivery in general, and mental health care delivery in particular, have suffered[2]. As an unintentional global stress test for health care systems, COVID-19 has revealed structural weaknesses in our acute mental health care services.

COVID-19 infection itself causes acute mental health disturbances as well as long-lasting neurological and psychiatric sequelae. In addition, the forced reduction in social contacts and activities during lockdowns, anxiety and stress in the face of impending economic hardship, and uncertainty during a global crisis have exposed previously undetected mental health problems, led to increased rates of relapse of existing psychiatric illness, and induced new psychiatric problems. This increase in psychiatric morbidity has led to a surge in service use, for which most mental health systems were not prepared[3].

Mental health care workers and administrators alike are struggling to uphold mental health care provision, resorting to creative measures, including new e-health solutions. Despite these efforts, it is proving impossible in many cases – and especially in institutional settings – to sustain services at pre-pandemic levels, leading to a degradation of the therapeutic alliance, one of the most critical success factors in psychiatric treatment[4]. The mental health crisis within the pandemic crisis has exposed a lack of robust policies backing the interventions needed to help people with mental illness, and can be taken as an indicator for the fragility of mental health care delivery.

In addition, as Johnson et al[1] describe in their review, patient or consumer access to acute psychiatric care is often characterized by a loss of autonomy and self-determination. Aggressive behavior and violence in psychiatric patients are used to justify more restrictive settings in inpatient facilities, in the interest of maintaining safety when dealing with patients who might otherwise harm themselves or be a danger to the community. However, recent evidence points in another direction: more open and empowering treatment approaches promoting reduction of coercion are able to reduce aggression and violence in emergency psychiatric settings[5], suggesting that it is feasible to implement and uphold services with a minimum use of coercion and maximal patient autonomy.

However, this is a demanding and long-term effort. Again, the COVID-19 pandemic shows how easily this progress can be lost. In times of a pandemic crisis, the level of involuntary admissions and coercive measures increases[6]. This is not necessarily caused by an increase in psychopathology, but also due to an increased need for safety of the population and mental health care workers during times of uncertainty[7]. Normative attitudes outweigh moral doubts in times of crises and may lead mental health care workers to use more coercion in treatment settings.

Lastly, the COVID-19 pandemic reminds us of the importance to focus not only on interventions for mental health crises, but also to help prevent these crises if possible. The mental health system should provide interventions to promote resilience and well-being, to facilitate self-care, and to support informal care. As the topic of Johnson et al[1] is acute psychiatric care, they understandably only give a short overview of secondary and tertiary prevention efforts. However, the importance of prevention cannot be underestimated in its value to counteract the development of mental health crises, thereby reducing the suffering of the affected persons as well as the strain on the mental health care system and health care costs.

We agree with the authors that new research and policies need to be promoted and that integrated local crisis care systems should be created to address the diverse needs of people with mental health crises. It is crucial to include people who use services, their families, communities and staff in all relevant sectors of mental health care delivery to design service systems that address the specific needs of patients and consumers. The COVID-19 pandemic has demonstrated the demand for better and more enduring service structures for people with mental illness. To achieve this goal, it is paramount to focus on the empowerment and de-stigmatization of service users[8].

In order to counter the structural stigmatization of mental health, politicians and policy makers need to be challenged and held accountable to include mental health care provision specifically in pandemic policies. The focus must shift from a fragmented, complex service system, including multiple crisis service models and leading to service gaps and unmet medical and psychiatric needs, toward a full continuum of psychiatric care[9]. Governments and agencies need to support and fund the development of comprehensive continua of mental health care, from inpatient beds in psychiatric institutions to low-threshold

services, based on evidence-based public policies and practices on a national level. International research groups, including scientists and service users from low- and middle-income countries, are the key to the collection and timely dissemination of data on the best models and practices, with the goal to provide the evidence for sustainable acute psychiatric care delivery.

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After the acute crisis – engaging people with psychosis in rehabilitation-oriented care

Johnson et al[1] make a forceful argument for the need to improve quality and access to acute psychiatric services. However, once the acute crisis abates, there are usually enduring symptoms and functional deficits associated with mental illness, notably for people living with psychotic disorders, such as schizophrenia. These individuals need access to rehabilitation-oriented services to prevent relapses and subsequent return to crisis services, and to help them achieve their personal recovery goals.

As Johnson et al note[1], there is evidence that early intervention for psychosis services (EIPS) are associated with reduced risk of relapse and re-hospitalization compared to treatment as usual[2]. The rationale for EIPS is that most disability associated with psychotic disorders occurs during the first few years after an initial psychotic episode, and that much of this disability can be prevented or reduced with comprehensive care focusing on risk factors for functional deterioration. These include disruption of peer and family networks, unemployment, stigma, discrimination, demoralization and trauma[2].

The goal of EIPS is to provide integrated care so that the acute crisis of a first episode of psychosis is followed by a focus on recovery, tailored to the individual's needs[2]. A range of psychological, psychosocial and pharmacological interventions is available to individuals within EIPS, although these vary across different services. Frequently used interventions include well-monitored pharmacological treatment, family psychoeducation, individual cognitive behaviour therapy (CBT), social skills training and vocational education[2].

EIPS show improved rates of remission and clinician- or researcher-defined recovery compared to treatment as usual. However, there is now a vast movement away from clinical classification of "recovery" as absence or reduction in symptoms, improvement in functioning and/or reduction in mental health service use, with instead an emphasis on personalized recovery, as defined by the person with lived experience[3].

While EIPS can improve outcomes for people in the early stages of psychotic illnesses, there are some individuals who have suboptimal response or fail to recover. Those at highest risk for poor outcomes are individuals with long duration of untreated psychotic symptoms prior to their first episode of psychosis, poor premorbid adjustment, high levels of negative symptoms at baseline, and poor cognitive functioning[4]. Further, while antipsychotics improve psychotic symptoms in most people, up to one in three people with schizophrenia will develop treatment resistant illness[5]. This is defined by ongoing psychotic symptoms and functional deficits following at least two adequate trials of first-line antipsychotic medications.

Many risk factors for poor outcome can be identified early in the course of a first episode of psychosis. There is therefore an opportunity to develop stratified pathways of care, in which those at highest risk for poor outcome are monitored closely and offered specialized treatments early. For example, those at high risk for persistent positive symptoms and functional decline could be offered early use of clozapine.

Clozapine is the most effective medication for reducing both positive symptoms of schizophrenia[6] and psychiatric hospitalizations[7]. Despite its widely accepted superiority for treatment resistant schizophrenia, there is often a delay of many years between onset of treatment resistant symptoms and commencement of this medication. Improving early access to clozapine in both high-income and low- and middle-income countries is essential to reduce the need for acute psychiatric care among people living with treatment resistant schizophrenia. This would also increase the chance for many more people living with schizophrenia to enjoy a good quality of life.

Early and persistent negative symptoms are another risk factor for poor outcome in early psychosis. Their underlying aetiopathology is unknown, and there are no evidence-based treatments for them. Antipsychotics, antidepressants, stimulants – including methylphenidate, d-amphetamine and modafinil – and anticonvulsants have all been trialled, but meta-analyses

suggest that their effectiveness is poor. Further trials are needed for these disabling symptoms.

Over and above pharmacological interventions for people with enduring psychosis, there is a need for a whole person approach including rehabilitation-oriented psychosocial interventions to reduce the need for acute crisis services[8]. Evidence-based rehabilitation-oriented interventions include CBT for psychosis (CBTp) and social cognition training to assist in managing the distress associated with psychotic symptoms and improving psychosocial functioning.

A subset of people with early psychosis will have high levels of cognitive impairment at initial presentation. Routine screening and comprehensive assessment of cognitive ability early in illness course can help identify these people. Early provision of interventions such as cognitive remediation may improve cognitive functioning and has been shown to improve psychosocial functioning in early psychosis patients[9].

Family based interventions, notably psychoeducation, have been shown to reduce rates of acute presentations and need for re-hospitalizations. Employment oriented interventions such as individual placement and support can assist in returning people living with psychosis to meaningful social roles through employment and education. Further research is needed to identify predictors of treatment response, so that these interventions can be targeted to those most likely to respond.

Comorbid alcohol and substance misuse can negatively impact the mental health trajectory of people living with enduring psychosis, leading to an increased need for acute psychiatric care. Evidence-based interventions, including motivational enhancement and relapse prevention, should be delivered as part of an integrated mental health care package to reduce acute relapse[8].

People living with psychosis have much higher rates of avertable physical health comorbidity, leading to a 20-year reduction in life span. This is driven by the higher rates of cardiometabolic illness, due in part to higher genetic risks, poor diet, increased sedentary behaviour, higher rates of smoking, and glucose dysregulating adverse drug reactions of second-generation antipsychotics. Early access to evidence-based physical health interventions to prevent obesity is crucial to reduce cardiometabolic illness burden, and acute physical health care needs. Multidisciplinary lifestyle interventions, including diet and exercise, have been repeatedly shown to be effective in reducing cardiometabolic comorbidity. Pharmacological interventions, notably metformin, can also modify weight gain as both primary prevention and secondary treatment. These interventions must commence in concert with early psychosis treatment.

There is an urgent need to improve quality and access to acute psychiatric services. However, these services – in both high-income and low- and middle-income countries – need to be backed up by rehabilitation-oriented services for people with psychosis. These early and enduring psychosis treatment services are crucial to break the cycle of reliance on acute crisis care for people living with psychosis, and to improve their quality of life.

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Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors

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People with schizophrenia die 15-20 years prematurely. Understanding mortality risk and aggravating/attenuating factors is essential to reduce this gap. We conducted a systematic review and random-effects meta-analysis of prospective and retrospective, nationwide and targeted cohort studies assessing mortality risk in people with schizophrenia versus the general population or groups matched for physical comorbidities or groups with different psychiatric disorders, also assessing moderators. Primary outcome was all-cause mortality risk ratio (RR); key secondary outcomes were mortality due to suicide and natural causes. Other secondary outcomes included any other specific-cause mortality. Publication bias, subgroup and meta-regression analyses, and quality assessment (Newcastle-Ottawa Scale) were conducted. Across 135 studies spanning from 1957 to 2021 (schizophrenia: N=4,536,447; general population controls: N=1,115,600,059; other psychiatric illness controls: N=3,827,955), all-cause mortality was increased in people with schizophrenia versus any non-schizophrenia control group (RR=2.52, 95% CI: 2.38-2.68, n=79), with the largest risk in first-episode (RR=7.43, 95% CI: 4.02-13.75, n=2) and incident (i.e., earlier-phase) schizophrenia (RR=3.52, 95% CI: 3.09-4.00, n=7) versus the general population. Specific-cause mortality was highest for suicide or injury-poisoning or undetermined non-natural cause (RR=9.76-8.42), followed by pneumonia among natural causes (RR=7.00, 95% CI: 6.79-7.23), decreasing through infectious or endocrine or respiratory or urogenital or diabetes causes (RR=3 to 4), to alcohol or gastrointestinal or renal or nervous system or cardio-cerebrovascular or all natural causes (RR=2 to 3), and liver or cerebrovascular, or breast or colon or pancreas or any cancer causes (RR=1.33 to 1.96). All-cause mortality increased slightly but significantly with median study year (beta=0.0009, 95% CI: 0.001-0.02, p=0.02). Individuals with schizophrenia <40 years of age had increased all-cause and suicide-related mortality compared to those ≥40 years old, and a higher percentage of females increased suicide-related mortality risk in incident schizophrenia samples. All-cause mortality was higher in incident than prevalent schizophrenia (RR=3.52 vs. 2.86, p=0.009). Comorbid substance use disorder increased all-cause mortality (RR=1.62, 95% CI: 1.47-1.80, n=3). Antipsychotics were protective against all-cause mortality versus no antipsychotic use (RR=0.71, 95% CI: 0.59-0.84, n=11), with largest effects for second-generation long-acting injectable antipsychotics (SGA-LAIs) (RR=0.39, 95% CI: 0.27-0.56, n=3), clozapine (RR=0.43, 95% CI: 0.34-0.55, n=3), any LAI (RR=0.47, 95% CI: 0.39-0.58, n=2), and any SGA (RR=0.53, 95% CI: 0.44-0.63, n=4). Antipsychotics were also protective against natural cause-related mortality, yet first-generation antipsychotics (FGAs) were associated with increased mortality due to suicide and natural cause in incident schizophrenia. Higher study quality and number of variables used to adjust the analyses moderated larger natural-cause mortality risk, and more recent study year moderated larger protective effects of antipsychotics. These results indicate that the excess mortality in schizophrenia is associated with several modifiable factors. Targeting comorbid substance abuse, long-term maintenance antipsychotic treatment and appropriate/earlier use of SGA-LAIs and clozapine could reduce this mortality gap.

Key words: Schizophrenia, psychosis, mortality, suicide, first-episode schizophrenia, antipsychotics, comorbidity, substance use disorder, cardiovascular disease, physical health, long-acting injectable antipsychotics, clozapine

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Schizophrenia is associated with one of the highest mortality risks of all psychiatric disorders[1]. While it is well recognized that individuals with this disorder die prematurely compared to the general population, reasons for the estimated life expectancy gap of 15-20 years are less clear[2].

Modifiable risk factors reportedly associated with greater and earlier mortality in individuals with schizophrenia include poorer lifestyle behaviors, reduced access to physical care, frequent comorbid illnesses, and use – or lack thereof – of antipsychotic medications[3,4]. However, it is unclear whether mortality risk changes in new-onset incident cases or evolves in established prevalent cases. A larger mortality gap has been reported in younger people, not only for suicide but also for physical health causes[5].

In a nationwide study from Finland that compared 34,809-42,712 individuals with schizophrenia with 3,877,129-4,515,838 people from the general population between 1984 and 2014, the higher all-cause standardized mortality ratio for those with schizophrenia compared to the general population remained stable during the 30 years of follow-up (1984=2.6; 2014=2.7)[6]. However, in a Danish nationwide cohort study, the standardized mortality gap appeared to be increasing by 0.03 annually between 1995 and 2014[7].

There is growing evidence supporting the protective effect of antipsychotic treatment versus non-use of antipsychotics in people with schizophrenia[8-10]. Notably, although antipsychotics have been associated with adverse cardiometabolic effects that can increase the risk of cardiovascular death[11-14] – which represents the largest absolute risk for mortality associated with schizophrenia[15-19] – antipsychotic use versus non-use has not been

associated with a greater risk of hospitalization for any physical disease (hazard ratio, HR=1.00, 95% CI: 0.98-1.03), including cardiovascular disorders (HR=1.00, 95% CI: 0.92-1.07)[10]. Rather, antipsychotic use versus non-use has been associated with a significantly decreased risk for death from cardiovascular illness in individuals with schizophrenia (HR=0.62, 95% CI: 0.57-0.67)[10].

This apparent paradox has been explained by healthier lifestyle behaviors, less psychosis-related stress/cortisol increase, and better help-seeking behaviors in antipsychotic-treated individuals. Recently, adherence versus non-adherence to antipsychotics has also been associated with decreased discontinuation risk of antidiabetics (adjusted hazard ratio, aHR=0.56, 95% CI: 0.47-0.66), statins (aHR=0.61, 95% CI: 0.53-0.70), antihypertensives (aHR=0.63, 95% CI: 0.56-0.71), and beta-blockers (aHR=0.79, 95% CI: 0.73-0.87) in within-subject analyses[20].

Additionally, among antipsychotic medications, differential risk attenuation of mortality risk in individuals with schizophrenia has been described[8-10]. For example, a Swedish prospective nationwide study on a register-based cohort followed for a median of 5.7 years reported an approximately 33% reduced mortality risk among individuals who received long-acting injectable antipsychotics (LAIs) compared with equivalent oral antipsychotics[9]. This greater protective effect of LAIs versus oral antipsychotics was substantiated in a Taiwanese nationwide cohort study with a median of 14 years of follow-up, which reported a 34% decreased all-cause mortality risk with LAIs, with an even stronger protective effect (i.e., 47% decreased mortality risk) in subjects switched to an LAI within the first two years of diagnosis of schizophrenia[8].

Finally, use of clozapine, one of the agents with the highest cardiometabolic risk burden[21,22], has also been associated with decreased all-cause mortality risk, such as in a Finnish nationwide database study with a median of 14.1 years of follow-up, where all-cause mortality was reduced by 61% and cardiovascular death risk was decreased by 45% versus non-use of antipsychotics[10]. Consistent with the previously noted association between antipsychotic use and adherence to cardiometabolic treatments, clozapine was associated with the largest reduction among all second-generation antipsychotics (SGAs) regarding discontinuation of statins, antidiabetics and beta-blockers[20].

Increased mortality in individuals with schizophrenia appears to be associated to a large degree with comorbid physical conditions and unhealthy lifestyle behaviors. These individuals have higher rates of cardiovascular risk factors than the general population, including (components of) metabolic syndrome[13] and diabetes[14], as well as sedentary behavior[2] and smoking[23], yet are less likely to receive education regarding smoking cessation and may not receive preventive or acute care for comorbid illnesses comparable to patients without schizophrenia[24-27]. Moreover, in addition to increased cardiovascular risk factors, individuals with schizophrenia also receive lower quality of care for cardiovascular disease[28].

The role of antipsychotics in specific-cause mortality in schizophrenia has not been definitively clarified, and there is still an ongoing debate regarding whether antipsychotic agents reduce overall mortality largely due to decreasing suicide-related mortality risk, while tending to increase natural-cause mortality risk owing to their adverse impact on cardiac repolarization, body weight and other cardiometabolic risk factors[4,29,30], a risk that may be aggravated in older age[31].

To the best of our knowledge, there has been no large-scale, comprehensive meta-analysis that has included several control groups, most relevant specific causes of mortality and antipsychotic treatments, as well as an analysis of factors aggravating or attenuating mortality in individuals with schizophrenia. Most of the prior meta-analyses included fewer than 30 studies. Many studies focused either on one specific causative factor (such as suicide, cardiovascular disease, or use of specific antipsychotic agents) or included schizophrenia among other severe mental illnesses.

To fill this gap, we performed a systematic review and meta-analysis examining risk of all-cause and specific-cause mortality in individuals with schizophrenia versus several control groups, as well as factors associated with increased or attenuated mortality risk in these persons, focusing also on representativeness of the sample, study quality and time trends.

METHODS

Search methods for identification of studies

We conducted a PRISMA 2020-compliant systematic review[32] searching Medline, PubMed and PsycINFO until September 9, 2021, using the search key (schizophrenia AND (mortal* OR death* OR fatal*)) NOT (animals [mesh] NOT humans [mesh]), and complemented it with manual search. The PRISMA 2020 checklist and abstract checklist are provided in the supplementary information.

Study eligibility criteria

Peer-reviewed publications of a cohort study (prospective or retrospective; nationwide or not) were eligible. We included only studies in which ≥70% of the participants had a diagnosis of schizophrenia and in which a minimum of 100 patients with this diagnosis were recruited. Publications had to include quantified reporting – e.g., odds ratio (OR), risk ratio (RR), HR, or raw numbers – of the relationship between schizophrenia diagnosis versus control group and any type of mortality. When a risk or protective factor was present that defined a subgroup of people with schizophrenia, such as cardiac illness or diabetes or substance use disorder comorbidity, only studies where the schizophrenia and control group were matched on that risk or protective factor were included.

We excluded non-cohort studies, such as case-control studies, reviews, meta-analyses and systematic reviews. Publications were also excluded if they did not provide mortality data, quanti-

tative data, or if the data were not meta-analyzable. Publications that contained non-peer-reviewed data (such as proceedings, poster abstracts or posters) were not considered. No language or time restrictions were applied.

Four independent raters (GC, LKS, MS, NS) selected studies and extracted outcome data as well as information on potential effect modifiers. The Newcastle-Ottawa Scale[33] was used to classify quality/risk of bias. When discrepancies occurred, a further rater (CUC) was consulted. Original study authors were contacted to provide missing data.

Outcomes

The primary outcome was RR of all-cause mortality in individuals with schizophrenia versus any control group. Key secondary outcomes were mortality due to suicide and natural causes. Additional secondary outcomes included other specific-cause mortality.

Analyses examined incident plus prevalent cohorts together and either prevalent or incident cohorts separately. Prevalent cases include all individuals living with schizophrenia within a specified timeframe, regardless of when the person was diagnosed with or developed the condition. Incident cases encompass all individuals who are newly identified within the period of observation as having schizophrenia, or all new cases of schizophrenia. Control groups consisted of the general population, regardless of underlying comorbid physical diseases (from here on, "general population"), or control samples matched by physical disease. Patients with schizophrenia were compared with both control populations combined, and with each one separately, whenever possible.

Extraction methodology

Whenever results for different degrees of adjustment of RR were presented, we always used the result that was adjusted for the largest number of variables. Whenever data for both prevalent and incident cohorts were presented, we extracted both. For studies where data were only presented graphically, we extracted the data from the respective figures. For studies that only provided data on the point estimates but did not include the standard deviation or 95% CI, we imputed the 95% CI as the mean of all studies with the available data.

Whenever only raw mortality data were reported, we calculated the mortality ratio by dividing the mortality rate for schizophrenia subjects by the rate for controls. When authors presented data by narrow or broad definitions, we picked the broad definition, to be more conservative and include as many potential deaths as possible. Whenever data on samples overlapping by at least 50% were reported in different publications, we used the data including 95% CIs from the larger sample.

Whenever a subgroup of patients with schizophrenia with a specific condition was the subject of a study (for example, schizophrenia with type 2 diabetes mellitus), the control group had to have that same condition. Whenever the exact number of the control group was not specified, but rather the group was defined by a region, state or country, we took the size of that population at the midpoint of the study period. When the sample size of the control group in subgroup analyses was not specified, we imputed it by applying the same ratio of the group with schizophrenia (e.g., same male to female ratio). In representative studies, if the control group was not provided, we extracted data from census sources matching the time of study.

Data analysis

We conducted a random-effects meta-analysis[34] and calculated the RR of primary and secondary outcomes. Given that the outcome of interest, mortality, is rare (i.e., less than 10%), and that all included studies used the same design and evaluated the same population of interest, we pooled ORs, RRs, HRs and standardized mortality ratios. When an association measure was not available, we used the raw data (i.e., number of events and sample sizes in schizophrenia and control groups) and calculated the unadjusted RR. When both adjusted and unadjusted effect sizes were available, we prioritized adjusted ones.

I^2 was used to measure heterogeneity[35], and Egger's test to assess publication bias[36]. When Egger's test revealed publication bias (i.e., $p<0.1$), we conducted trim and fill analyses, and calculated the fail-safe number[37].

Sources of heterogeneity were explored with meta-regression, sensitivity and subgroup analyses. Random-effects meta-regression analyses were conducted with follow-up time, median study year, number of variables adjusted for, mean age, gender, and sample size as moderator variables. Sensitivity analyses were conducted in studies comparing schizophrenia with the general population, and in studies matching control groups by underlying physical conditions, as well as in incident and prevalent schizophrenia samples. Subgroup analyses were also conducted by use of nationwide versus more restricted samples, Newcastle-Ottawa Scale quality score, adjustment of results, mean age of the sample, incident or prevalent sample, and antipsychotic class prescribed. We chose to analyze the effect of treatment with antipsychotics using subgroups (by class or formulation or specific medication) as the unit of analysis, instead of using the pooled result of the overall study as the unit of analysis, since a single study might have reported on several different antipsychotic subgroups. Comprehensive Meta Analysis Version 2.0 was used for all analyses.

RESULTS

Search results

An initial search retrieved 8,345 abstracts; removal of duplicates resulted in 6,390 abstracts for review. Of these, a total of 135

studies[5-10,38-166] were included, after excluding 463 articles upon full text assessment (see Figure 1, Table 1 and supplementary information). We ultimately included 4,536,447 individuals with schizophrenia who were compared with 1,115,600,059 control subjects from the general population.

Studies compared subjects with schizophrenia (N=3,494,716) versus the general population (N=1,097,856,754) (n=72); schizophrenia subjects (N=29,616) versus general population groups matched for physical comorbidities (N=17,733,923) (n=30); and schizophrenia individuals (N=19,011) versus groups with other mental disorders (N=3,827,955) (n=6). Additionally, 27 studies (N=994,273) investigated the association between present/absent risk/protective factors and mortality within two groups of subjects with schizophrenia.

Studies were conducted in the US (n=20), Denmark (n=19), Taiwan (n=17), Sweden (n=10), Finland (n=9), Canada (n=9), the UK (n=9), China (n=6), Israel (n=5), France (n=4); 3 each in Italy, Hong Kong, the Netherlands, Korea, or multiple countries; 2 each in Australia, Japan and Spain; and one each in Ethiopia, Germany, Hungary, India, Norway and Singapore.

There were 22 (16.3%) prospective and 113 (83.7%) retrospective cohort studies, with 85 (63.0%) being nationwide database studies. Study periods ranged from 1957 to 2021.

Nearly one-third of the studies (32.6%) included in the meta-analysis did not report an age range. When an age range was provided, 23 studies (17.0%) reported the minimal age as >15 years and another 22 studies (16.3%) used >18 years. The remaining 46 studies listed widely heterogeneous age ranges, with upper and lower extremes ranging from 10 to 109 years old.

Altogether, 20 studies (14.8%) exclusively or also included incident (i.e., earlier-phase) cases with schizophrenia, two studies (1.5%) included first-episode patients, and five studies (3.7%) focused on treatment-resistant schizophrenia. Regarding outcomes, 49 studies (36.3%) only reported on all-cause mortality, 25 (18.5%) only on a specific cause of mortality, and 63 (46.7%) on both (see Table 1).

Primary outcome: all-cause mortality

Across 79 studies, schizophrenia was associated with significantly higher all-cause mortality as compared with any control group (RR=2.52, 95% CI: 2.38-2.68, I^2=99.7%) (see Table 2). Patients with schizophrenia had substantially higher all-cause mortality versus the general population (RR=2.94, 95% CI: 2.75-3.13, I^2=99.7%, n=57) (see Table 2 and Figure 2). The association

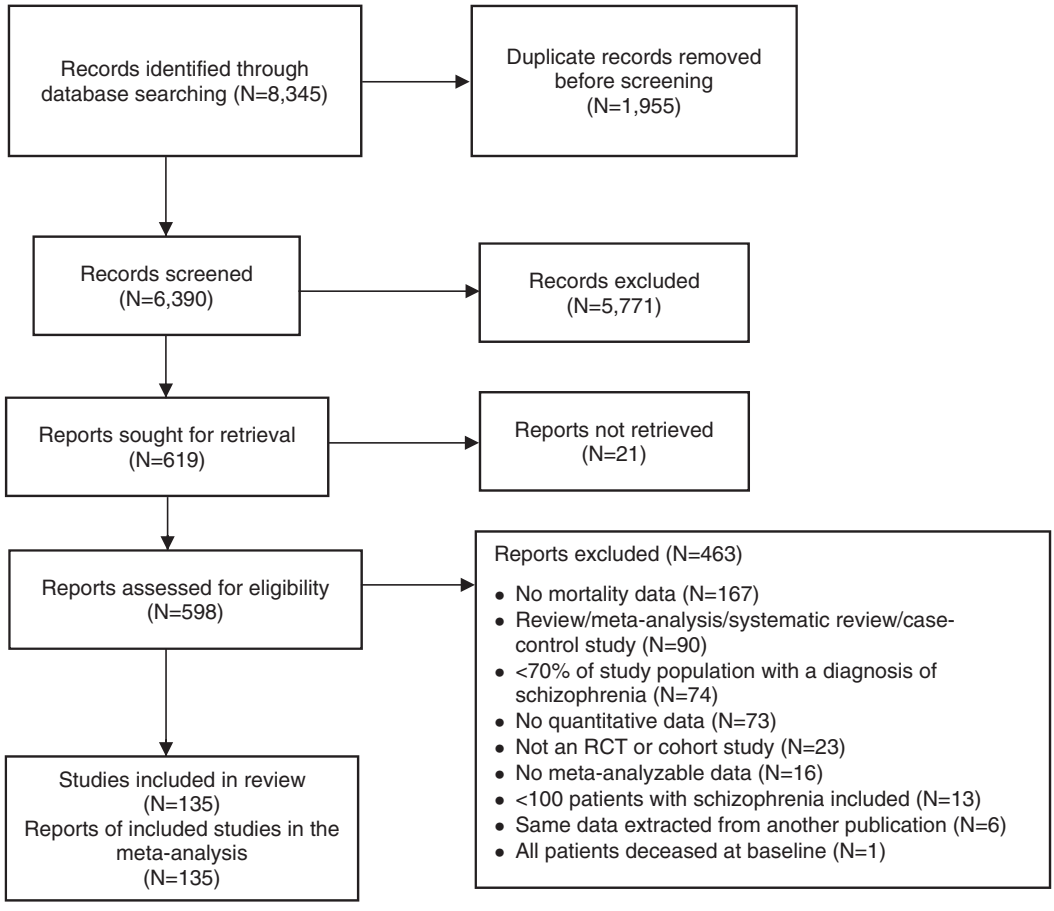

Figure 1 PRISMA flow chart. RCT – randomized controlled trial

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Alleback & Wistedt[38]	Sweden	1971-1981	Schizophrenia vs. general population	P	1,190	16,902	All-cause, suicide, various specific causes, undetermined	9
Amaddeo et al[39]	Italy	1982-1991	Schizophrenia vs. general population	P	3,172	153,352	All-cause	9
Attar et al[40]	Denmark	1995-2013	Schizophrenia vs. general population	P	726	2,178	Cardio-cerebrovascular	9
Bagewadi et al[41]	India	2009-2011	Schizophrenia vs. general population	P	325	NA	All-cause	9
Berardi et al[42]	Italy	2008-2017	Schizophrenia vs. general population	P	7,940	4,250,075	All-cause, natural, various specific causes	9
Bitter et al[5]	Hungary	2005-2013	Schizophrenia vs. general population	P	65,165	390,599	All-cause	9
Black & Fisher[43]	US	1970-1988	Schizophrenia vs. general population	P	356	2,869,448	All-cause, natural, undetermined	9
Bouza et al[44]	Spain	2004-2004	Schizophrenia vs. general population	P	16,776	3,951,000	All-cause	9
Bralet et al[45]	France	1991-1999	Schizophrenia vs. general population	P	150	552,303	All-cause	8
Brown et al[46]	UK	1981-2006	Schizophrenia vs. general population	P	370	24,328,853	All-cause, suicide, natural, various specific causes, undetermined	9
Buda et al[47]	US	1934-1974	Schizophrenia vs. general population	P	332	NA	Suicide, natural, various specific causes, undetermined	9
Castagnini et al[48]	Denmark	1995-2008	Schizophrenia vs. general population	I	4,576	3,565,833	All-cause, suicide, natural, various specific causes, undetermined	9
Chan et al[49]	Hong Kong	2006-2016	Schizophrenia vs. general population	I	3,105	13,545	Natural, various specific causes	9
Chen et al[50]	Taiwan	2000-2016	Schizophrenia vs. general population	P	170,322	22,710,322	Cardiovascular	9
Chen et al[51]	Taiwan	1999-2010	Schizophrenia vs. general population	P	7,531	22,547,531	All-cause	9
Chen et al[52]	Taiwan	1998-2004	Schizophrenia vs. general population	I	5,515	24,238	All-cause, natural, undetermined	9
Cheng et al[53]	Taiwan	1998-2008	Schizophrenia vs. general population	P	2,457	22,561,450	All-cause, natural, various specific causes, undetermined	9
Crump et al[54]	Sweden	2001-2008	Schizophrenia vs. general population	P	25,359	6,908,922	All-cause, injury, other	9
Curkendall et al[55]	Canada	1994-1998	Schizophrenia vs. general population	P	3,022	13,110	All-cause, natural	8
Daumit et al[56]	US	1992-2001	Schizophrenia vs. general population	P	2,303	5,171,640	Cardiovascular	8
Dickerson et al[57]	US	1999-2009	Schizophrenia vs. general population	P	517	2,448,017	Natural	7
Dickerson et al[58]	US	1999-2012	Schizophrenia vs. general population	P	710	182,165,000	Natural	9
Enger et al[59]	US	1995-1999	Schizophrenia vs. general population	P	1,920	11,520	All-cause, natural, cardiovascular	9

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors *(continued)*

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Fors et al[60]	Sweden	1991-2000	Schizophrenia vs. general population	P	255	1,530	All-cause, natural, cardiovascular, undetermined	9
Gatov et al[61]	Canada	1993-2012	Schizophrenia vs. general population	P	34,338	8,793,478	All-cause	9
Girardi et al[62]	Italy	2008-2018	Schizophrenia vs. general population	P	12,196	9,787,004	Suicide, natural, various specific causes	9
Guan et al[63]	The Netherlands	1999-2007	Schizophrenia vs. general population	P	4,590	23,062	All-cause, suicide, natural, other	9
Haugland et al[64]	US	1975-1978	Schizophrenia vs. general population	P	351	NA	All-cause	9
Hayes et al[65]	UK	2000-2014	Schizophrenia vs. general population	P	22,497	241,884	All-cause, suicide, cardiovascular	9
Heila et al[66]	Finland	1980-1996	Schizophrenia vs. general population	P	58,761	7,314,595	All-cause, suicide	9
Hellemose et al[67]	Denmark	1970-2011	Schizophrenia vs. general population	I	17,530	5,389,084	Other	9
Hennessy et al[68]	US	1993-1996	Schizophrenia vs. general population	P	136,927	29,086	Cardiovascular	7
Hewer & Rössler[69]	Germany	1984-1986	Schizophrenia vs. general population	P	8,927	61,057,927	All-cause, suicide, natural	9
Kilbourne et al[70]	US	1999-2006	Schizophrenia vs. general population	P	22,817	38,859	Cardiovascular	9
Kim et al[71]	Korea	2002-2013	Schizophrenia vs. general population	I	9,387	1,025,340	All-cause	9
Kiviniemi et al[72]	Finland	1995-2001	Schizophrenia vs. general population	I	7,591	5,120,000	All-cause, suicide, natural, various specific causes, undetermined	9
Kredentser et al[73]	Canada	1999-2008	Schizophrenia vs. general population	P	9,038	978,128	All-cause, suicide, natural, various specific causes	9
Kugathasan et al[74]	Denmark	1995-2015	Schizophrenia vs. general population	P	30,210	5,432,821	All-cause, natural, various specific causes	9
Kugathasan et al[75]	UK	2013-2017	Schizophrenia vs. general population	P	36,425	218,297	Various specific causes	9
Kurdyak et al[76]	Canada	2007-2010	Schizophrenia vs. general population	I	13,385	12,851,821	All-cause, suicide, injury, other	9
Lahti et al[77]	Finland	1969-2004	Schizophrenia vs. general population	I	204	12,735	Cardio-cerebrovascular	9
Laursen et al[78]	Denmark, Finland, Sweden	2000-2007	Schizophrenia vs. general population	P	66,088	19,691,360	All-cause, natural, cardio-cerebrovascular, undetermined	9
Laursen et al[79]	Denmark	1992-2006	Schizophrenia vs. general population	P	30,614	8,999,225	Cardiovascular	9
Laursen et al[80]	Denmark	1995-2007	Schizophrenia vs. general population	P	16,079	4,873,115	Natural	9
Lomholt et al[7]	Denmark	1995-2014	Schizophrenia vs. general population	P	38,500	6,176,414	All-cause	9
Luo et al[81]	China	2007-2010	Schizophrenia vs. general population	P	2,071	1,909,205	All-cause	9
Meesters et al[82]	The Netherlands	2008-2012	Schizophrenia vs. general population	P	157	25,788	All-cause	9

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors *(continued)*

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Mortensen & Juel[83]	Denmark	1957-1986	Schizophrenia vs. general population	P	6,178	2,494,178	All-cause, suicide, natural, various specific causes	6
Mortensen & Juel[84]	Denmark	1970-1987	Schizophrenia vs. general population	I	9,156	5,131,156	All-cause, suicide, natural, various specific causes	6
Newman & Bland[85]	Canada	1976-1985	Schizophrenia vs. general population	P	3,623	4,479,623	All-cause, suicide, natural, various specific causes	6
Nielsen et al[86]	Denmark	1980-2010	Schizophrenia vs. general population	P	14,974	1,326,393	All-cause	9
Olfson et al[87]	US	2001-2007	Schizophrenia vs. general population	I	1,138,853	173,699,853	All-cause, suicide, natural, various specific causes	9
Olfson et al[88]	US	2007-2016	Schizophrenia vs. general population	P	668,836	311,580,000	Suicide, other non-natural	9
Ösby et al[89]	Sweden	1973-1995	Schizophrenia vs. general population	I	7,784	1,792,216	All-cause, suicide, natural, various specific causes, undetermined	9
Pan et al[90]	Taiwan	2001-2016	Schizophrenia vs. general population	P	170,322	23,000,000	Suicide, other non-natural	9
Pan et al[91]	Taiwan	2005-2008 2010-2013	Schizophrenia vs. general population	P	95,632 104,561	2,292,000 229,200	All-cause, suicide, natural, various specific causes	9
Phillippe et al[92]	France	1993-2002	Schizophrenia vs. general population	P	3,470	33,264,661	All-cause, natural	6
Phillips et al[93]	China	1995-1999	Schizophrenia vs. general population	P	102	19,121	Suicide, natural	9
Ran et al[94]	China	1994-2004	Schizophrenia vs. general population	P	500	123,562	All-cause, suicide, injury, natural	9
Ruschena et al[95]	Australia	1995-1995	Schizophrenia vs. general population	P	25,202	35,361,211	All-cause, suicide, injury, natural, undetermined	7
Talaslahti et al[96]	Finland	1992-2008	Schizophrenia vs. general population	P	9,461	1,891,543	All-cause, suicide, natural, various specific causes	9
Tanskanen et al[6]	Finland	1984 1994 2014	Schizophrenia vs. general population	P	159,858	16,701,991	Suicide, natural, cardiovascular, other	9
Teferra et al[97]	Ethiopia	2001-2005	Schizophrenia vs. general population	P	307	68,685	All-cause	9
Tenback et al[98]	The Netherlands	2006-2008	Schizophrenia vs. general population	P	7,415	105,141	All-cause	9
Tokuda et al[99]	Japan	1987-2004	Schizophrenia vs. general population	P	1,108	190,157	All-cause	9
Tornianen et al[100]	Sweden	2006-2010	Schizophrenia vs. general population	I	48,441	1,032,760	All-cause, suicide, various specific causes	9
Tran et al[101]	France	1993-2003	Schizophrenia vs. general population	P	3,434	3,434	Cardiovascular	9
Westman et al[102]	Sweden	1987-2010	Schizophrenia vs. general population	P	46,911	10,678,728	All-cause, suicide, injury, cardio-cerebrovascular, other	9
Wood et al[103]	US	1972-1976	Schizophrenia vs. general population	P	8,779	235,558	All-cause	9
Yung et al[104]	China	2006-2016	Schizophrenia vs. general population	P	817	8,987	All-cause, cerebrovascular	9
Yung et al[105]	Hong Kong	2006-2016	Schizophrenia vs. general population	P	46,896	7,500,000	All-cause, various specific causes	9

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors *(continued)*

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Zilber et al[106]	Israel	1978-1983	Schizophrenia vs. general population	P	9,282	NA	All-cause, suicide, natural, various specific causes	9
Attar et al[107]	Sweden	2000-2018	Schizophrenia vs. general population with acute myocardial infarction	P	1,008	285,325	All-cause	9
Babidge et al[108]	Australia	1988-1998	Schizophrenia vs. no schizophrenia homeless	P	455	708	All-cause	9
Bodén et al[109]	Sweden	1997-2010	Schizophrenia vs. general population with acute myocardial infarction	P	541	209,592	All-cause, cardiovascular	9
Bradford et al[110]	US	2001-2005	Schizophrenia vs. general population with lung cancer	P	835	34,644	All-cause	9
Chan et al[111]	Hong Kong	2001-2016	Schizophrenia vs. general population with diabetes mellitus	P	6,991	75,673	All-cause, diabetes mellitus	9
Chong et al[112]	Singapore	2000-2006	Schizophrenia with vs. without tardive dyskinesia	P	241	561	All-cause, natural, various specific causes	9
Chou et al[113]	Taiwan	2000-2008	Schizophrenia vs. no schizophrenia with cancer	P	1,131	6,377	All-cause	9
Chou et al[114]	Taiwan	2000-2008	Schizophrenia vs. general population with pneumonia	P	6,040	13,878	All-cause	9
Closson et al[115]	Canada	1998-2012	Schizophrenia vs. general population with HIV	P	835	13,331	All-cause	9
Crump et al[116]	Sweden	2003-2009	Schizophrenia vs. general population with ischemic heart disease or cancer	P	8,277	6,097,834	All-cause	9
Druss et al[117]	US	1994-1995	Schizophrenia vs. general population with acute myocardial infarction	P	161	88,241	All-cause	9
Fleetwood et al[118]	UK	1991-2014	Schizophrenia vs. no schizophrenia with acute myocardial infarction	P	923	235,310	Cardiovascular	9
Fond et al[119]	France	2020-2020	Schizophrenia vs. general population with COVID	P	823	50,750	COVID	9
Guerrero Fernandez de Alba et al[120]	Spain	2012-2015	Schizophrenia vs. general population with diabetes mellitus	P	931	52,266	All-cause	9
Hauck et al[121]	Canada	2008-2015	Schizophrenia vs. general population with myocardial infarction	P	1,145	108,610	All-cause	9
Jeon et al[122]	Korea	2019-2020	Schizophrenia vs. general population with COVID	P	159	2,976	COVID	9
Kang et al[123]	Taiwan	2002-2004	Schizophrenia vs. general population with stroke	P	485	2,910	Cerebrovascular	9
Kapral et al[124]	Canada	2002-2017	Schizophrenia vs. no schizophrenia with stroke	P	612	52,473	Cerebrovascular, other	9
Kershenbaum et al[125]	UK	2013-2019	Schizophrenia vs. anxiety disorders	P	238	1,115	All-cause	9

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors *(continued)*

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Kugathasan et al[126]	Denmark	1995-2015	Schizophrenia vs. general population with myocardial infarction	P	631	101,510	All-cause	9
Kurdyak et al[127]	Canada	2002-2006	Schizophrenia vs. general population with acute myocardial infarction	P	842	71,668	Cardiovascular	9
Laursen et al[128]	Denmark	1998-2008	Schizophrenia vs. general population with stroke	P	3,660	877,507	All-cause, cardiovascular, undetermined	9
Liao et al[129]	Taiwan	2004-2007	Schizophrenia vs. general population with surgery	P	8,967	44,835	Other	9
Mohamed et al[130]	US	2004-2014	Schizophrenia vs. other severe mental illness vs. no severe mental illness with myocardial infarction	P	23,582	6,322,796	Cardiovascular	9
Shen et al[131]	Taiwan	2005-2007	Schizophrenia vs. general population in intensive care unit	P	203	2,239	All-cause	9
Sögaard et al[132]	Denmark	2000-2015	Schizophrenia vs. general population with atrial fibrillation	P	534	2,552,772	Cardiovascular	9
Toender et al[133]	Denmark	1999-2017	Schizophrenia vs. general population with diabetes mellitus	P	1,004	184,470	All-cause, diabetes mellitus, other	9
Tsai et al[134]	Taiwan	1999-2008	Schizophrenia vs. general population with stroke	P	1,377	4,329	All-cause	9
Tsai et al[135]	Taiwan	1999-2010	Schizophrenia vs. general population with osteoporotic fractures	P	30,335	151,675	All-cause	9
Tzur Bitan et al[136]	Israel	2020-2021	Schizophrenia vs. no schizophrenia with COVID	P	25,539	51,078	COVID	8
Wellejus Albertsen et al[137]	Denmark	2000-2013	Schizophrenia vs. general population with acute myocardial infarction	P	1,160	36,685	Cardiovascular	9
Alaräisänen et al[138]	Finland	1997-2005	Schizophrenia vs. other mental disorder	I	100	422	Suicide	9
Dickerson et al[139]	US	1999-2018	Schizophrenia vs. bipolar disorder or major depressive disorder	P	861	1,745	Natural	9
Hayes et al[140]	UK	2007-2010	Schizophrenia vs. bipolar disorder	P	4,270	6,109	All-cause	9
Kodesh et al[141]	Israel	2002-2012	With vs. without very late onset schizophrenia	P	329	94,120	All-cause	9
Chen et al[142]	Taiwan	1998-2008	Schizophrenia on SGA vs. FGA	I	812	1,624	All-cause	9
Cho et al[143]	UK	2008-2015	TRS with vs. without clozapine	TRS	1,025	2,817	All-cause	9
Cullen et al[144]	US	1994-2004	Schizophrenia with or without annual antipsychotic continuity	P	2,132	-	All-cause, suicide, cardiovascular	9
Dickerson et al[145]	US	1999-2004	Schizophrenia with vs. without Toxoplasma	P	358	-	Natural	9

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors *(continued)*

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Fontanella et al[146]	US	2006-2013	Schizophrenia with vs. without benzodiazepines with or without antipsychotics	P	5,212	32,694	All-cause, suicide, natural	9
Funayama et al[147]	Japan	1999-2016	Schizophrenia with vs. without catatonia	P	140	1,710	All-cause	9
Hayes et al[148]	UK	2007-2011	TRS with vs. without clozapine	TRS	617	9,437	All-cause	9
Hjorthoj et al[149]	Denmark	1969-2013	Schizophrenia with vs. without substance use disorder	P	29,549	41,470	All-cause, suicide, various specific causes	9
Horsdal et al[150]	Denmark	2000-2012	Schizophrenia with vs. without abnormal C-reactive protein or white blood cell levels	I	208	1,025	All-cause	9
Huang et al[8]	Taiwan	2002-2017	Schizophrenia with oral vs. LAI antipsychotic	I	2,614	2,614	Suicide, natural	9
Kadra et al[151]	UK	2007-2014	Schizophrenia vs. bipolar disorder	P	5,896	7,782	All-cause	9
Kiviniemi et al[152]	Finland	1998-2003	First-episode schizophrenia with or without antipsychotics	I	5,266	6,713	All-cause, suicide, cardiovascular	9
Kugathasan et al[153]	Denmark	1980-2015	Schizophrenia with vs. without physical health multimorbidity	P	9,775	1,798	All-cause	9
Lahteenvuo et al[154]	Finland, Sweden	1972-2007 2006-2016	Schizophrenia with vs. without substance use disorder	P	8,110 4,514	30,860 14,616	Suicide, injury, natural	9
Liu et al[155]	China	2006-2010	Schizophrenia vs. other mental disorders	P	7,628	3,810,782	All-cause	9
Oh et al[156]	Korea	2003-2017	Schizophrenia with vs. without antipsychotics	P	77,139	86,923	All-cause, suicide, various specific causes	9
Pridan et al[157]	Israel	2007-2012	TRS with vs. without clozapine	TRS	43	527	All-cause	9
Ran et al[158]	China	1994-2015	Men vs. women and older vs. younger people with schizophrenia	P	510	123,062	All-cause, suicide, natural, other	9
Strom et al[159]	Multicountry	2002-2006	Schizophrenia on ziprasidone vs. olanzapine	P	9,077	18,154	All-cause, suicide, cardiovascular, other	9
Strømme et al[160]	Norway	2005-2014	Schizophrenia with vs. without antipsychotics	P	101	696	All-cause	9
Stroup et al[161]	US	2001-2009	TRS with vs. without clozapine	TRS	3,123	6,246	All-cause	9
Taipale et al[9]	Sweden	2006-2013	Schizophrenia with vs. without antipsychotics	P I	34,426	-	All-cause	9
Taipale et al[10]	Finland	1996-2015	Schizophrenia with vs. without antipsychotics	P I	62,250	-	All-cause, suicide, cardiovascular	9
Tang et al[162]	Taiwan	2001-2015	Schizophrenia on oral vs. LAI antipsychotics	P	58,615	87,247	Cardiovascular	9

Table 1 Included studies reporting on risk of all-cause and specific-cause mortality in schizophrenia versus control group, and on mitigating/risk factors *(continued)*

	Country	Years	Comparison	Incident/prevalent	Number of patients	Number of controls	Mortality outcomes	NOS
Taub et al[163]	Israel	2012-2014	Schizophrenia on clozapine with vs. without physical illness	P	2,406	1,817	All-cause	9
Tiihonen et al[164]	Finland	2000-2007	Schizophrenia with vs. without antipsychotics, antidepressants or benzodiazepines	I	2,192	2,588	All-cause	9
Wimberley et al[165]	Denmark	1996-2013	TRS with vs. without clozapine	TRS	1,372	2,370	All-cause, suicide, natural, other	9
Wu & Shur-Fen Gau[166]	Taiwan	2001-2012	Schizophrenia with vs. without antipsychotics or benzodiazepines	P	32,512	68,718	All-cause	9

NOS – Newcastle-Ottawa Scale, I – incident, P – prevalent, TRS – treatment-resistant schizophrenia, NA – not available, SGA – second generation antipsychotic, FGA – first generation antipsychotic, LAI – long-acting injectable antipsychotic

was the highest in two studies specifically including individuals with first-episode schizophrenia (RR=7.43, 95% CI: 4.02-13.75, I^2=93.0%), and significantly higher in incident than prevalent schizophrenia (RR=3.52, 95% CI: 3.09-4.00, I^2=97.1%, n=7 vs. RR=2.86, 95% CI: 2.62-3.12, I^2=99.67, n=50, p=0.009) (see Table 2, Figures 3-4 and supplementary information).

Compared with controls matched for physical diseases, the mortality risk of individuals with schizophrenia was attenuated but still significant (RR=1.66, 95% CI: 1.42-1.94, I^2=97.2%, n=22) (see Table 2). Specifically, individuals with schizophrenia had significantly higher mortality compared with controls matched for acute myocardial infarction (RR=1.82, 95% CI: 1.49-2.22, I^2=83.1%, n=6), diabetes mellitus (RR=1.91, 95% CI: 1.08-3.38, I^2=99.4, n=4), and stroke (RR=1.35, 95% CI: 1.22-1.50, I^2=0%, n=2) (see Table 2).

No significantly increased mortality risk emerged when schizophrenia was compared with other psychiatric disorders, except for bipolar disorder (RR=1.26, 95% CI: 1.03-1.53, I^2=25.4%, n=3) (see Table 2).

Regarding risk and protective factors for all-cause mortality, having a substance use disorder comorbid with schizophrenia increased mortality (RR=1.62, 95% CI: 1.47-1.80, I^2=57.4%, n=3) (see Table 2).

Wherever publication bias was detected, we conducted trim and fill analyses, which confirmed the magnitude and significance of the findings in the primary analyses, with a fail-safe N ranging from 545 to 27,164,601 (see also supplementary information).

Key secondary outcomes: suicide-related mortality and natural causes of mortality

Suicide-related mortality

Across 28 studies, schizophrenia was associated with increased mortality by suicide compared with the general population (RR=9.76, 95% CI: 7.60-12.55, I^2=99.5%) (see Table 2 and Figure 2), suggesting that suicide is the greatest relative risk factor for mortality in individuals with schizophrenia. There was a numerically but not statistically significantly greater suicide-related mortality among the incident versus prevalent cohort (RR=12.7, 95% CI: 5.25-30.53, I^2=99.8, n=5 vs. RR=9.28, 95% CI: 7.31-11.78, I^2=98.8%, n=23, p=0.51) (see Table 2, Figures 3-4 and supplementary information).

Wherever publication bias was detected, we conducted trim and fill analyses, which confirmed the magnitude and significance of the primary findings, with a fail-safe N ranging from 25,581 to 229,490 (see also supplementary information).

Natural causes of mortality

Across 59 studies, schizophrenia was associated with higher natural-cause mortality (which excludes mortality due to suicide or accident or poisoning) compared with either the general population or control groups matched for a physical disease (RR=2.00, 95% CI: 1.85-2.15, I^2=99.5%) (see Table 2).

Higher natural-cause mortality was confirmed across 44 studies involving comparisons with the general population (RR=2.16, 95% CI: 1.99-2.36, I^2=99.6%), without differences between incident and prevalent schizophrenia (RR=2.15, 95% CI: 1.86-2.48, I^2=94.6, n=6 vs. RR=2.15, 95% CI: 1.96-2.37, I^2=99.1%, n=38, p=0.939) (see Table 2, Figures 3-4 and supplementary information).

Across 16 studies involving prevalent populations with physical disease-matched controls, natural-cause mortality risk was also significantly increased (RR=1.56, 95% CI: 1.35-1.82, I^2=94.0%), including specifically matched patients with acute myocardial infarction (RR=1.66, 95% CI: 1.24-2.22, I^2=96.4%, n=5) (see Table 2).

Wherever publication bias was detected, we conducted trim

Table 2 All-cause and cause-specific mortality risk in schizophrenia versus control groups

	Incident/ prevalent	N. studies	Risk ratio	95% CI	p	I^2	Egger's p
All-cause mortality							
Schizophrenia vs. any other population	I + P	79	**2.523**	**2.377-2.678**	**0.000**	99.7	0.001
	P	72	**2.432**	**2.253-2.626**	**0.000**	99.591	0.690
First-episode schizophrenia vs. general population	I	2	**7.433**	**4.017-13.754**	**0.000**	92.965	NA
Schizophrenia vs. general population	I + P	57	**2.938**	**2.753-3.135**	**0.000**	99.733	0.050
	I	7	**3.516**	**3.092-3.998**	**0.000**	97.114	0.840
	P	50	**2.859**	**2.622-3.117**	**0.000**	99.669	0.360
Schizophrenia vs. no schizophrenia (all matched)	P	22	**1.664**	**1.425-1.943**	**0.000**	97.226	0.530
Schizophrenia vs. no schizophrenia (matched for acute myocardial infarction)	P	6	**1.821**	**1.491-2.224**	**0.000**	83.146	0.840
Schizophrenia vs. no schizophrenia (matched for diabetes mellitus)	P	4	**1.913**	**1.082-3.380**	**0.026**	99.414	0.500
Schizophrenia vs. no schizophrenia (matched for stroke)	P	2	**1.351**	**1.219-1.498**	**0.000**	0.000	NA
Schizophrenia vs. other mental disorder	I + P	5	2.130	0.648-7.002	0.213	99.349	0.110
	P	5	2.130	0.648-7.002	0.213	99.349	0.110
Schizophrenia vs. bipolar disorder	P	3	**1.257**	**1.031-1.533**	**0.023**	25.362	0.210
Schizophrenia with vs. without substance use disorder	P	3	**1.625**	**1.467-1.799**	**0.000**	57.443	0.680
Mortality due to suicide							
Schizophrenia vs. general population	I + P	28	**9.764**	**7.598-12.549**	**0.000**	99.478	0.030
	I	5	**12.654**	**5.245-30.530**	**0.000**	99.802	0.050
	P	23	**9.281**	**7.311-11.782**	**0.000**	98.793	0.680
Mortality due to natural cause							
Schizophrenia vs. any other population	I + P	59	**1.996**	**1.851-2.153**	**0.000**	99.464	0.020
	P	53	**1.967**	**1.793-2.158**	**0.000**	99.201	0.040
Schizophrenia vs. general population	I + P	44	**2.162**	**1.985-2.355**	**0.000**	99.571	0.004
	I	6	**2.149**	**1.861-2.481**	**0.000**	94.602	0.270
	P	38	**2.154**	**1.961-2.367**	**0.000**	99.182	0.140
Schizophrenia vs. no schizophrenia (all matched)	P	16	**1.565**	**1.346-1.821**	**0.000**	94.001	0.030
Schizophrenia vs. no schizophrenia (matched for acute myocardial infarction)	P	5	**1.659**	**1.238-2.223**	**0.001**	96.379	0.070
Mortality due to cardio-cerebrovascular diseases							
Schizophrenia vs. any other population	I + P	30	**2.028**	**1.678-2.452**	**0.000**	99.470	0.020
Schizophrenia vs. general population	I + P	28	**2.099**	**1.797-2.451**	**0.000**	99.008	0.001
	I	4	**3.470**	**1.792-6.719**	**0.000**	97.883	0.570
	P	24	**1.984**	**1.729-2.275**	**0.000**	97.690	0.210
Schizophrenia vs. no schizophrenia (all matched)	P	2	1.329	0.907-1.946	0.144	97.625	NA
Mortality due to cardiovascular diseases							
Schizophrenia vs. any other population	I + P	25	**2.089**	**1.764-2.474**	**0.000**	99.289	0.020
	P	20	**1.963**	**1.653-2.331**	**0.000**	98.841	0.220
Schizophrenia vs. general population	I + P	19	**2.205**	**1.824-2.666**	**0.000**	99.412	0.050
	I	5	**2.701**	**1.802-4.050**	**0.000**	98.514	0.250
	P	14	**2.058**	**1.680-2.522**	**0.000**	99.120	0.370
Schizophrenia vs. no schizophrenia (all matched)	P	7	**1.855**	**1.392-2.473**	**0.000**	91.665	0.480
Schizophrenia vs. no schizophrenia (matched for acute myocardial infarction)	P	4	**1.847**	**1.515-2.252**	**0.000**	73.575	0.360

Table 2 All-cause and cause-specific mortality risk in schizophrenia versus control groups *(continued)*

	Incident/ prevalent	N. studies	Risk ratio	95% CI	p	I^2	Egger's p
Mortality due to cerebrovascular diseases							
Schizophrenia vs. any other population	I + P	16	**1.458**	**1.168-1.822**	**0.001**	97.435	0.090
	P	11	1.386	0.993-1.936	0.055	98.027	0.260
Schizophrenia vs. general population	I + P	13	**1.598**	**1.250-2.042**	**0.000**	97.748	0.220
	I	5	**1.764**	**1.357-2.292**	**0.000**	72.580	0.090
	P	8	**1.583**	**1.062-2.359**	**0.024**	98.505	0.490
Schizophrenia vs. no schizophrenia (all matched)	P	3	0.972	0.520-1.817	0.929	91.905	0.240
Schizophrenia vs. no schizophrenia (matched for stroke)	P	2	0.724	0.173-3.038	0.659	95.719	NA
Mortality due to diabetes mellitus							
Schizophrenia vs. any other population	I + P	7	**2.512**	**1.623-3.889**	**0.000**	99.121	0.170
	P	6	**2.271**	**1.444-3.572**	**0.000**	98.201	0.920
Schizophrenia vs. general population	I + P	5	**3.159**	**2.420-4.123**	**0.000**	94.848	0.270
	P	4	**2.878**	**1.858-4.458**	**0.000**	94.485	0.630
Schizophrenia vs. no schizophrenia (matched for diabetes mellitus)	P	2	**1.483**	**1.032-2.131**	**0.033**	95.695	NA
Mortality due to any cancer							
Schizophrenia vs. general population	I + P	25	**1.327**	**1.187-1.482**	**0.000**	97.942	0.001
	I	5	1.315	0.982-1.760	0.066	93.121	0.060
	P	20	**1.328**	**1.157-1.524**	**0.000**	97.109	0.420
Mortality due to endocrine diseases							
Schizophrenia vs. general population	I + P	9	**3.802**	**1.750-8.262**	**0.001**	97.438	0.500
	I	3	**4.217**	**1.747-10.179**	**0.001**	76.243	0.390
	P	6	**3.519**	**1.216-10.185**	**0.020**	98.350	0.640
Mortality due to gastrointestinal diseases							
Schizophrenia vs. general population	I + P	12	**2.859**	**2.069-3.950**	**0.000**	96.838	0.930
	I	4	**2.384**	**1.939-2.932**	**0.000**	0.000	0.910
	P	8	**3.060**	**2.046-4.577**	**0.000**	97.959	0.800
Mortality due to any infectious diseases							
Schizophrenia vs. general population	I + P	10	**3.840**	**2.103-7.012**	**0.000**	97.025	0.460
	P	8	**4.344**	**2.228-8.471**	**0.000**	97.679	0.410
Mortality due to any liver diseases							
Schizophrenia vs. general population	I + P	2	**1.964**	**1.899-2.032**	**0.000**	0.000	NA
Mortality due to any neurological diseases							
Schizophrenia vs. general population	I + P	8	**2.347**	**1.942-2.838**	**0.000**	6.879	0.400
	I	4	**1.972**	**1.126-3.452**	**0.018**	25.381	0.270
	P	4	**2.435**	**2.245-2.641**	**0.000**	0.000	0.840
Mortality due to any respiratory diseases							
Schizophrenia vs. general population	I + P	15	**3.748**	**2.989-4.699**	**0.000**	97.563	0.790
	I	4	**3.267**	**2.365-4.515**	**0.000**	60.784	0.430
	P	11	**3.860**	**2.963-5.029**	**0.000**	98.217	0.720
Mortality due to any urogenital diseases							
Schizophrenia vs. general population	I + P	9	**3.328**	**2.062-5.372**	**0.000**	98.032	0.640
	P	7	**3.752**	**2.183-6.450**	**0.000**	98.518	0.560

Significant values of risk ratio are highlighted in bold. I – incident, P – prevalent, TRS – treatment-resistant schizophrenia, FGA – first-generation antipsychotic, SGA, second-generation antipsychotic, LAI – long-acting injectable antipsychotic, NA – not available

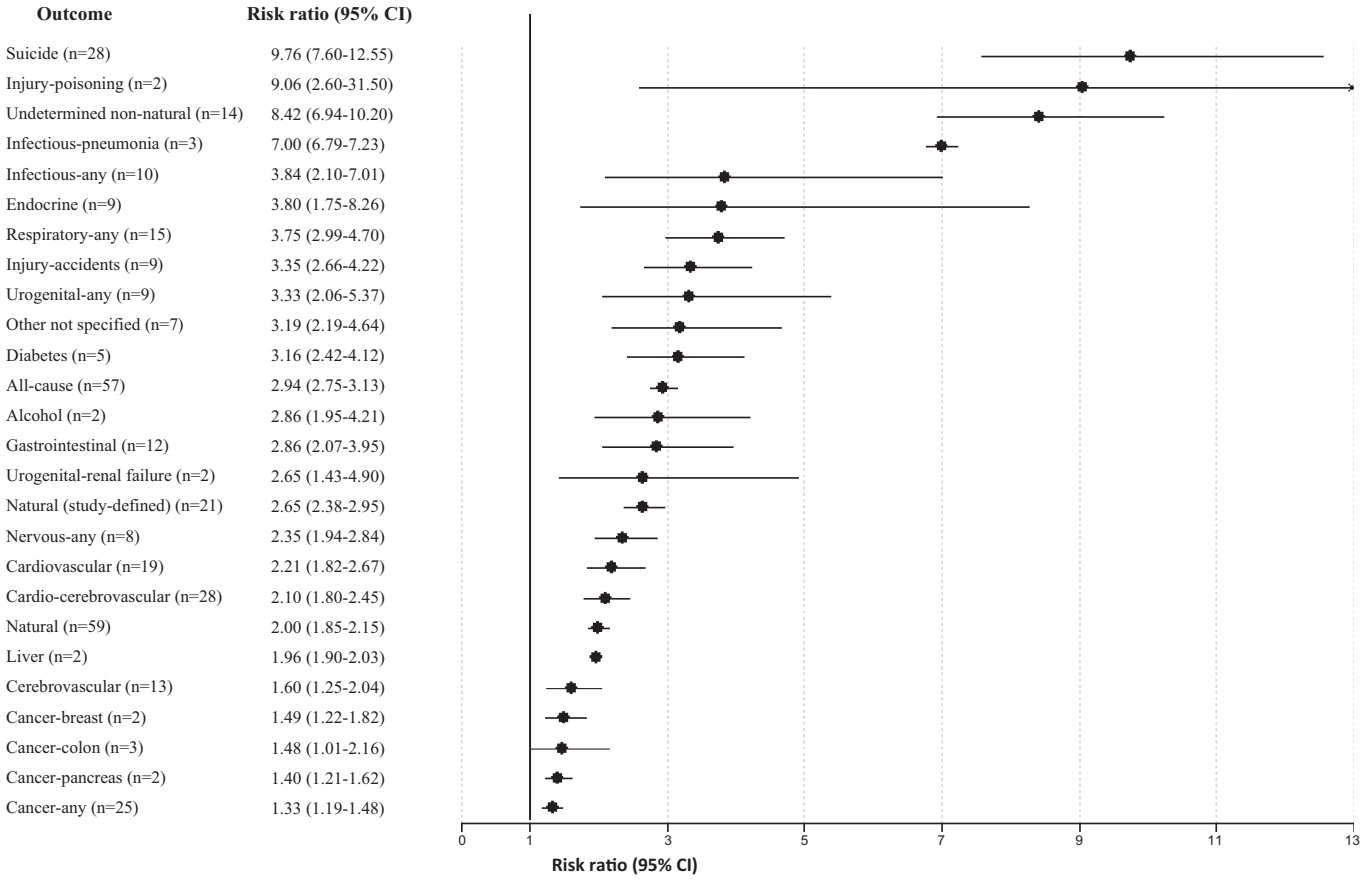

Figure 2 Significant findings for all-cause and cause-specific mortality risk in incident plus prevalent schizophrenia versus the general population

and fill analyses, which confirmed the magnitude and significance of the primary findings (with a fail-safe N ranging from 235 to 282,469), except for a slight reduction of the effect size in comparison with physical disease-matched controls (four studies trimmed, RR=1.35, 95% CI: 1.17-1.56) (see also supplementary information).

Additional secondary outcomes: other specific-cause mortality

Cardiovascular and/or cerebrovascular diseases

Across 30 studies, schizophrenia was associated with higher cardio-cerebrovascular-related mortality compared with either the general population or control groups matched for a physical illness (RR=2.03, 95% CI: 1.68-2.45, I^2=99.5%) (see Table 2). Separating causes, higher mortality from cardiovascular diseases (RR=2.09, 95% CI: 1.76-2.47, I^2=99.3%, n=25) as well as from cerebrovascular diseases (RR=1.46, 95% CI: 1.17-1.82, I^2=97.4%, n=16) was observed among individuals with schizophrenia (see Table 2).

Comparing schizophrenia with the general population, significant findings emerged for the composite mortality outcome (RR=2.10, 95% CI: 1.80-2.45, I^2=99.0%, n=28), as well as for mortality due to cardiovascular diseases (RR=2.21, 95% CI: 1.82-2.67, I^2=99.4%, n=19) and to cerebrovascular diseases (RR=1.60, 95% CI: 1.25-2.04, I^2=97.7%. n=13). Mortality due to cardio-cerebrovascular diseases was substantially higher in incident (RR=3.47, 95% CI: 1.79-6.72, I^2=97.9%, n=4) than in prevalent schizophrenia (RR=1.98, 95% CI: 1.73-2.27, I^2=97.7%, n=24) (see Table 2 and Figure 2).

Compared with physical disease-matched controls, patients with schizophrenia had significantly higher mortality from cardiovascular diseases (RR=1.86, 95% CI: 1.39-2.47, I^2=91.7%, n=7), including cohorts that were specifically matched for acute myocardial infarction (RR=1.85, 95% CI: 1.52-2.25, I^2=73.6%, n=4) (see Table 2).

Other specific causes

Individuals with schizophrenia had significantly higher mortality than the general population from pneumonia (RR=7.00, 95% CI: 6.79-7.23, n=3), any infectious diseases (RR=3.84, 95% CI: 2.10-7.01, n=10), any endocrine diseases (RR=3.80, 95% CI: 1.75-8.26, n=9), any respiratory diseases (RR=3.75, 95% CI: 2.99-

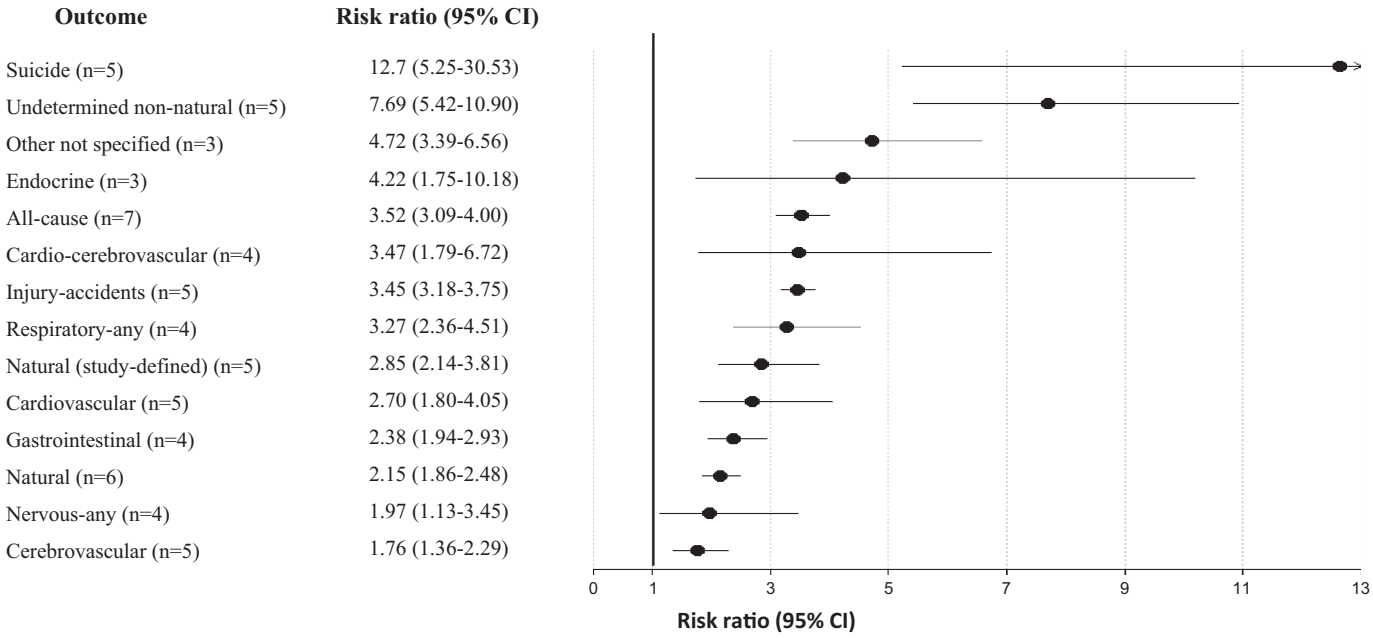

Figure 3 Significant findings for all-cause and cause-specific mortality risk in incident schizophrenia versus the general population

4.70, n=15), any urogenital diseases (RR=3.33, 95% CI: 2.06-5.37, n=9), diabetes mellitus (RR=3.16, 95% CI: 2.42-4.12, n=5), any gastrointestinal diseases (RR=2.86, 95% CI: 2.07-3.95, n=12), any neurological diseases (RR=2.35, 95% CI: 1.94-2.84, n=8), any liver diseases (RR=1.96, 95% CI: 1.90-2.03, n=2), and any cancer (RR=1.33, 95% CI: 1.19-1.48, n=25) (see Table 2 and Figure 2).

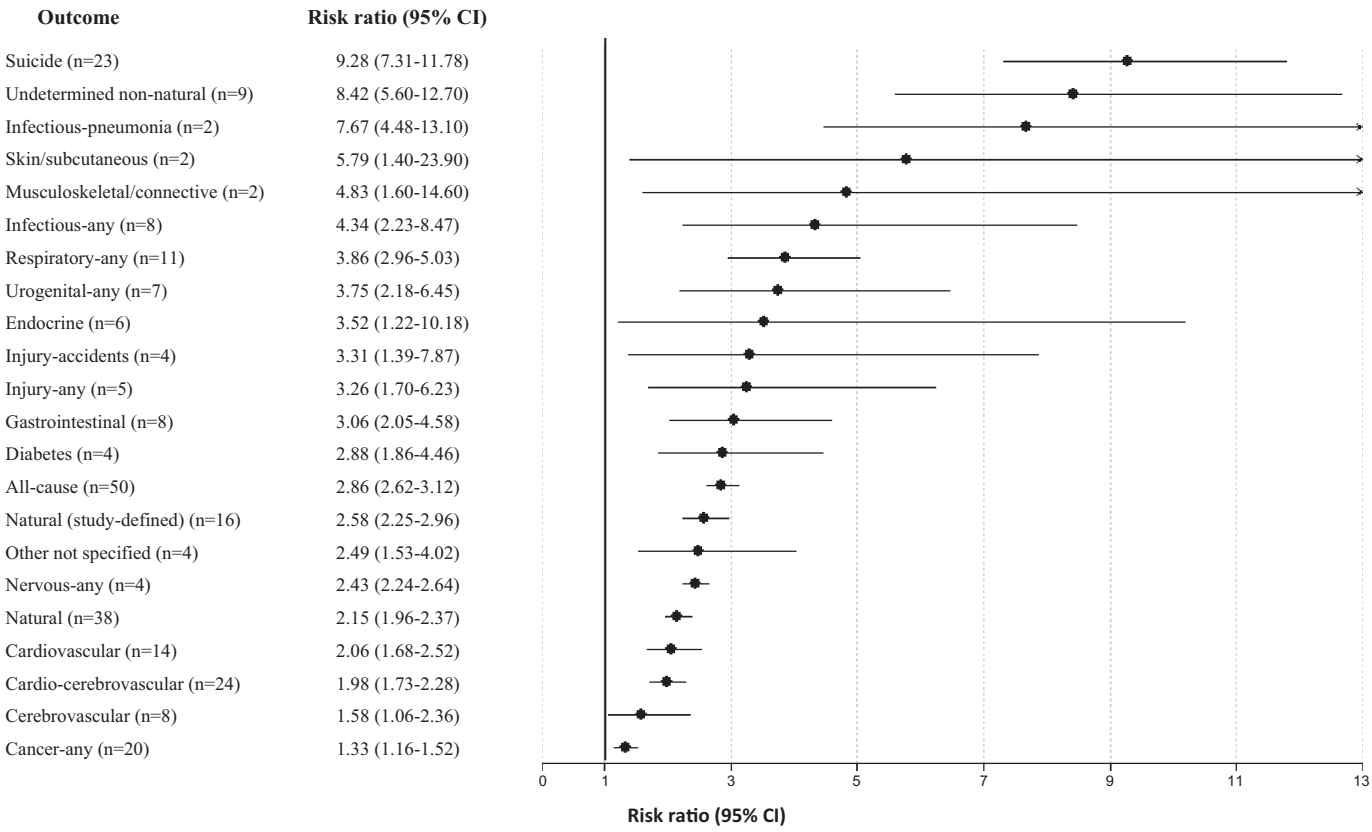

Figure 4 Significant findings for all-cause and cause-specific mortality risk in prevalent schizophrenia versus the general population

Among individuals with schizophrenia, mortality was significantly higher than the general population also from injury-poisoning (RR=9.06, 95% CI: 2.60-31.50, n=2) and undetermined non-natural causes (RR=8.42, 95% CI: 6.94-10.20, n=14) (see Figure 2 and supplementary information).

In incident schizophrenia, no significant association was found with death due to cancer (RR=1.31, 95% CI: 0.98-1.76, n=5), whereas the association was observed in prevalent schizophrenia (RR=1.33, 95% CI: 1.16-1.52, n=20) (see Table 2 and Figure 4). There was instead a significantly increased risk of mortality in both incident and prevalent schizophrenia cohorts due to endocrine diseases (incident: RR=4.22, 95% CI: 1.75-10.18, n=3; prevalent: RR=3.52, 95% CI: 1.22-10.18, n=6), gastrointestinal diseases (incident: RR=2.38, 95% CI: 1.94-2.93, n=4; prevalent: RR=3.06, 95% CI: 2.04-4.58, n=8), neurological diseases (incident: RR=1.97, 95% CI: 1.13-3.45, n=4; prevalent: RR=2.43, 95% CI: 2.24-2.64, n=4) and respiratory diseases (incident: RR=3.27, 95% CI: 2.36-4.51, n=4; prevalent: RR=3.86, 95% CI: 2.96-5.03, n=11) (see Table 2 and Figures 2-4).

Subgroup analyses and meta-regression

Use of any antipsychotic versus non-use was associated with a reduction of all-cause mortality in patients with incident plus prevalent schizophrenia (RR=0.71, 95% CI: 0.59-0.84, I^2=97.7%, n=11). Reduction of all-cause mortality risk versus no antipsychotic treatment differed significantly across antipsychotic subgroups (p=0.0001), in descending order as follows: any SGA LAI (RR=0.39, 95% CI: 0.27-0.56, I^2=81.0%, n=3), clozapine (RR=0.43, 95% CI: 0.34-0.55, I^2=77.9%, n=3), any LAI (RR=0.47, 95% CI: 0.39-0.58, I^2=91.8%, n=2), any oral SGA (RR=0.47, 95% CI: 0.45-0.50, I^2=18.9%, n=4), any first-generation antipsychotic (FGA) LAI (RR=0.50, 95% CI: 0.43-0.57, I^2=68.9%, n=3), any SGA (RR=0.53, 95% CI: 0.44-0.63, I^2=91.0%, n=4), any oral antipsychotic (RR=0.64, 95% CI: 0.51-0.80, I^2=95.9%, n=4), and any FGA (RR=0.73, 95% CI: 0.55-0.97, I^2=97.0%, n=5). There was a borderline significant all-cause mortality reduction among individuals with treatment-resistant schizophrenia who received clozapine compared with other medications (RR=0.70, 95% CI: 0.49-1.00, I^2=57.9%, n=5) (see Figure 5 and supplementary information).

In incident schizophrenia, the largest protective association emerged for SGA LAIs (RR=0.15, 95% CI: 0.04-0.55, n=1), whereas the protective effect was not significant for any oral antipsychotics, or FGA in any formulation (p=0.07 for comparison across antipsychotics). In prevalent schizophrenia, the largest association emerged for SGA LAIs again (RR=0.42, 95% CI: 0.29-0.59, n=2), and the smallest for any antipsychotic (RR=0.69, 95% CI: 0.57-0.84, n=7) (p=0.0001 for comparison across antipsychotics) (see supplementary information).

Use of any antipsychotic versus non-use was not associated with a reduction of suicide-related mortality in patients with incident plus prevalent schizophrenia (RR=0.73, 95% CI: 0.47-1.12, I^2=94.4%, n=4). Reduction of suicide-related mortality versus no antipsychotic treatment differed significantly across antipsychotic subgroups (p=0.0001), in descending order as follows: clozapine (RR=0.22, 95% CI: 0.16-0.30, I^2=0%, n=2), any SGA LAI (RR=0.43, 95% CI: 0.24-0.78, I^2 not available, n=1), any LAI (RR=0.60, 95% CI: 0.47-0.77, I^2 not available, n=1), any SGA oral (RR=0.64, 95% CI: 0.54-0.74, I^2=0, n=2), any FGA LAI (RR=0.64, 95% CI: 0.49-0.85, I^2 not available, n=1), and any SGA (RR=0.68, 95% CI: 0.56-0.82, I^2=44.2%, n=2). In contrast, compared to no antipsychotic, any FGA (RR=1.05, 95% CI: 0.37-2.99, I^2=97.2%, n=2) and oral FGAs (RR=1.13, 95% CI: 0.33-3.93, I^2=95.7%, n=2) did not protect individuals with schizophrenia against suicide-related mortality (see Figure 5 and supplementary information).

In incident schizophrenia, the largest protective association regarding suicide-related mortality emerged for clozapine (RR=0.29, 95% CI: 0.14-0.62, n=1), while, in contrast, oral FGAs were associated with increased mortality (RR=2.17, 95% CI: 1.36-3.48, n=1) (p=0.0001 for comparison across antipsychotics). In prevalent schizophrenia, the lowest risk of suicide-related mortality emerged for clozapine (RR=0.21, 95% CI: 0.15-0.29, n=1), and the closest to null effect emerged for any antipsychotic (RR=0.73, 95% CI: 0.36-1.49, n=2) (p=0.0001 for comparison across antipsychotics) (see supplementary information).

In incident plus prevalent schizophrenia, any antipsychotic versus no antipsychotic use was protective against natural causes of mortality (RR=0.76, 95% CI: 0.59-0.97, I^2=90.7%, n=3). Reduction of natural-cause mortality versus no antipsychotic treatment differed significantly across antipsychotic subgroups (p=0.04), in descending order as follows: clozapine (RR=0.50, 95% CI: 0.29-0.86, I^2=21.3%, n=2), any oral SGA (RR=0.57, 95% CI: 0.52-0.62, I^2=0%, n=2), any oral antipsychotic (RR=0.62, 95% CI: 0.59-0.66, I^2 not available, n=1), any SGA (RR=0.65, 95% CI: 0.48-0.89, I^2=71.4%, n=2), any SGA LAI (RR=0.66, 95% CI: 0.52-0.84, I^2 not available, n=1), any LAI (RR=0.69, 95% CI: 0.62-0.77, I^2 not available, n=1), any FGA LAI (RR=0.70, 95% CI: 0.62-0.78, I^2 not available, n=1). In contrast, any FGA or any oral FGA were not associated with lower natural-cause mortality (see Figure 5 and supplementary information).

In incident schizophrenia, no significant reduction of natural-cause mortality emerged for any antipsychotic subgroup versus no antipsychotic use. Oral FGAs were associated with increased natural-cause mortality (RR=2.20, 95% CI: 1.29-3.77, n=1) (p=0.0004 for comparison across antipsychotics). In prevalent schizophrenia, the largest protective effect emerged for clozapine (RR=0.55, 95% CI: 0.47-0.64, n=1), and the smallest for FGA LAIs (RR=0.70, 95% CI: 0.62-0.78, n=1) (p=0.0005 for comparison across antipsychotics) (see supplementary information).

In subgroup analyses of incident plus prevalent schizophrenia cohorts by age, the risk of all-cause mortality was significantly higher for patients aged <40 vs. ≥40 years (RR=3.93, 95% CI: 3.34-4.63 vs. RR=2.66, 95% CI: 2.18-3.26, p=0.003). A similar difference was observed for suicide-related mortality (RR=17.58, 95% CI: 12.36-24.99 vs. RR=4.69, 95% CI: 1.77-12.45, p=0.01). There was no significant difference between the two age groups for natural-cause mortality (see supplementary information).

No consistent and significant differences emerged from subgroup analyses considering nationwide versus other samples,

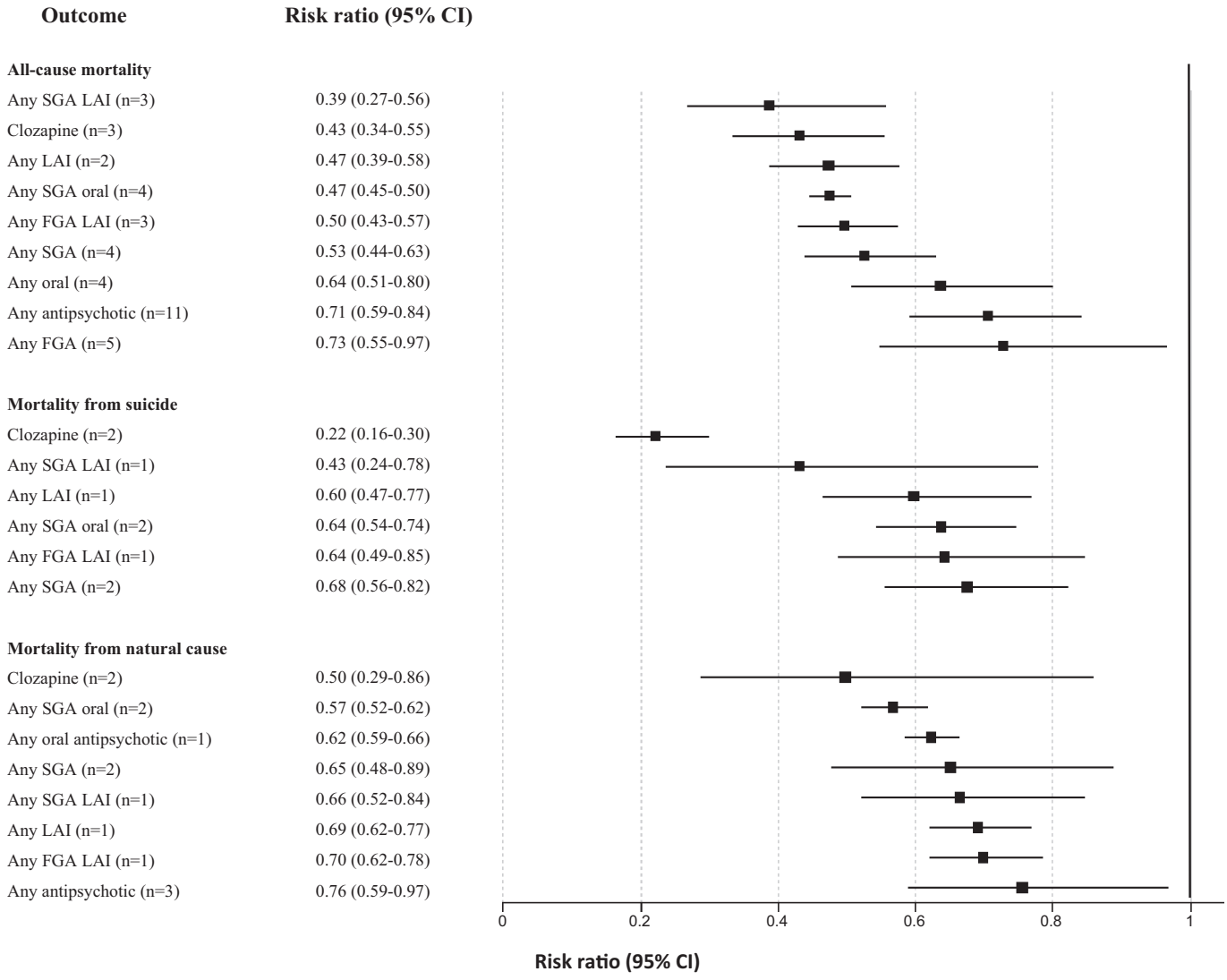

Figure 5 Findings in subgroup analyses of mortality risk due to any cause, suicide, and natural death by antipsychotic treatment within incident plus prevalent schizophrenia versus no antipsychotic. FGA – first-generation antipsychotic, SGA – second-generation antipsychotic, LAI – long-acting injectable antipsychotic

quality of studies, and adjustment of results, suggesting that findings concerning mortality are not systematically influenced by these moderators (see supplementary information).

In meta-regression analyses, we found in incident plus prevalent schizophrenia a significant increase of all-cause mortality (beta=0.0009, 95% CI: 0.001-0.02, p=0.02) and of natural-cause mortality (beta=0.01, 95% CI: 0.006-0.02, p=0.0002) with increasing median year of study publication, without a significant time trend for suicide-related mortality (beta=0.006, 95% CI: –0.01 to 0.03, p=0.56) (see supplementary information).

For all-cause mortality, in incident plus prevalent schizophrenia, more recent study year moderated a larger protective effect of any antipsychotic (beta=–0.11, 95% CI: –0.15 to –0.06) and of oral FGA versus no antipsychotic (beta=–0.11, 95% CI: –0.17 to –0.05). Similarly, for suicide-related mortality, more recent study year moderated a larger protective effect of any FGA versus no antipsychotic in incident plus prevalent schizophrenia (beta=–0.27, 95% CI: –0.36 to –0.18).

Longer duration of follow-up and more variables used to adjust the analyses increased the protective effect against suicide-related mortality of any antipsychotic in prevalent schizophrenia (beta=–0.14, 95% CI: –0.24 to –0.04, and beta =–0.23, 95% CI: –0.40 to –0.06, respectively). Higher percentage of females increased the risk of suicide-related mortality in incident schizophrenia (beta=0.36, 95% CI: 0.23-0.49, p<0.0001).

For natural-cause mortality, the protective effect of any FGA versus no antipsychotic in incident plus prevalent schizophrenia was increased by more recent study year (beta=–0.23, 95% CI: –0.33 to –0.13) and more variables used to adjust the analyses (beta=–0.12, 95% CI: –0.17 to –0.07). Natural-cause mortality versus any other population was greater in higher quality studies in incident plus prevalent schizophrenia (beta=0.11, 95% CI: 0.04-

0.18). Natural-cause mortality versus the general population was also greater in higher quality studies in incident plus prevalent schizophrenia (beta=0.13, 95% CI: 0.06-0.20), as well as in incident schizophrenia (beta=0.20, 95% CI: 0.08-0.31) and in prevalent schizophrenia (beta=0.11, 95% CI: 0.02-0.19). Natural-cause mortality was also larger, in incident schizophrenia, with higher number of variables that analyses were adjusted for (beta=0.12, 95% CI: 0.06-0.18).

DISCUSSION

Schizophrenia is one of the mental disorders with the highest mortality risk. This meta-analysis of 135 cohort studies comparing 4.5 million schizophrenia patients with about 1.11 billion people from the general population comprehensively quantified this increased risk. Specifically, we observed a 2.9-fold increased all-cause mortality in patients with schizophrenia versus the general population, and a somewhat lower but still significantly 1.6-fold increased risk versus physical disease-matched general population controls.

In addition, we identified significantly greater specific-cause mortality among individuals with schizophrenia versus the general population, which was particularly pronounced for suicide (9.7-fold); other non-natural causes, including poisoning (8- to 9-fold); and pneumonia (7-fold). The mortality risk remained greater for infectious, endocrine and respiratory diseases (3.7-3.8-fold); injury or accidents (3.3-fold); diabetes mellitus (3.2-fold); alcohol use and gastrointestinal diseases (2.9-fold); urogenital diseases (2.6-fold); neurological diseases (2.3-fold); cardiovascular diseases (2.2-fold); liver diseases (2-fold); and cerebrovascular diseases (1.6-fold); also extending to breast, colon, pancreas and any cancer (1.3- to 1.5-fold).

The relative increase in mortality compared to the general population was larger in incident (i.e., earlier-phase) than prevalent (i.e., more chronic) schizophrenia cohorts. Moreover, all-cause and suicide-related mortality were higher in patients <40 years old, whereas this was not the case for natural-cause mortality. Comorbid substance use disorder increased the all-cause mortality gap, while antipsychotic treatment versus no treatment decreased this gap. The largest protective effect was observed with SGA LAIs and clozapine. In contrast to this protective effect, FGAs increased suicide-related and natural-cause mortality in incident schizophrenia.

We found that first-episode schizophrenia was associated with a 7.4-fold higher all-cause mortality risk versus the general population, indicating the critical importance of providing a swift and accurate diagnosis followed by initiating effective treatment. The lifetime prevalence of completed suicide in patients with schizophrenia has been reported to be 5.6%, with the majority of these suicides occurring near illness onset[167]. Moreover, suicide attempts have been found to be predicted by greater severity of psychotic illness and of depressive symptoms[168], two factors that should prompt clinicians to screen for and guard against suicide attempts in the early phase of the illness. Furthermore, our finding that females with schizophrenia have a significantly higher risk increase than males for suicide-related mortality compared to the general population should prompt clinicians to extend the focus from males, who are still at the highest risk for completed suicide[169], to this additional high-risk group.

All-cause mortality was increased in persons with schizophrenia even when they were matched with general population controls for many relevant physical diseases. These included cardiovascular, cerebrovascular, endocrine, gastrointestinal, infectious, liver, neurological, respiratory and urogenital diseases, diabetes mellitus and cancer. Importantly, the relative mortality risk for cardio-cerebrovascular diseases was substantially greater in the incident (RR=3.47) versus prevalent (RR=1.98) cohorts, which is perhaps reflective of the lower overall frequency of these diseases in the younger general population and of their earlier onset in people with schizophrenia, likely due to poorer lifestyle behaviors[170-172] and to the effect of antipsychotic and other medications[21,173].

Disparities between individuals with schizophrenia and the general population with respect to the implementation of screening procedures (e.g., for cardiovascular risk factors and disorders, and for cancer) and the quality of medical care, including a lack of advice for lifestyle changes such as smoking cessation and physical activity, have been repeatedly reported[2,27,28,43,174,175]. Addressing smoking is of particular importance, given the 70-162% increased risk of asthma, chronic obstructive pulmonary disease and pneumonia in subjects with schizophrenia[176], and considering our finding that pneumonia confers the highest risk of death among natural causes. Thus, to close the mortality gap in individuals with schizophrenia, smoking cessation interventions, cardiovascular and cancer screening and monitoring, consistent healthy lifestyle instructions, as well as early interventions for detected physical diseases, should be regarded as imperative. Since individuals with schizophrenia may be less likely to receive or seek help from a medical health care provider than people from the general population, mental health care providers need to orchestrate physical care for these individuals as part of a comprehensive and collaborative care model[17].

Comorbid substance use disorders were found in our meta-analysis to be a significant risk factor for increased mortality in people with schizophrenia. This finding is likely due to the multiple adverse physical as well as intentional or accidental suicide-related effects of these disorders[177-181]. Additionally, comorbid substance use, and cannabis use in particular, can worsen adherence to antipsychotics[182-184]. All these factors point to the need to screen for and address substance use disorders as early as possible when treating patients with schizophrenia[185,186].

This meta-analysis found that, compared with no antipsychotic use, antipsychotic treatment was associated with reduced all-cause mortality in patients with schizophrenia. Specifically, factors associated with a reduction in all-cause mortality included the use of any LAI, any SGA and, especially, of clozapine. These findings support prior research which found that continuous clozapine use was associated with significantly lower long-term all-cause mortality compared with other antipsychotics in patients with schizophrenia, despite the adverse impact of clo-

zapine on cardiometabolic risk factors[187]. We also observed a borderline significant reduction in all-cause mortality among patients with treatment-resistant schizophrenia who were treated with clozapine compared with other antipsychotics, with lack of significance likely being due to low power of these analyses.

Recently, a Finnish national database study[20] indicated that patients with schizophrenia who were taking antipsychotics, especially LAIs and clozapine, were significantly less likely to interrupt ongoing treatment with statins, antidiabetic agents, anti-hypertensive medications, and beta-blockers. Such an association between the use of antipsychotics and better adherence to medical treatments – and potentially also closer and more regular medical monitoring as might be the case with clozapine and LAIs – is likely to be a mediator of the protective effect of antipsychotic use on mortality risk in people with schizophrenia. Studies that specifically test this hypothesis are warranted.

The use of any SGA or clozapine also had a significant protective effect against suicide-related mortality in prevalent schizophrenia, compared with no use of antipsychotics, which was not observed with FGAs. While the anti-suicidal efficacy of clozapine has been established[188], the differential finding favoring SGAs may be due to the fact that suicide in schizophrenia is often associated with the emergence of depression[168]. FGAs do not improve or even induce depressive symptoms, while many SGAs have been shown to be effective in treating these symptoms[189-191].

We found that, in incident schizophrenia, FGAs were even associated with an increased mortality risk due to suicide. This finding should caution against the use of these medications as first-line agents, in particular in earlier-phase patients. The fact that this increased mortality risk in incident schizophrenia was not found with FGA LAIs points to a potentially mediating effect of poorer adherence with oral FGAs or a protective effect of LAI use due to increased surveillance and, possibly, treatment of emergent depression.

Thus, in addition to underscoring the importance of comprehensive physical health monitoring and integrated or collaborative care to address and improve both physical and mental health problems in patients with schizophrenia, this meta-analysis points to the need for antipsychotic maintenance treatment, monitoring for and mitigating antipsychotic non-adherence, also through a broader and earlier consideration of SGA LAIs. Furthermore, our findings point to the need to screen for and treat substance use disorders as well as depression as important clinical strategies to reduce overall and specific-cause mortality in individuals with schizophrenia.

We found a slight but significant increase of the excess mortality in people with schizophrenia by median study year of investigation (ranging from 1957 to 2021). This finding further emphasizes the urgency with which the mortality gap in these people needs to be addressed.

Among the strengths of this meta-analysis are the large number of studies (n=135) that met the inclusion criteria, the substantial number of patients with schizophrenia (4,536,447) and general population controls (1,115,600,059); and the high quality of the studies included, with results being consistent and robust even after all trim and fill analyses. Moreover, directions for future research are provided, as analyses adjusted for more potentially relevant confounders and longer follow-up were associated with greater protective effects of antipsychotic medications against the increased mortality risk.

However, the results of this meta-analysis have to be interpreted within its limitations. First, meta-analyzed studies were observational cohort investigations. Their non-randomized nature cannot imply causality. However, since mortality is a relatively rare and late-onset/distal event, randomized controlled trials – that generally include relatively few individuals, have a modest follow-up duration and many dropouts, and that also exclude many patients that may be more severely mentally and physically ill[192] – are not the best or most feasible studies to quantify mortality risk and identify generalizable aggravating and protective factors. For the study of mortality risk, longitudinal cohort and, especially, nationwide database studies represent more appropriate study options. Furthermore, consistent with our meta-analysis, two smaller meta-analyses focusing on patients in randomized controlled trials reported similar results – i.e., an about 30-50% lower mortality among patients randomized to antipsychotics compared with patients randomized to placebo[193,194].

Second, although we were able to include as many as 135 individual studies, with a large number of individuals with schizophrenia and even more control subjects from the general population, some findings were based on five or fewer studies. The need for additional studies is particularly important with respect to the quantitative evaluation of specific factors that increase or decrease the existing mortality gap. Third, there was substantial inconsistency in the definitions of age groups across the included studies, which limited our ability to comprehensively analyze the effect of age on all-cause and specific-cause mortality risk. Future studies should report age both categorically across relevant age groups as well as continuously.

Fourth, few studies specifically evaluated mortality risk in patients with first-episode or treatment-resistant schizophrenia, two subgroups of considerable clinical interest. Fifth, some studies did not quantify the number of the general population control group, but used instead regional or nationwide control groups restricted to certain time periods and/or age groups. In such instances, we estimated the number of general population controls based on census-based (sub)population numbers at the time of data collection, which may have introduced some imprecision. Sixth, studies used different metrics to report mortality: in order to pool results, we combined risk estimates that have somewhat different characteristics, which could have led to some imprecision. However, since mortality is a relatively rare event and since all included studies used the same cohort design and evaluated the same population of interest, the degree of imprecision is likely low.

Finally, although we preferred the risk estimate that was adjusted for the most likely potential confounders, we also included unadjusted risk estimates, and adjustments may not have included all/the most relevant covariates that are associated with mortality risk. However, we were not interested in isolating the genetic or narrowly illness-related effect of schizophrenia on mortality

risk, but rather in estimating the differential risk of all-cause and specific-cause mortality in individuals with schizophrenia who differ in many psychological, behavioral, social and environmental respects from the general population and other control groups. The potential residual confounding from a statistical standpoint, therefore, represents the reality of individuals living with schizophrenia and ensures the desired generalizability of the findings.

CONCLUSIONS

This meta-analysis provides the largest and most comprehensive quantitative assessment of the all-cause and detailed specific-cause mortality risk of individuals with schizophrenia versus the general population and other control groups, additionally focusing on reported aggravating and protective factors. It confirms that the mortality gap between patients with and without schizophrenia is high, being highest for suicide-related mortality but extending to multiple other specific-cause mortality reasons. Results of this mortality gap in individuals with schizophrenia were based on high-quality data in >97% of the studies and were robust and confirmed in multiple subgroup and meta-regression analyses. Importantly, the increased mortality was associated with certain modifiable risk factors, which can inform clinical practice.

Consistent and long-term use of SGAs, SGA LAIs and, if indicated, clozapine in patients with schizophrenia across all stages of illness can reduce the mortality risk, as antipsychotics are protective compared to non-use of antipsychotics against many kinds of mortality, including that due to cardio-cerebrovascular disease. This finding indicates that even antipsychotics with elevated cardiometabolic adverse effects, such as clozapine, can reduce overall mortality, which is not counterbalanced by larger but supported by reduced cardiometabolic-related mortality. Results were confirmed or even stronger in more recent, higher quality, adjusted studies, and those with longer follow-up. Finally, despite heightened awareness of the mortality gap of people with severe mental illness and especially with schizophrenia, this gap seems to be increasing slightly with time, including data as recent as 2021.

These results underscore the urgency with which the mortality disparity in individuals with schizophrenia need to be addressed at multiple levels. Clinicians should routinely monitor patients with schizophrenia for cardiovascular risk and physical diseases and also screen for and address substance use disorders and depression. In addition, they should screen patients with first-episode schizophrenia, both males and females, for suicide risk and depression, and avoid FGAs.

Overall, integrated mental and physical health care of individuals with schizophrenia must be at the center of mental health research and policy making agendas. Data from this meta-analysis point to the responsibility of reducing mortality risk by screening for and optimizing the management of physical as well as psychiatric comorbidities, and by earlier use of LAIs and, if indicated, clozapine in individuals with schizophrenia. This information should be considered by treatment guidelines and incorporated into actionable policies by health care administrators.

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Patterns and correlates of patient-reported helpfulness of treatment for common mental and substance use disorders in the WHO World Mental Health Surveys

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Patient-reported helpfulness of treatment is an important indicator of quality in patient-centered care. We examined its pathways and predictors among respondents to household surveys who reported ever receiving treatment for major depression, generalized anxiety disorder, social phobia, specific phobia, post-traumatic stress disorder, bipolar disorder, or alcohol use disorder. Data came from 30 community epidemiological surveys – 17 in high-income countries (HICs) and 13 in low- and middle-income countries (LMICs) – carried out as part of the World Health Organization (WHO)'s World Mental Health (WMH) Surveys. Respondents were asked whether treatment of each disorder was ever helpful and, if so, the number of professionals seen before receiving helpful treatment. Across all surveys and diagnostic categories, 26.1% of patients (N=10,035) reported being helped by the very first professional they saw. Persisting to a second professional after a first unhelpful treatment brought the cumulative probability of receiving helpful treatment to 51.2%. If patients persisted with up through eight professionals, the cumulative probability rose to 90.6%. However, only an estimated 22.8% of patients would have persisted in seeing these many professionals after repeatedly receiving treatments they considered not helpful. Although the proportion of individuals with disorders who sought treatment was higher and they were more persistent in HICs than LMICs, proportional helpfulness among treated cases was no different between HICs and LMICs. A wide range of predictors of perceived treatment helpfulness were found, some of them consistent across diagnostic categories and others unique to specific disorders. These results provide novel information about patient evaluations of treatment across diagnoses and countries varying in income level, and suggest that a critical issue in improving the quality of care for mental disorders should be fostering persistence in professional help-seeking if earlier treatments are not helpful.

Key words: Helpfulness of treatment, professional help-seeking, heterogeneity of treatment effects, patient-centered care, treatment adherence, mood disorders, anxiety disorders, post-traumatic stress disorder, substance use disorders, precision psychiatry

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Mental and substance use disorders are highly prevalent worldwide. Conservative estimates indicate that approximately 20% of individuals meet criteria for a mental disorder within the past 12 months, with lifetime rates of about 30%[1,2]. Mental and substance

use disorders are associated with marked distress, impairment in everyday life functioning, and early mortality[e.g.,3-5]. The economic costs of these disorders to individuals, families and society are enormous, encompassing lost income and productivity, disability payments, and costs of health care and social services[6,7].

Randomized controlled trials (RCTs) have documented that a range of pharmacological and psychosocial treatments are effective in treating many people with mental and substance use disorders. Questions can be raised, though, about the generalizability of the results of RCTs, as these studies are mostly carried out in high-income countries (HICs) and exclude patients with the complex comorbidities known to be very common in the real world.

In addition, outside the context of controlled trials, patients often seek multiple treatments over time and across multiple settings. RCTs do not provide information over the life course and the many different services patients seek over time. It is important to understand this process and whether it varies as a function of disorders.

Although symptom reduction is typically the primary and often exclusive focus of clinical trials, patients are known to have broader notions about what constitutes effective treatment[8]. It is essential to evaluate treatment effectiveness from the patient perspective in real-world settings. A broad assessment of patient-reported treatment helpfulness can be a useful first step in doing this, by allowing patients to provide an overall summary evaluation of how treatment has affected their well-being and functioning in life domains important to them.

The likelihood of help-seeking leading to a treatment that the patient considers helpful is a joint function of: a) the probability that a given patient will consider a specific treatment helpful and b) the probability that the patient will persist in help-seeking if a prior treatment was not helpful. Population-based surveys provide the opportunity to trace these two pathways over many patients, identify both aggregate distributions, and examine predictors of receiving patient-defined helpful treatment, as mediated through these two pathways.

We carried out a series of disorder-specific investigations that looked at the extent to which individuals view their treatment as helpful. The disorders included major depressive disorder, bipolar disorder, generalized anxiety disorder, post-traumatic stress disorder (PTSD), social phobia, specific phobia, and alcohol use disorder. These investigations were conducted in a cross-national series of general population surveys that asked respondents about their lifetime experiences of seeking professional treatments. The samples were drawn from both HICs and low/middle-income countries (LMICs). Prior reports focused on individual disorders[9-15]. We found that the great majority of people in the general population who seek treatment for mental disorders believe that they were helped. However, no one treatment was found to be helpful for all patients, and only a minority of patients reported that they were helped by the first professional from whom they received treatment. Perseverance was required to obtain treatment that patients considered helpful. However, substantial proportions of patients reported that they gave up their professional help-seeking efforts before helpful treatment was received, even though many of these individuals continued to suffer.

The present study provided an opportunity to address new questions by looking at the data across all disorders. We had several goals: to estimate variation across disorders in the proportion of patients reporting that their treatment was helpful; to examine the number of professionals that patients needed to see to receive a treatment that they considered helpful; to examine persistence in professional help-seeking among patients whose earlier treatments were not helpful; to estimate consistency across disorders of predictors of helpfulness at the patient-disorder level; and to disaggregate the significant predictors into the separate associations predicting helpfulness of individual professionals and persistence in help-seeking after earlier treatments not being helpful. It is plausible to expect differences across disorders because treatments are not equally available or effective for all disorders.

We also looked at variation between HICs and LMICs in reported helpfulness of treatment and persistence in help-seeking, and tried to identify any common or unique factors that influence patient-reported treatment helpfulness and persistence in seeking further treatments across disorders and countries. Information about variations of these sorts may be helpful in identifying where emphasis is most needed for developing more effective treatments and/or providing more readily accessible services.

METHODS

Sample

The World Health Organization (WHO)'s World Mental Health (WMH) Surveys are a coordinated set of community epidemiological surveys administered to probability samples of the non-institutionalized household population in countries throughout the world[16].

Data for the present study come from 30 WMH surveys (Table 1). Seventeen surveys were carried out in countries classified by the World Bank as HICs (Argentina, Australia, Belgium, France, Germany, Israel, Italy, Japan, The Netherlands, New Zealand, Northern Ireland, Poland, Portugal, Saudi Arabia, the US, and two in Spain). The other thirteen surveys were conducted in countries classified as LMICs (Brazil, Iraq, Lebanon, Mexico, Nigeria, Peru, People's Republic of China, Romania, South Africa, and two each in Bulgaria and Colombia).

Twenty of these 30 surveys were based on nationally representative samples (14 in HICs, 6 in LMICs), three on samples of all urbanized areas in the country (Argentina, Colombia, Mexico), three on samples of selected states (Nigeria) or metropolitan areas (Japan, Peru), and four on samples of single states (Murcia, Spain) or metropolitan areas (Sao Paolo, Brazil; Medellin, Colombia; Shenzhen, People's Republic of China). Response rates ranged from 45.9% (France) to 97.2% (Medellin, Colombia) and averaged 68.9% across surveys.

Table 1 World Mental Health sample characteristics

Country	Sample composition	Field dates	Age range	Sample size		Response rate
				Part I	Part II	
High-income						
Argentina	Eight largest urban areas of the country (about 50% of total national population)	2015	18-98	3,927	2,116	77.3
Australia	Nationally representative	2007	18-85	8,463	8,463	60.0
Belgium	Nationally representative (selected from a national register of Belgium residents)	2001-2	18-95	2,419	1,043	50.6
France	Nationally representative (selected from a national list of households with listed telephone numbers)	2001-2	18-97	2,894	1,436	45.9
Germany	Nationally representative	2002-3	19-95	3,555	1,323	57.8
Israel	Nationally representative	2003-4	21-98	4,859	4,859	72.6
Italy	Nationally representative (selected from municipality resident registries)	2001-2	18-100	4,712	1,779	71.3
Japan	Eleven metropolitan areas	2002-6	20-98	4,129	1,682	55.1
The Netherlands	Nationally representative (selected from municipal postal registries)	2002-3	18-95	2,372	1,094	56.4
New Zealand	Nationally representative	2004-5	18-98	12,790	7,312	73.3
North Ireland	Nationally representative	2005-8	18-97	4,340	1,986	68.4
Poland	Nationally representative	2010-1	18-65	10,081	4,000	50.4
Portugal	Nationally representative	2008-9	18-81	3,849	2,060	57.3
Saudi Arabia	Nationally representative	2013-6	18-65	3,638	1,793	61.0
Spain	Nationally representative	2001-2	18-98	5,473	2,121	78.6
Spain (Murcia)	Regionally representative (Murcia region)	2010-2	18-96	2,621	1,459	67.4
United States	Nationally representative	2001-3	18-99	9,282	5,692	70.9
High-income total				89,404	50,218	63.0
Low/middle-income						
Brazil (São Paulo)	São Paulo metropolitan area	2005-8	18-93	5,037	2,942	81.3
Bulgaria 1	Nationally representative	2002-6	18-98	5,318	2,233	72.0
Bulgaria 2	Nationally representative	2016-7	18-91	1,508	578	61.0
Colombia	All urban areas of the country (about 73% of total national population)	2003	18-65	4,426	2,381	87.7
Colombia (Medellin)	Medellin metropolitan area	2011-2	19-65	3,261	1,673	97.2
Iraq	Nationally representative	2006-7	18-96	4,332	4,332	95.2
Lebanon	Nationally representative	2002-3	18-94	2,857	1,031	70.0
Mexico	All urban areas of the country (about 75% of total national population)	2001-2	18-65	5,782	2,362	76.6
Nigeria	21 of 36 states (57% of national population)	2002-4	18-100	6,752	2,143	79.3
Peru	Five urban areas (about 38% of total national population).	2004-5	18-65	3,930	1,801	90.2
People's Republic of China (Shenzhen)	Shenzhen metropolitan area	2005-7	18-88	7,132	2,475	80.0
Romania	Nationally representative	2005-6	18-96	2,357	2,357	70.9
South Africa	Nationally representative	2002-4	18-92	4,315	4,315	87.1
Low/middle-income total				57,007	30,623	80.6
Total				146,411	80,841	68.9

Measures

Interviews

The interview schedule used in the WMH surveys was the WHO Composite International Diagnostic Interview (CIDI) Version 3.0[17], a fully structured diagnostic interview designed to be used by trained lay interviewers. A standardized seven-day training program was given to all WMH interviewers across countries. The program culminated in an examination that had to be passed before the interviewer could be authorized to participate in data collection[18]. The interview schedule was developed in English and translated into other languages using a standardized WHO translation protocol[19].

Interviews were administered face-to-face in respondents' homes after obtaining informed consent using procedures approved by local institutional review boards. Interviews were in two parts. Part I was administered to all respondents and assessed core DSM-IV mental disorders (N=146,411 respondents across all surveys). Part II assessed additional disorders and correlates and was administered to 100% of respondents who met lifetime criteria for any Part I disorder plus a probability subsample of other Part I respondents (N=80,841).

Disorders

Although the CIDI generates diagnoses according to both ICD-10 and DSM-IV criteria, only DSM-IV criteria were used in the analyses reported here. We considered seven lifetime disorders: major depressive disorder, bipolar disorder (including bipolar I, bipolar II and sub-threshold bipolar disorder), four anxiety disorders (generalized anxiety disorder, PTSD, social phobia and specific phobia), and alcohol use disorder (either alcohol abuse without dependence or alcohol dependence). We carried out separate analyses of patient-reported treatment helpfulness for major depressive and manic/hypomanic episodes in bipolar disorder, so a total of eight diagnostic categories were considered.

A good concordance was found[20] between DSM-IV diagnoses based on the CIDI and those based on independent clinical reappraisal interviews carried out using the Structured Clinical Interview for DSM-IV[21]. Organic exclusions but not diagnostic hierarchy rules were used in making diagnoses. The CIDI included retrospective disorder age-of-onset reports based on a special question probing sequence that has been shown experimentally to improve recall accuracy[22]. In assessing age of onset, respondents were asked to date their age when they first met criteria for the full syndrome of each disorder, not the first symptom of the disorder.

Patient-reported treatment helpfulness

Respondents who met lifetime DSM-IV criteria for each of the eight diagnostic categories were asked about age of onset and "*Did you ever (*emphasis in original*) in your life talk to a medical doctor or other professional about your…?" (*wording varied across diagnostic categories*)*. If the answer was yes, the interviewer went on to ask "*How old were you the first time* (emphasis in original) *you talked to a professional about your…?*" (same wording as prior question). The term "other professionals" was defined and presented to the respondent in a show card before asking this question as including psychologists, counselors, spiritual advisors, herbalists, acupuncturists, and other healing professionals.

Respondents who said that they had talked to a professional were then asked "*Did you ever get treatment for your …* (same wording as in prior question) *that you considered helpful or effective?*" (emphasis in original). The next question then varied depending on whether the respondent reported ever receiving helpful or effective treatment. If so, the interviewer asked "*How many professionals did you ever* (emphasis in original) *talk to about your…* (same wording as in prior question) *up to and including the first time you ever got helpful treatment?"*. If, on the other hand, the respondent reported never receiving helpful or effective treatment, the interviewer asked "*How many professionals did you ever* (emphasis in original) *talk to about your…?*" (same wording as in prior question). We focused on respondents who reported treatment starting no earlier than 1990.

Predictors

We considered six different kinds of predictors of patient-reported treatment helpfulness: focal diagnostic category, socio-demographics, prior lifetime comorbidities, treatment type(s) received, treatment timing, and childhood adversities.

Focal diagnostic category was represented as a series of eight dummy-coded predictor variables that allowed us to examine the significance of differences across the above-mentioned categories in patient-reported treatment helpfulness. Socio-demographic characteristics included age at first treatment (continuous), gender, marital status (married, never married, previously married) at the time of first treatment, level of educational attainment among non-students (quartiles defined by within-country distributions), and student status at the time of first treatment.

Prior lifetime comorbid conditions included lifetime onset of each of the other seven diagnostic categories considered here prior to age at first treatment of the focus diagnostic category. We also included two other comorbid diagnostic categories involving substance use disorders (substance dependence and substance abuse without dependence). The substances considered in the latter assessment included both prescription medications (used without a prescription or more than prescribed) and illicit drugs. The precise substances included in the assessment and the names used to describe them varied across surveys in line with differences in the drugs used in the countries. We did not include substance use disorders among the focal diagnostic categories because too few surveys assessed treatment helpfulness

Table 2 Lifetime prevalence of the DSM-IV disorders considered in the analysis, proportions of cases receiving treatment, and proportions of patients reporting that treatment was helpful

	Lifetime disorder prevalence			Respondents receiving treatment			Respondents reporting that treatment was helpful		
	%	SE	N	%	SE	N	%	SE	N
Major depressive disorder									
All	8.8	0.1	80,332	37.2	0.7	7,448	68.2	1.1	2,726
High-income countries	10.0	0.2	41,778	47.1	1.0	4,438	70.1	1.2	2,082
Low/middle-income countries	7.4	0.2	38,554	22.5	1.0	3,010	62.4	2.2	644
Generalized anxiety disorder									
All	4.5	0.1	113,226	34.6	0.8	5,674	70.0	1.4	1,897
High-income countries	5.3	0.1	76,775	38.4	0.9	4,617	70.9	1.4	1,701
Low/middle-income countries	2.8	0.1	36,451	19.2	1.8	1,057	62.8	4.9	196
Social phobia									
All	4.6	0.1	117,856	22.8	0.7	5,686	65.1	1.6	1,322
High-income countries	5.9	0.1	71,916	24.8	0.8	4,538	65.9	1.7	1,148
Low/middle-income countries	2.5	0.1	45,940	15.8	1.3	1,148	60.4	5.1	174
Specific phobia									
All	7.7	0.1	112,507	13.7	0.5	9,179	47.5	1.8	1,296
High-income countries	8.2	0.1	59,815	16.7	0.6	5,496	47.3	2.0	944
Low/middle-income countries	7.0	0.2	52,692	9.7	0.7	3,683	48.0	3.5	352
Post-traumatic stress disorder									
All	4.4	0.1	52,979	23.5	1.0	3,511	57.0	2.4	779
High-income countries	5.3	0.1	37,422	26.4	1.1	2,906	57.6	2.4	726
Low/middle-income countries	2.3	0.1	15,557	6.8	1.2	605	43.8	9.2	53
Major depressive episode in bipolar disorder									
All	1.2	0.1	55,206	43.9	2.6	624	65.1	3.9	280
High-income countries	1.3	0.1	36,919	47.9	3.0	481	64.6	4.2	235
Low/middle-income countries	0.9	0.1	18,287	31.9	4.8	143	67.3	9.3	45
Mania/hypomania									
All	2.3	0.1	91,416	26.6	1.3	2,178	63.1	2.4	598
High-income countries	2.7	0.1	58,991	28.9	1.5	1,705	63.0	2.5	503
Low/middle-income countries	1.6	0.1	32,425	19.3	2.2	473	63.5	6.1	95
Alcohol use disorder									
All	9.5	0.1	93,843	11.8	0.5	9,378	44.5	2.3	1,137
High-income countries	11.5	0.2	53,903	14.2	0.7	6,867	44.0	2.5	974
Low/middle-income countries	6.7	0.2	39,940	6.4	0.8	2,511	46.8	5.3	163
All diagnostic categories									
All				23.0	0.3	43,678	61.7	0.7	10,035
High-income countries				27.1	0.4	31,048	62.6	0.7	8,313
Low/middle-income countries				13.8	0.5	12,630	57.6	1.9	1,722

SE – standard error

for these disorders for analysis.

Treatment type was defined as the cross-classification of variables for: a) whether the respondent reported receiving medication, talk therapy, or both, as of the age at first treatment; and b) types of professionals seen as of that age, including mental health specialists (psychiatrist, psychiatric nurse, psychologist, psychiatric social

Table 3 Conditional probabilities of patient-reported treatment helpfulness by number of professionals seen pooled across diagnostic categories

Number of professionals seen	All countries			High-income countries			Low/middle-income countries		
	%	SE	N	%	SE	N	%	SE	N
1	26.1	0.6	10,035	25.4	0.7	8,313	29.2	1.4	1,722
2	34.0	1.0	5,261	33.6	1.1	4,530	36.2	2.9	731
3	32.2	1.4	2,705	32.3	1.6	2,329	32.0	3.3	376
4	26.2	1.9	1,454	26.2	2.1	1,260	25.8	5.0	194
5	24.3	1.9	876	25.1	2.1	766	19.2	3.8	110
6	24.7	2.8	539	24.8	3.1	483	24.2	5.7	56
7	17.8	2.8	360	18.0	3.0	321	16.5	7.3	39
8	17.9	4.1	277	19.1	4.4	248	6.1	4.3	29
9	4.5	1.7	222	3.7	1.7	198	10.5	7.1	24
10	31.5	4.5	208	34.5	4.9	187	4.9	3.8	21
11	16.8	5.4	95	7.9	3.8	81	56.9	13.8	14
12	15.1	4.2	82	16.7	4.6	73	0.0	0.0	9
13	3.2	1.8	63	2.3	2.0	55	10.3	2.3	8
14	1.5	1.5	59	1.6	1.6	52	0.0	0.0	7
15	22.9	8.4	58	25.8	9.4	51	0.0	0.0	7
16	0.0	0.0	45	0.0	0.0	39	0.0	0.0	6
17	0.0	0.0	45	0.0	0.0	39	0.0	0.0	6
18	3.2	3.2	44	3.7	3.7	38	0.0	0.0	6
19	6.6	1.4	43	0.0	0.0	37	46.1	10.8	6
20	23.7	8.1	42	25.8	8.9	37	0.0	0.0	5

SE – standard error

worker, mental health counselor), primary care providers, human services providers (social worker or counselor in a social services agency, spiritual advisor), and complementary/alternative medicine providers (i.e., other type of healers or self-help groups).

Treatment timing included a dichotomous measure for whether the respondent's first treatment for the focal diagnostic category occurred before the year 2000 or subsequently, and a continuous variable for length of delay in years between age of onset of the diagnostic category and age at first treatment.

Childhood adversities were assessed by twelve questions about experiences that occurred before respondents were age 18[23]. Based on exploratory latent class analysis, dichotomously scored responses were combined into two dichotomous indicators of maladaptive family functioning adversities and other adversities. The maladaptive family functioning childhood adversities included four types of parental maladjustment (mental illness, substance abuse, criminality, violence) and three types of maltreatment (physical abuse, sexual abuse, neglect). The other childhood adversities included three types of interpersonal loss (parental death, parental divorce, other separation from parents), life-threatening respondent physical illness, and family economic adversity. The questions about parental death, divorce, and other loss (e.g., respondent's foster care placement) included non-biological as well as biological parents.

Analysis methods

The analysis sample was limited to people with first lifetime treatment of at least one focal diagnostic category during or after 1990. The dataset was stacked across the eight diagnostic categories. Information about the focal diagnostic category was included as a series of dummy-coded predictor variables. Cross-tabulations at the person-visit level were used to examine conditional probabilities of: a) patient-reported helpfulness of treatment by number of professionals seen and b) conditional probabilities of persisting in help-seeking after previously receiving treatments that were considered not helpful. Standard discrete-time survival analysis methods[24] were then used to calculate cumulative survival curves for probabilities of patient-reported helpfulness and persistence across number of professionals seen.

Modified Poisson regression models for binary outcomes[25] were then estimated to examine baseline (i.e., as of age at first treatment) predictors of receiving helpful treatment at the patient level regardless of number of professionals seen. Coefficients and 95% confidence intervals (CI) were exponentiated to obtain risk ratios (RRs). In the case of the indicator variable for focal diagnostic category, these RRs were centered to interpret variation across the categories. The product of these centered

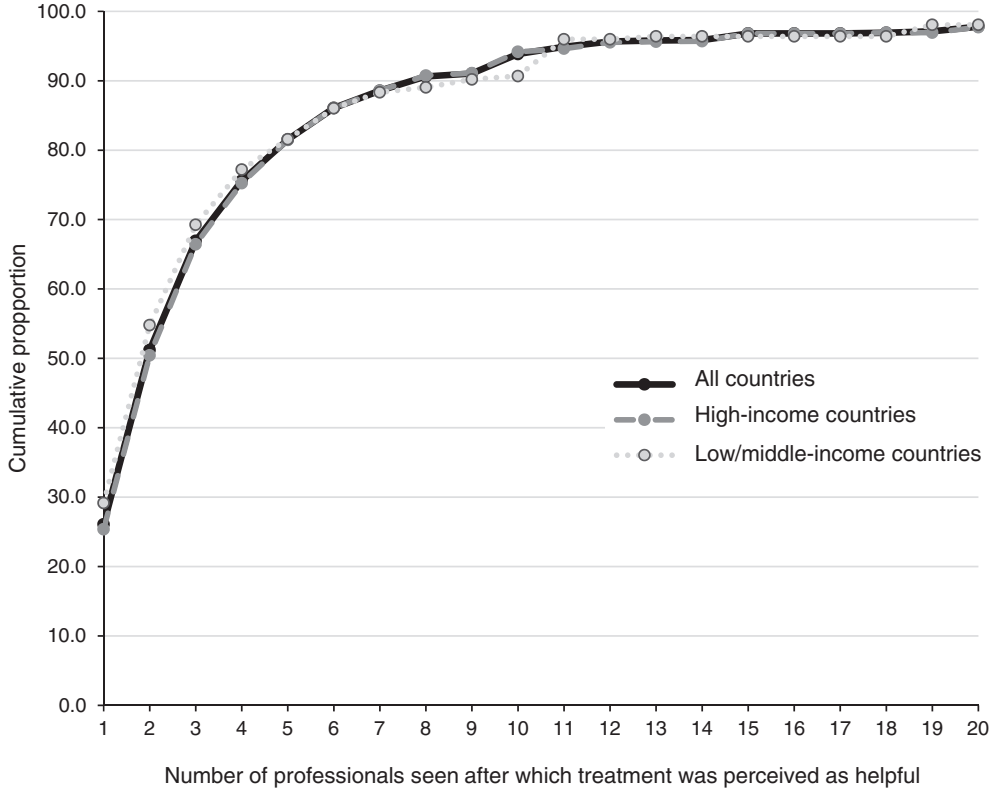

Figure 1 Cumulative proportion of patients who would be expected to receive helpful treatment by number of professionals seen pooled across all diagnostic categories

RRs across all diagnostic categories equals 1.0, allowing each individual RR to be interpreted as relative to the average across all categories.

The same link function and transformations were then used to decompose each significant patient-level predictor to investigate whether the association of that predictor with the outcome was due to one, the other, or both of the two component associations: a) the association of the predictor with conditional RR of an individual professional being helpful; and b) the association of the predictor with conditional RR of persistence in help-seeking after not previously receiving helpful treatment. Finally, interactions were estimated between diagnostic categories and each predictor to investigate the possibility of variation in predictor strength across disorders. Importantly, these interactions were examined one at a time rather than together, to avoid problems with model instability.

Weights were applied to the data to adjust for differential probabilities of selection (due to only one person being surveyed in each household, no matter how many eligible adults lived in the household) and differential non-response rates (documented by discrepancies between the census population distributions of socio-demographic or geographic variables and the distributions of these same variables in the sample). In addition, Part II respondents were weighted to adjust for the under-sampling of Part I respondents without disorders. The latter weight resulted in prevalence estimates of Part I disorders in the weighted Part II sample being virtually identical to those in the Part I sample[26].

Because of this weighting and the geographic clustering of the WMH survey designs, all statistical analyses were carried out using the Taylor series linearization method[27], a design-based method implemented in the SAS 9.4 software system[28]. Statistical significance was evaluated consistently using 0.05-level two-sided design-based tests.

RESULTS

Disorder prevalence, treatment, and patient-reported treatment helpfulness

The lifetime disorder prevalence in the total sample ranged from a high of 9.5% for alcohol use disorder (11.5% in HICs; 6.7% in LMICs) to a low of 1.2% for major depressive episode in bipolar disorder (1.3% in HICs; 0.9% in LMICs). The prevalence was consistently higher in HICs than LMICs (X^2_1=10.8-398.0, p=0.001 to <0.001) (Table 2).

Roughly one-fourth (23.0%) of respondents stacked across diagnostic categories received treatment, but this proportion was nearly twice as high in HICs as LMICs (27.1% vs. 13.8%, X^2_1=382.4, p<0.001). The proportion receiving treatment also varied significantly across diagnostic categories, both in the total sample (X^2_7=1402.0, p<0.001) and in the country income group sub-samples (X^2_7=1308.6, p<0.001 in HICs; X^2_7=230.4, p<0.001

Table 4 Conditional probabilities of persistence in professional help-seeking after previous treatments that were not helpful pooled across diagnostic categories

Previous number of professionals seen	All countries			High-income countries			Low/middle-income countries		
	%	SE	N	%	SE	N	%	SE	N
1	70.7	0.7	7,382	72.9	0.8	6,179	60.3	1.8	1,203
2	75.5	1.0	3,524	75.2	1.1	3,030	77.3	2.4	494
3	80.4	1.1	1,823	80.8	1.2	1,564	77.8	2.7	259
4	81.2	1.8	1,079	81.6	2.0	937	78.8	4.1	142
5	82.7	1.8	644	86.6	1.8	563	60.7	6.1	81
6	87.4	2.1	408	87.4	2.3	364	87.9	6.0	44
7	90.6	2.3	305	93.1	1.9	270	71.5	11.5	35
8	94.1	3.4	233	93.8	3.7	207	97.1	2.7	26
9	97.7	1.0	213	97.5	1.2	192	100	0.0	21
10	66.7	5.7	135	63.5	6.4	116	85.4	8.0	19
11	98.2	1.3	84	98.0	1.4	75	100	0.0	9
12	84.0	8.5	68	83.7	9.5	59	86.2	10.7	9
13	99.3	0.7	60	99.2	0.8	53	100	0.0	7
14	100	0.0	58	100.0	0.0	51	100	0.0	7
15	97.7	2.0	47	99.6	0.4	40	86.2	12.2	7
16	100	0.0	45	100.0	0.0	39	100	0.0	6
17	91.8	7.7	45	90.6	8.8	39	100	0.0	6
18	100	0.0	43	100.0	0.0	37	100	0.0	6
19	100	0.0	42	100.0	0.0	37	100	0.0	5

SE – standard error

in LMICs). This variation was very similar in HICs and LMICs (Pearson correlation=.88), although consistently higher in HICs than LMICs (X^2_1=7.1-261.0, p=0.008 to <0.001), from a high of 43.9% (47.9% in HICs; 31.9% in LMICs) for major depressive episode in bipolar disorder to a low of 11.8% (14.2% in HICs; 6.4% in LMICs) for alcohol use disorder.

Stacked across all diagnostic categories, 61.7% of patients reported being helped by treatment, with the proportion somewhat higher in HICs than LMICs (62.6% vs. 57.6%, X^2_1=6.4, p=0.012). The proportion of patients who reported being helped varied significantly across diagnostic categories, both in the total sample (X^2_7=189.6, p<0.001) and in the country income group sub-samples (X^2_7=168.3, p<0.001 in HICs; X^2_7=25.73, p<0.001 in LMICs). This variation was very similar in HICs and LMICs (Pearson correlation=.80), from a high of 70.0% for generalized anxiety disorder (70.9% in HICs; 62.8% in LMICs) to a low of 44.5% for alcohol use disorder (44.0% in HICs; 46.8% in LMICs).

Differences between HICs and LMICs in the proportion of patients who reported being helped by treatment were non-significant for all but one diagnostic category (X^2_1=0.0-2.7, p=0.93 to 0.10). The exception was major depressive disorder, with a higher proportion of patients in HICs than LMICs reporting that they had been helped by treatment (70.1% vs. 62.4%, X^2_1=9.7, p=0.002).

Conditional and cumulative probabilities of treatment being helpful

Across all surveys and diagnostic categories, 26.1% of patients (N=10,035) reported being helped by the very first professional they saw (Table 3). This is less than half the 61.7% who reported being helped at all, indicating that most patients saw two or more professionals before they received treatment that they considered helpful.

Conditional (on persisting in help-seeking after prior professionals not being helpful) probabilities of being helped were marginally higher for the second and third professionals seen (34.0-32.2%) and then successively lower for the fourth to sixth (26.2-24.7%) and seventh/eighth (17.8-17.9%) professionals seen. Conditional probabilities became much more variable and generally lower for the ninth to twelfth professionals seen (averaging 10.7%). Differences between HICs and LMICs were for the most part non-significant (see Table 3).

Survival analysis showed that cumulative probability of being helped rose to 51.2% among patients who persevered in seeing a second professional after not being helped by the first, to 66.9% after the third, 75.6% after the fourth, and rose to 90.6% after the eighth (Figure 1). Differences between HICs and LMICs were small and statistically non-significant (X^2_1=2.4, p=0.12).

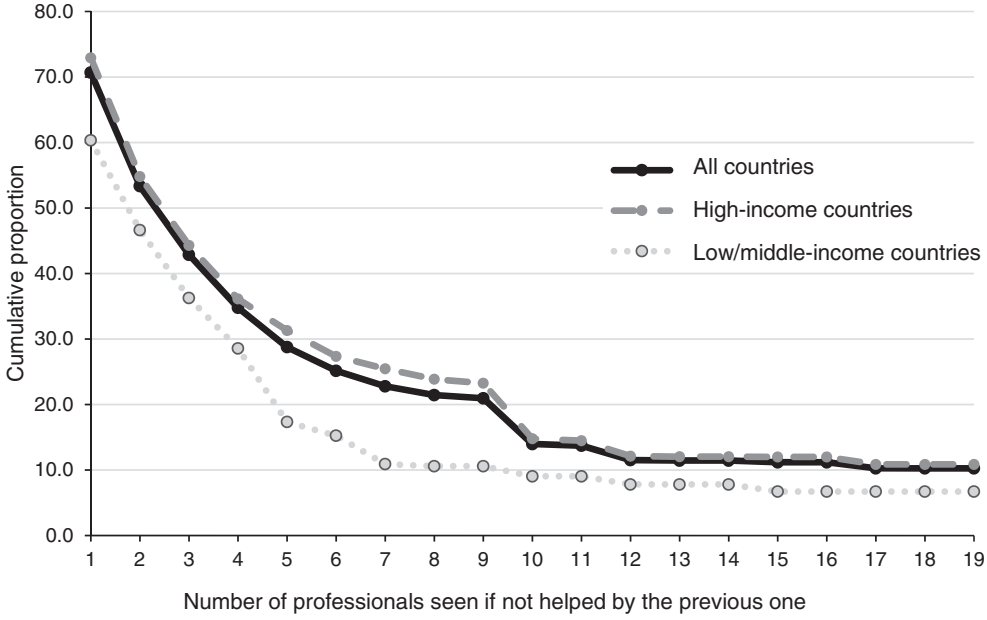

Figure 2 Cumulative proportion of patients who would be expected to persist in professional help-seeking after previous treatments were not helpful pooled across all diagnostic categories

Persistence in help-seeking following prior unhelpful treatment

The last results make it clear that persistence in help-seeking pays off. But, how persistent are patients in continuing to seek professional help after earlier unhelpful treatments? Across all surveys and diagnostic categories, 70.7% of patients who were not helped by an initial professional persisted in seeing a second (Table 4), but this proportion was significantly higher in HICs than LMICs (72.9% vs. 60.3%, X^2_1=40.9, p<0.001). Conditional (on prior professionals not being helpful) probabilities of persistence were even higher after seeing additional professionals, with generally non-significant differences between HICs and LMICs (see Table 4).

However, survival analyses showed that the cumulative probability of persistence in help-seeking decreased markedly after continued unhelpful treatments (Figure 2) and significantly more so in LMICs than HICs (X^2_1=35.2, p<0.001). For example, only 53.3% of patients (54.8% in HICs; 46.6% in LMICs) continued their professional help-seeking after not being helped by a second professional; 34.8% (36.1% in HICs; 28.6% in LMICs) after a fourth, and 25.2% (27.3% in HICs; 15.2% in LMICs) after a sixth.

Whereas Figure 1 estimated that 90.6% of patients would be helped if they persisted in help-seeking with up to eight professionals, the results in Figure 2 estimate that only 22.8% (25.5% in HICs; 10.9% in LMICs) of patients would persist that long in their help-seeking.

Predictors of treatment helpfulness

We examined predictors of ever receiving helpful treatment pooled across all diagnostic categories and all professionals seen (Table 5). Significant variation in RRs was found across diagnostic categories (X^2_7=60.7, p<0.001), with higher than average (across categories) RR for major depressive disorder, generalized anxiety disorder, and social phobia (1.16-1.19) and lower than average RR for specific phobia and alcohol use disorder (0.88-0.68).

In addition, RR of patient-reported treatment helpfulness was significantly and positively associated with age at first treatment, high education, prior history of substance abuse without dependence, and treatment occurring either in the mental health specialty sector with medication, in the complementary/alternative medicine sector, or in multiple sectors. RR was significantly and negatively associated with prior history of generalized anxiety disorder and treatment delay.

Decomposition focused on significant patient-level predictors. The higher-than-average RRs for major depressive disorder, generalized anxiety disorder, and social phobia were all due to a combination of significantly increased RRs of both individual professionals being helpful (RR=1.11-1.11) and persisting in help-seeking (RR=1.05-1.08). The lower-than-average RR for specific phobia and alcohol use disorder were due to significantly reduced RRs of individual professionals being helpful for both disorders (RR=0.86-0.81) in conjunction with reduced RR of persisting in help-seeking for alcohol use disorder (RR=0.81).

The increased RRs associated with age at first treatment and high education were both due to associations with helpfulness of individual professionals (RR=1.09-1.05) rather than with persistence in help-seeking after earlier treatments were not helpful. The increased RR associated with prior history of substance abuse without dependence, instead, was due to significantly increased persistence in help-seeking (RR=1.04) and non-significant increased helpfulness of individual professionals (RR=1.05).

Table 5 Significant predictors of patient-level treatment helpfulness decomposed through associations with the helpfulness of individual professionals and persistence in help-seeking pooled across diagnostic categories and number of professionals seen

	Patient-level treatment helpfulness				Helpfulness of individual professionals				Persistence in help-seeking after prior unhelpful treatment			
	%	SE	RR	95% CI	%	SE	RR	95% CI	%	SE	RR	95% CI
Focal diagnostic category												
Major depressive disorder	28.3	0.6	1.19*	1.12-1.26	26.6	0.8	1.11*	1.02-1.21	24.8	0.9	1.08*	1.04-1.11
Bipolar disorder												
Major depressive episode	3.1	0.2	0.94	0.75-1.17	3.9	0.5	0.85	0.62-1.16	4.2	0.6	1.06	0.97-1.16
Mania/hypomania	6.1	0.3	1.11	0.98-1.27	6.4	0.4	1.08	0.91-1.29	6.4	0.4	1.03	0.95-1.12
Generalized anxiety disorder	19.0	0.4	1.19*	1.12-1.27	20.0	0.6	1.11*	1.01-1.21	19.4	0.7	1.07*	1.04-1.10
Post-traumatic stress disorder	6.0	0.3	0.99	0.83-1.17	5.6	0.3	1.14	0.89-1.46	5.7	0.3	0.93	0.84-1.02
Specific phobia	12.8	0.4	0.88*	0.77-0.99	12.0	0.8	0.86*	0.73-1.00	12.8	1.1	1.01	0.94-1.08
Social phobia	13.4	0.4	1.16*	1.08-1.24	14.2	0.6	1.11*	1.01-1.22	14.2	0.7	1.05*	1.01-1.08
Alcohol use disorder	11.4	0.5	0.68*	0.58-0.79	11.4	0.7	0.81*	0.67-0.98	12.6	0.9	0.81*	0.75-0.87
X^2_7				60.7*				18.6*				54.4*
Socio-demographics												
Mean age at starting treatment	33.2	0.2	1.03*	1.01-1.06	31.9	0.3	1.09*	1.06-1.12	31.3	0.4	0.99	0.98-1.01
X^2_1				6.9*				30.9*				1.0
Education												
Level among non-students	2.3	0.0	1.02*	1.00-1.05	2.3	0.0	1.05*	1.02-1.08	2.2	0.0	1.00	0.99-1.01
Student status	12.7	0.5	0.97	0.87-1.07	14.6	1.1	0.94	0.82-1.08	16.1	1.3	1.00	0.95-1.05
X^2_2				11.8*				25.5*				0.2
Prior history of comorbid disorders												
Generalized anxiety disorder	12.8	0.5	0.93*	0.87-0.99	14.7	0.9	0.91*	0.84-1.00	15.6	1.2	0.97	0.94-1.00
Substance abuse without dependence	5.5	0.4	1.11*	1.02-1.20	6.7	0.9	1.05	0.93-1.18	7.1	1.1	1.04*	1.00-1.08
X^2_{10}				20.1*				27.2*				14.4
Treatment type												
Mental health specialty sector + medication	51.0	0.9	1.20*	1.12-1.27	61.1	1.2	0.88*	0.81-0.95	62.0	1.4	1.19*	1.15-1.23
Complementary/alternative medicine	19.0	0.7	1.08*	1.03-1.14	25.7	1.2	0.88*	0.82-0.94	27.4	1.4	1.06*	1.04-1.08
Multiple	59.8	0.8	1.11*	1.03-1.20	70.0	1.0	1.04	0.94-1.16	71.4	1.3	1.18*	1.12-1.24
X^2_5				194.0*				85.5*				481.1*
Treatment timing												
Treatment delay	9.6	0.2	0.96*	0.94-0.98	9.0	0.2	0.98	0.95-1.01	9.1	0.3	0.97*	0.96-0.98
X^2_1				14.0*				1.6				19.7*

*significant at the 0.05 level, SE – standard error, RR – adjusted risk ratio, CI – confidence interval

Table 6 Significant predictors of variation in patient-level treatment helpfulness between patients receiving treatment for alcohol use disorder (AUD) compared to other diagnostic categories decomposed through associations with the helpfulness of individual professionals and persistence in help-seeking pooled across number of professionals seen

	Patient-level treatment helpfulness		Helpfulness of individual professionals		Persistence in help-seeking after prior unhelpful treatment	
	RR	95% CI	RR	95% CI	RR	95% CI
Gender (female)						
AUD	0.78*	0.64-0.96	0.77*	0.61-0.97	0.98	0.91-1.06
Others	1.05*	1.00-1.10	1.07*	1.00-1.14	1.02	0.99-1.04
Treatment type (psychotherapy)						
AUD	1.44*	1.14-1.82	1.09	0.82-1.45	1.20*	1.07-1.36
Others	1.01	0.95-1.07	0.92*	0.84-1.00	1.04	1.00-1.07

*significant at the 0.05 level, RR – adjusted risk ratio, CI – confidence interval

The increased RRs associated with treatment occurring in the mental health specialty sector with medication, in the complementary/alternative medicine sector, and in multiple sectors were more complex, as all involved significantly increased persistence in help-seeking (RR=1.19-1.06), but none involved significantly increased helpfulness of individual professionals. In fact, helpfulness of individual professionals was significantly reduced for two of these treatments (RR=0.88-0.88). The reduced RRs associated with treatment delay and prior generalized anxiety disorder, finally, were due to consistently decreased component associations with both helpfulness of individual professionals (RR=0.98-0.91) and persistence in help-seeking (RR=0.97-0.97), although the RR of treatment delay with persistence in help-seeking and individual professionals being helpful for prior generalized anxiety disorder were the only statistically significant components.

Variation in predictors across diagnostic categories

We next examined variation in predictors of patient-level treatment helpfulness across focal diagnostic categories. Two predictors had significantly different RRs predicting treatment helpfulness for alcohol use disorder versus the other diagnostic categories (gender and treatment type) (see Table 6). Four other predictors had significantly different RRs predicting treatment helpfulness within the remaining categories (education, treatment delay, starting treatment after 2000, and childhood adver-

Table 7 Significant predictors of patient-level variation in treatment helpfulness across diagnostic categories other than alcohol use disorder decomposed through associations with the helpfulness of individual professionals and persistence in help-seeking pooled across number of professionals seen

	Treatment helpfulness at the patient level		Helpfulness of individual professionals		Persistence in help-seeking after prior unhelpful treatment	
	RR	95% CI	RR	95% CI	RR	95% CI
Student status						
Major depressive disorder	1.21*	1.07-1.37	1.14	0.94-1.40	1.07	1.00-1.14
Specific phobia	0.73*	0.57-0.93	0.63*	0.47-0.84	1.08	0.98-1.19
Treatment delay						
Major depressive disorder	0.93*	0.89-0.97	0.96	0.90-1.01	0.96*	0.93-0.99
Post-traumatic stress disorder	0.86*	0.78-0.94	0.89*	0.80-0.99	0.95*	0.91-0.99
Started treatment after 2000						
Post-traumatic stress disorder	0.76*	0.66-0.89	0.89	0.72-1.10	0.87*	0.80-0.95
Childhood adversities						
Post-traumatic stress disorder, MFF	0.73*	0.60-0.88	0.67*	0.52-0.86	0.91	0.83-1.01
Post-traumatic stress disorder, other	0.57*	0.42-0.76	0.64*	0.46-0.89	0.78*	0.66-0.92

*significant at the 0.05 level, RR – adjusted risk ratio, CI – confidence interval
Maladaptive family functioning childhood adversities (MFF) included physical abuse, sexual abuse, neglect, parent mental disorder, parent substance use disorder, parent criminal behavior, and family violence. Other childhood adversities included parent death, parent divorce, other loss of a parent, physical illness, and family economic adversity.

sities) (see Table 7).

The significant gender difference (X^2_1=7.8, p=0.005) in patient-level treatment helpfulness for alcohol use disorder compared to the other categories occurred because women treated for the former condition were significantly less likely than men to report that treatment was helpful (RR=0.78), whereas women treated for other diagnostic categories were significantly more likely than men to report that treatment was helpful (RR=1.05) (Table 6). Decomposition showed that the interaction was due to gender differences in the helpfulness of individual professionals rather than to differences in persistence in help-seeking.

The significantly higher RR of patient-level treatment helpfulness of psychotherapy than other treatment types for alcohol use disorder was not due to a higher RR of helpfulness at the level of the individual professional, but rather to a higher probability of persistence after earlier unhelpful treatments (RR=1.20).

The significant effect of education in predicting variation in treatment helpfulness across the other diagnostic categories was due to patients who were students at the time of starting treatment differing from other patients (X^2_6=30.7, p<0.001) rather than to an association involving level of educational attainment among non-students (X^2_6=8.7, p=0.19). Students were significantly more likely than other patients to receive helpful treatment for major depressive disorder (RR=1.21), due to elevated but non-significant associations of being a student with individual professionals being helpful as well as with persistence in help-seeking (Table 7). Students were significantly less likely than other patients, instead, to be helped by treatment for specific phobia (RR=0.73). This was true because individual professionals were less likely to be helpful in treating students than other patients with this disorder (RR=0.63). Students did not differ from other patients in patient-level RR of treatment helpfulness for any of the other diagnostic categories (X^2_1=0.2-3.4, p=0.66 to 0.06).

We reported above (Table 5) that treatment delay predicted reduced patient-level treatment helpfulness overall, and that this occurred because patients who were delayed in getting treatment were less likely than other patients to persist in help-seeking. However, this association was significant only for major depressive disorder and PTSD (RR=0.93-0.86), in both cases due to reduced persistence in help-seeking (RR=0.96-0.95) and for PTSD also reduced helpfulness of individual professionals (RR=0.89). Initial treatment delay did not predict reduced RR of patient-level treatment helpfulness for any other diagnostic category (X^2_1=0.0-2.1, p=0.88 to 0.15).

The significant variation in helpfulness by whether treatment started after the year 2000 was due exclusively to an association among patients in treatment for PTSD (RR=0.76), with non-significantly reduced RR of individual professional treatment helpfulness (RR=0.89) and significantly reduced RR of persistence in help-seeking (RR=0.87). There was no significant association between year of treatment starting and patient-level helpfulness for any other diagnostic categories (X^2_1=0.0-1.8, p=0.92 to 0.18).

The significant variation in helpfulness depending on childhood adversities (X^2_{12}=31.8, p=0.002) was due to variation associated with both maladaptive family functioning adversities (X^2_6=15.4, p=0.018) and other adversities (X^2_6=22.1, p=0.001), in both cases with childhood adversities predicting reduced RR of helpful treatment only for PTSD (RR=0.73-0.57). There was no significant association between childhood adversities and patient-level treatment helpfulness in other diagnostic categories (X^2_1=0.0-3.5, p=0.91 to 0.06).

DISCUSSION

The lifetime prevalence of disorders across diagnostic categories was 1.2 to 11.5%, consistently higher in HICs than LMICs. About one-fourth of these disorders received some type of treatment (23.0%), but this rate was approximately two times as high in HICs as LMICs (27.1% vs. 13.8%). Bipolar disorder and major depressive disorder were most likely to be treated, and alcohol use disorder least likely. These statistics convey that both prevalence of disorder and receipt of treatment are higher in HICs than LMICs, and that there is considerable variation across diagnoses in probability of receipt of treatment.

A central goal of the study was to evaluate respondent ratings of treatment helpfulness. Overall, 61.7% rated treatment as being helpful, with only a slightly higher percentage among HICs than LMICs (62.6% vs. 57.6%). Treatment was most likely to be rated helpful for generalized anxiety disorder (70.0%) and least likely for alcohol use disorder (44.5%). There were for the most part no differences between HICs and LMICs in the proportion of patients with specific disorders who reported treatment as helpful. The one exception was major depressive disorder, where a higher proportion of patients in HICs than LMICs reported that treatment was helpful (70.1% vs. 62.4%).

A second goal of the study was to evaluate the number of professionals that patients needed to see before receiving a treatment that they considered to be helpful. We found that only about half the patients who reported receiving helpful treatment were helped by the first professional they saw (26.1% helped by the first professional seen vs. 61.7% helped overall). In other words, seeking help from two or more professionals was the norm among patients who received helpful treatment. Cumulative probability of receiving helpful treatment nearly doubled to 51.2% among individuals who sought treatment from a second professional. Less dramatic increments occurred after seeing additional professionals, with a projected cumulative probability of receiving helpful treatment of 90.6% after the eighth professional seen. There were few significant differences between HICs and LMICs in this regard.

A third goal of the study was to evaluate persistence in professional help-seeking among patients whose earlier treatments were not helpful. Across all diagnostic categories, 70.7% of patients reported persisting in help-seeking by seeing a second professional if the first professional was not helpful, with conditional probabilities of persistence continuing to be high (in the range 66.7-100% up through 20 professionals seen) after earlier unhelpful treatments. These conditional probabilities were somewhat higher in HICs than LIMCs. Despite the high conditional probabilities, though, cumulative probabilities of persistence decreased

markedly over successive professionals, with only 22.8% of patients overall (25.5% in HICs; 10.9% in LMICs) expected to persist in seeking treatment from up to eight professionals, the number needed for more than 90% of patients to receive helpful treatment.

We also looked at predictors of helpfulness at the patient-disorder level and then disaggregated the significant predictors into the separate associations with helpfulness of individual professionals and persistence in help-seeking after earlier treatments that were not helpful. We found that the variation across diagnostic categories in probability of treatment being helpful was driven by five disorders: three of them with higher-than-average RR of treatment helpfulness (major depressive disorder, generalized anxiety disorder, social phobia) and two with lower-than-average RR of treatment helpfulness (specific phobia, alcohol use disorder). In almost all these cases, the significant patient-level association was due to significantly increased persistence in help-seeking rather than significantly increased helpfulness of individual professionals. Why it should be that treatments differ in helpfulness in these ways across disorders remains to be clarified.

Net of these differences across diagnostic categories, we found a complex series of significant associations between diverse predictors and RR of patient-level treatment helpfulness. We began by examining these predictors pooled across all diagnostic categories and then we disaggregated the predictors by these categories. The most stable predictors were those significant at the aggregate level that did not vary in importance across focal diagnostic categories. There were five such stable predictors: age at first treatment, educational attainment among non-students, two prior lifetime comorbid disorders (generalized anxiety disorder, substance abuse without dependence), and treatment type.

The first two of these five – age at first treatment and level of educational attainment among non-students – were associated with significantly increased RR of individual professional treatment helpfulness, but were unrelated to persistence in help-seeking. A plausible possibility is that increasing age and education are both indicators of maturity and cognitive complexity, both of which might reasonably be expected to promote treatment success across diagnostic categories.

The third stable predictor, prior comorbid generalized anxiety disorder, predicted reduced RR of individual professional treatment helpfulness, but was unrelated to persistence in help-seeking. This is an intriguing result, as a considerable amount of research has shown that comorbid generalized anxiety disorder predicts reduced treatment response for major depressive disorder[29]. We are unaware, though, of any research on comorbid generalized anxiety disorder predicting reduced treatment response for other mental disorders. This might be a fruitful avenue of investigation.

The fourth stable predictor, prior comorbid substance abuse without dependence, was associated with increased persistence in help-seeking across all diagnostic categories. The meaning of this result is not clear, but it is worthy of investigation in future research on patterns and predictors of persistence in help-seeking.

The final stable predictor, treatment type, was more complex, because it was due to elevated RR of patient-level treatment helpfulness across several different types of treatment (medication prescribed by a mental health specialist, complementary/alternative medicine, and treatment in multiple sectors), but none of these involved increased RR of individual professional treatment helpfulness. Instead, increased persistence in help-seeking accounted for the patient-level associations of these treatment types with treatment helpfulness. In two cases (medication and complementary/alternative medicine), these treatments were associated with significantly reduced RR of individual professional treatment helpfulness, possibly indicating that more severe cases received these types of treatment.

Other predictors varied in importance across diagnostic categories. Two of these were unique to alcohol use disorder. One of them, being male, predicted significantly increased RR of individual professional treatment helpfulness for alcohol use disorder but no other diagnoses. The other, receiving psychotherapy in the absence of any other treatment, predicted increased persistence in help-seeking for alcohol use disorder but not for any other diagnostic categories. The explanations for these specifications are unclear, but plausible speculations can be made. For example, it might be that the preponderance of males among patients with alcohol use disorder means that some of the most common treatments, some of which are delivered in group formats, are more effective for men than women. The selection of psychotherapy as the only treatment modality may indicate a more serious engagement with the treatment process for patients with alcohol use disorder, thereby predicting increased RR of persistence in help-seeking.

Three other noteworthy predictors that varied in importance across disorders other than alcohol use disorder were student status, treatment delay, and childhood adversities. Students were more likely than other patients to be helped when treated for major depressive disorder, but less likely to be helped when treated for specific phobia. It is unclear why these differences occurred, but it is plausible that they involve differential effects of timely treatment, which in the case of major depressive disorder might be related to good treatment response, while in the case of specific phobia might be a severity marker given the comparatively low treatment rate of this condition. WMH data are limited in their ability to explore these hypotheses, because the retrospective evaluations make it impossible to assess disorder severity at the time of starting treatment. However, these findings could be the starting point for prospective studies in more focused disorder-specific patient samples.

Both types of childhood adversities considered here were found to be associated with significantly reduced RR of patient-level helpfulness, but only for PTSD and largely because of reduced RR of individual professionals being helpful. This might reflect a special difficulty in treating PTSD associated with childhood traumas, a possibility consistent with the rationale underlying the inclusion of a special diagnostic category for complex PTSD in the ICD-11 diagnostic system[30,31].

These results provide useful information on several fronts. First, it is important to note that about one-fourth of patients were helped by the first professional they saw, that the cumula-

tive probability of being helped almost doubled after seeing a second professional, and that persistence in help-seeking paid off, with more than 90% of patients being helped after seeing up to eight professionals. Yet fewer than one-fourth of patients persisted that long in their help-seeking. The implication is clear that a research priority should be to increase understanding of the determinants of persistence in help-seeking.

Second, similarities and differences between HICs and LMICs are instructive. Across each of the diagnoses, lifetime disorder prevalence was higher in HICs than LMICs, and for each disorder the proportion of individuals who received treatment was nearly double in HICs compared to LMICs. However, once treatment occurred, few differences were found between HICs and LMICs in patient-reported treatment helpfulness. This meant that persistence was needed equally in LMICs and HICs to be sure of receiving helpful treatment. Yet persistence in help-seeking was significantly lower in LMICs than HICs. This means that the greater proportional burden of unmet need for treatment in LMICs than HICs is due to a combination of lower entry into treatment and lower persistence. Many of the barriers that create these differences are structural ones, not investigated here[32].

Third, we found numerous significant predictors of patient-level treatment helpfulness, some of them consistent across disorders but most varying in importance across disorders. Disaggregation found that some of these variables were important because they predicted differential response to treatment, while others were important because they predicted differential persistence in help-seeking after earlier unhelpful treatments.

The first of these two disaggregated components is related to the burgeoning research area of precision psychiatry[33-39]. Our results may add information to models aimed to guide the matching of patients to the treatment that is likely to be of most value to them. The second component is somewhat neglected, but of equal importance, since helpful treatment typically requires persistence in help-seeking. Some epidemiological research has been carried out on treatment dropout[40] and interventions have been developed to reduce it[41,42]. There is some emerging research showing that case management can be useful in encouraging continuation of help-seeking with new professionals when earlier treatments are not helpful[43]. But we are aware of no comparable research designed to investigate barriers and interventions to increase persistence in help-seeking among patients with common mental disorders. Our results suggest that this type of work could be of great value.

Several limitations of this study are worth noting. First, we had limited information about the exact nature of the interventions that respondents received. Information was also lacking on quality of treatment delivery and adherence on the part of patients. These factors made it impossible to compare the effectiveness of different interventions or types of professionals. Because of this, it would be a mistake to interpret our results regarding the associations of treatment types with patient-reported helpfulness as evidence that these types do not differ in quality. Indeed, we know that the type and quality of training of the professional makes a difference and that the WMH design obscures this variation because of not being based on experimental assignment[44].

Second, respondent evaluations of treatment helpfulness were based on unspecified criteria. Even though the patient perspective on treatment quality is becoming a focus of increasing interest, not least of all because it is a strong predictor of treatment adherence[8], more information is needed about the basis of these evaluations to move beyond the basic level of analysis presented here. In addition, treatment helpfulness needs to be thought of as being graded rather than a dichotomy and as changing over time as patient needs change.

Third, interactions were examined one at a time, rather than together, to avoid problems with model instability. Further analyses beyond those reported here are needed to investigate joint associations of multiple significant interactions, but preferably based on a more disaggregated analysis than we were able to carry out here. In the ideal case, these future analyses should be conducted with long-term prospective data in clinical samples rather than with the retrospective data used in this study, but following patients over much longer periods of time than in typical clinical studies.

Despite these limitations, this study provides unique, albeit preliminary, information about treatment helpfulness from the patient perspective in real-world contexts and over a diverse set of diagnostic categories and countries. We find that treatments are perceived as helpful, but that this varies across diagnoses, and that persistence in help-seeking is typically needed to find helpful treatment. The cumulative probability of success in finding helpful treatment is very high if help-seeking is persistent, but this persistence is the heretofore neglected key.

It is important to recognize that these results are distinct from, but complement, those in randomized controlled trials. The latter evaluate the impacts of individual treatments. The present study, instead, underscores the fact that initial treatments often are not successful in the real world, but that persistent help-seeking across the myriad of evidence-based treatments that exist for common mental disorders has a very high probability of resulting in a positive outcome.

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Reappraising the variability of effects of antipsychotic medication in schizophrenia: a meta-analysis

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It is common experience for practising psychiatrists that individuals with schizophrenia vary markedly in their symptomatic response to antipsychotic medication. What is not clear, however, is whether this variation reflects variability of medication-specific effects (also called "treatment effect heterogeneity"), as opposed to variability of non-specific effects such as natural symptom fluctuation or placebo response. Previous meta-analyses found no evidence of treatment effect heterogeneity, suggesting that a "one size fits all" approach may be appropriate and that efforts at developing personalized treatment strategies for schizophrenia are unlikely to succeed. Recent advances indicate, however, that earlier approaches may have been unable to accurately quantify treatment effect heterogeneity due to their neglect of a key parameter: the correlation between placebo response and medication-specific effects. In the present paper, we address this shortcoming by using individual patient data and study-level data to estimate that correlation and quantitatively characterize antipsychotic treatment effect heterogeneity in schizophrenia. Individual patient data (on 384 individuals who were administered antipsychotic treatment and 88 who received placebo) were obtained from the Yale University Open Data Access (YODA) database. Study-level data were obtained from a meta-analysis of 66 clinical trials including 17,202 patients. Both individual patient and study-level analyses yielded a negative correlation between placebo response and treatment effect for the total score on the Positive and Negative Syndrome Scale (PANSS) (ρ=–0.32, p=0.002 and ρ=–0.39, p<0.001, respectively). Using the most conservative of these estimates, a meta-analysis of treatment effect heterogeneity provided evidence of a marked variability in antipsychotic-specific effects between individuals with schizophrenia, with the top quartile of patients experiencing beneficial treatment effects of 17.7 points or more on the PANSS total score, while the bottom quartile presented a detrimental effect of treatment relative to placebo. This evidence of clinically meaningful treatment effect heterogeneity suggests that efforts to personalize antipsychotic treatment of schizophrenia have potential for success.

Key words: Antipsychotic medication, schizophrenia, variability of effects, medication-specific effects, non-specific effects, placebo response, treatment effect heterogeneity, personalization of treatment, precision medicine

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When using antipsychotic medication in routine care, it is apparent to the practising psychiatrist that symptoms improve considerably in some patients, while in others there is less improvement, and in some cases there is even a worsening of symptoms. A patient's overall observed response to a medication is made up of two components. The first component includes medication-specific effects, which are also called "treatment effects". The second component consists of factors not directly related to medication, such as natural fluctuation in symptoms, external life events and expectation effects, which in clinical trials are subsumed by the term "placebo response". In the clinical setting, we cannot determine whether the observed variability of symptomatic change between patients reflects variation of medication-specific effects, termed "treatment effect heterogeneity", as opposed to variation of placebo response.

Quantifying treatment effect heterogeneity is important for research and clinical practice. If considerable heterogeneity exists, this means that medication has markedly different effects in different individuals. This in turn suggests scope for personalized treatment, and justifies efforts to identify patient factors associated with good and poor response to treatment[1-4]. In contrast, if heterogeneity does not exist, this suggests that the variation seen clinically is due almost entirely to factors unrelated to medication, and that all patients will experience a similar magnitude of medication-specific benefit. In this latter case, the implication is that a "one size fits all" approach is appropriate for the prescribing of antipsychotic medication, and that attempts at developing predictive models to allow treatment personalization are doomed to failure.

There have been several recent meta-analytic attempts to investigate whether treatment effect heterogeneity exists, focusing on antipsychotics, antidepressants, and non-pharmacological interventions[5-11]. These analyses assumed that the presence of treatment effect heterogeneity would result in increased variability of symptomatic response in active treatment arms, as compared to placebo arms, of randomized controlled trials (RCTs)[5,7,8]. These meta-analyses, based on study-level data, found no evidence of greater variability in the active treatment arm for a range of treatments, including antipsychotic treatment of schizophrenia. They concluded that treatment effects are likely to be relatively constant, suggesting limited scope for personalization of treatment[5-11].

These findings were surprising, given the widespread clinical belief that patients differ substantially in their response to medication. They are also in contrast to previous research using individual patient data, which suggested that treatment effects vary between patients, with those who are most severely ill at baseline benefitting the most from active treatment[12-15].

An explanation for these discrepant findings is that the conclusions drawn from the variability meta-analyses rest on invalid assumptions regarding the correlation between the treatment effect and placebo response[9,16]. Specifically, the conclusion that the absence of increased variability in active arms suggests an absence of treatment effect heterogeneity is valid only when the above correlation is zero or positive. It is, however, possible that individuals with a greater placebo response have a smaller medication-specific benefit, i.e., that a negative correlation exists between placebo response and treatment effect. In this case, treatment effect heterogeneity will exist even when variability of overall symptomatic change in placebo and active treatment groups is the same, or even if the active treatment group displays lower variability of overall symptomatic change[8,9,16].

Previous meta-analyses have implicitly assumed a positive correlation between placebo response and treatment effect, even though *a priori* a negative correlation might be considered more likely, since a large placebo response effectively precludes a large treatment effect, due to the fact that all rating scales possess a lower limit. However, this correlation between treatment effect and placebo response has not been previously estimated. As a result, formal estimation of the heterogeneity of treatment effects using aggregate data from RCTs has previously not been possible.

It is of major importance to quantify treatment effect heterogeneity in schizophrenia, given its implications for attempts to personalize treatment. In order to do this, we must first estimate the correlation between treatment effect and placebo response. A growing body of literature exists that cannot be accurately interpreted in the absence of this parameter. In the present paper, we estimate this value via complementary approaches, using both individual patient data and study-level treatment effects from clinical trials. We then apply this value to the results of a variability meta-analysis, in order to formally estimate the heterogeneity of antipsychotic treatment effects, rather than relying on the primarily intuitive interpretations of previous meta-analyses[5,7].

METHODS

Individual patient data

We used the Yale University Open Data Access (YODA) database[17] to identify acute treatment clinical trials of antipsychotic medication in schizophrenia including adults aged 18-65 who had a period of placebo treatment prior to a period of active treatment, with Positive and Negative Syndrome Scale (PANSS)[18] scores recorded in both periods.

One trial (Sch-703) met these criteria, using the following design: individuals with schizophrenia who were receiving antipsychotic treatment and were symptomatically stable were withdrawn from current medication and then randomized to placebo or active treatment for the duration of a 6-week double-blind period. Those who completed the double-blind period, or completed at least 21 days of double-blind treatment followed by discontinuation due to lack of efficacy, then entered an open-label extension in which they received active treatment.

Study-level data

We used all studies from a recent meta-analysis[5], which included randomized double-blind placebo-controlled trials of antipsychotic monotherapy in the treatment of adults aged 18-65 with schizophrenia.

We extracted the mean and variance (standard deviation, standard error, or confidence intervals) of symptom change for total, positive and negative symptom ratings from each study for the active treatment and placebo groups. In studies where there were multiple active arms, the number of patients in the placebo group was divided by the number of arms.

Brief Psychiatric Rating Scale (BPRS)[19] scores were converted to PANSS scores using the method described by Leucht et al[20], to maximize the number of studies that could be included.

Estimating correlation of treatment effect and placebo response from individual patient data

In order to calculate a correlation coefficient (ρ) between treatment effect and placebo response, we first estimated treatment effects at the individual level. In order to ensure robustness of findings, we did this using two separate methods, which rest upon different assumptions.

In the first method, termed subsequently the "open-label method", the placebo response for individuals randomized to the placebo arm during the double-blind period was quantified as the change in PANSS score between the start of the double-blind period and the point at which that individual left the double-blind portion of the trial. The estimated treatment effect was then calculated as the change in symptom severity from the end of the double-blind period (at which point the subject switched from placebo to active treatment) to the end of the open-label period (i.e., the period during which the individual was receiving active treatment). This method relies on the assumption that, if the participant had been initially randomized to the other arm (i.e., active treatment), the score observed at the end of the double-blind period should equal the score we actually observe at the end of an open-label period of equal duration.

The second method, termed subsequently the "linear model method", was based on a simple linear regression model. More specifically, we fit a linear model with symptom severity at the end of the double-blind period as the outcome variable. Treatment, age, gender, and baseline severity were covariates, and the interactions of all covariates with treatment were also included. Following model fitting, we were able to then estimate treatment effects at the individual level using that individual's baseline covariates. This method makes the usual assumption of linearity and additivity of the effects of the covariates and treatment on the outcome.

Then, for both methods, we estimated the Spearman correlation coefficient (ρ) between placebo response and treatment effect, for positive and negative PANSS subscales as well as for the PANSS total score. Further details regarding both approaches and their assumptions are provided in the supplementary information.

Estimating correlation of treatment effect and placebo response from study-level data

As a third method, we used data on study-level placebo response and treatment effect from RCTs included in the abovementioned meta-analysis[5] to calculate a Spearman correlation coefficient (ρ) between the two. After weighting by number of patients in each arm, we pooled study-level estimates for positive and negative symptom PANSS subscales, in addition to total PANSS scores. Analyses were carried out using the package wCorr (Version 1.9.1) in R. This method makes the assumption that the correlation between treatment effect and placebo response at the individual level equals that at the study level.

Estimating treatment effect heterogeneity

The variability ratio (VR) is defined as follows, with σ_{AT} denoting the standard deviation of symptomatic change in the active treatment arm, and σ_{PL} representing the standard deviation of the placebo treatment arm: $VR = \frac{\sigma_{AT}}{\sigma_{PL}}$.

VR is therefore easily calculated from study-level data. The variable of clinical interest, however, is the standard deviation of the treatment effect (σ_{TE}). This can be estimated if VR and the correlation (ρ) between placebo response and treatment effect are known[9,16]: $\sigma_{TE} = \sigma_{PL}\left(\sqrt{VR^2 - 1 + \rho^2} - \rho\right)$.

We calculated VR for each study using the published study-level data from RCTs of antipsychotic treatment of schizophrenia[5]. We then calculated σ_{TE} for each study through the formula above, using the most conservative estimate of ρ derived from our three methods (i.e., the value corresponding to the correlation of lowest absolute magnitude). Finally, we combined the values of σ_{TE} from all studies via a random effects meta-analysis. To put the estimate of variability into perspective and to help assess its clinical importance, we also estimated the average treatment effect in the same RCTs, by performing a random effects meta-analysis using the observed mean difference between drug and placebo arms.

In addition to a single summary estimate across all trials, meta-analyses were also performed with studies grouped according to antipsychotics used. Meta-analyses were also conducted for positive and negative PANSS subscales where their scores were reported, using the relevant value of ρ calculated above. In a sensitivity analysis, we repeated the calculations using instead the most liberal value for ρ (i.e., the value corresponding to the correlation of highest absolute magnitude) among the three methods.

RESULTS

Individual patient data correlations

The eligible trial identified from the YODA database (see Table 1) included 384 individuals who were administered antipsychotic treatment and 88 individuals who received placebo during the double-blind period.

The open-label method yielded a strong negative correlation between the estimated treatment effect and placebo response for PANSS total (ρ=–0.62, p<0.001), positive (ρ=–0.61, p<0.001), and negative (ρ=–0.35, p<0.001) symptom scores (Figure 1).

The linear model method also yielded a negative correlation between the estimated treatment effect and placebo response, as observed for PANSS total (ρ=–0.32, p=0.002), positive (ρ=–0.29, p=0.006), and negative (ρ=–0.26, p<0.013) symptom scores (Figure 2).

Study-level data correlations

Data were analyzed from 66 clinical trials including 17,202 patients (see supplementary information)[5]. Consistent with correlations estimated from the individual patient data, across studies, we found a moderate negative correlation between placebo response and treatment effect for total (ρ=–0.39, p<0.001), as well as positive (ρ=–0.25, p=0.01) and negative (ρ=–0.38, p<0.001) symptom scores (Figure 3).

Table 1 Characteristics of the clinical trial providing individual patient data

YODA number	Sch-703
Clinical trial number	00650793
Description	6-week double-blind period followed by 52-week open-label period
Double-blind treatment	Paliperidone (6-12 mg daily), olanzapine (10 mg daily) Placebo
Open-label treatment	Paliperidone (3-12 mg daily)
Number of patients	384 (antipsychotic) 88 (placebo)
Patients' age, years (mean±SD)	36.6±10.8 (antipsychotic) 38.1±10.6 (placebo)
Patients' gender (% female)	50.5 (antipsychotic) 51.1 (placebo)
Duration of double-blind phase, days (mean±SD)	40.8±6.2 (antipsychotic) 35.7±10.0 (placebo)
Duration of open-label phase, days (mean±SD)	37.3±15.1 (antipsychotic) 33.8±16.9 (placebo)

YODA – Yale University Open Data Access

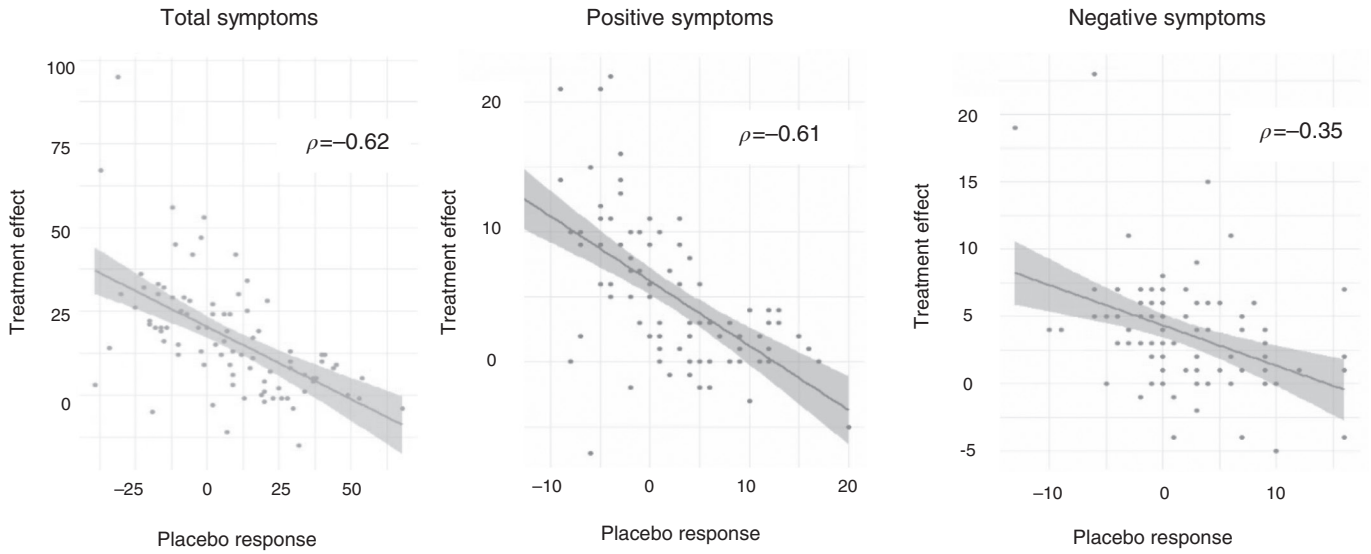

Figure 1 Correlation between treatment effects (estimated using the open-label method) and placebo response. Each point represents a participant.

Thus, we concluded that all three methods (which employ different assumptions) gave consistent evidence of a negative correlation between placebo response and treatment effect.

Treatment effect heterogeneity

Using the linear model method values of ρ, as these were the most conservative, a meta-analysis of treatment effect heterogeneity estimated the standard deviation for total symptoms to be 13.47 PANSS points (95% CI: 12.69-14.29, p<0.001, I^2=45%) (Figure 4). For positive symptoms, the estimate was 3.97 (95% CI: 3.66-4.30, p<0.001, I^2=53%) (Figure 5). For negative symptoms, it was 2.80 (95% CI: 2.54-3.08, p<0.001, I^2=57%) (Figure 6). When we used the least conservative estimates for ρ (those derived from the open-label method), the distribution of treatment effects was wider, pointing to even larger variability of treatment, with standard deviations for total, positive and negative symptoms of 23.3, 7.4 and 3.7 points, respectively.

The mean treatment effect was estimated as 8.6 points (95% CI: 7.8-9.4, I^2=38%, p<0.001) for total symptoms, 2.7 (95% CI: 2.3-3.1, I^2=35%, p<0.001) for positive symptoms, and 1.8 (95% CI: 1.5-2.0, I^2=27%, p<0.001) for negative symptoms.

The expected distribution of treatment effects based on these

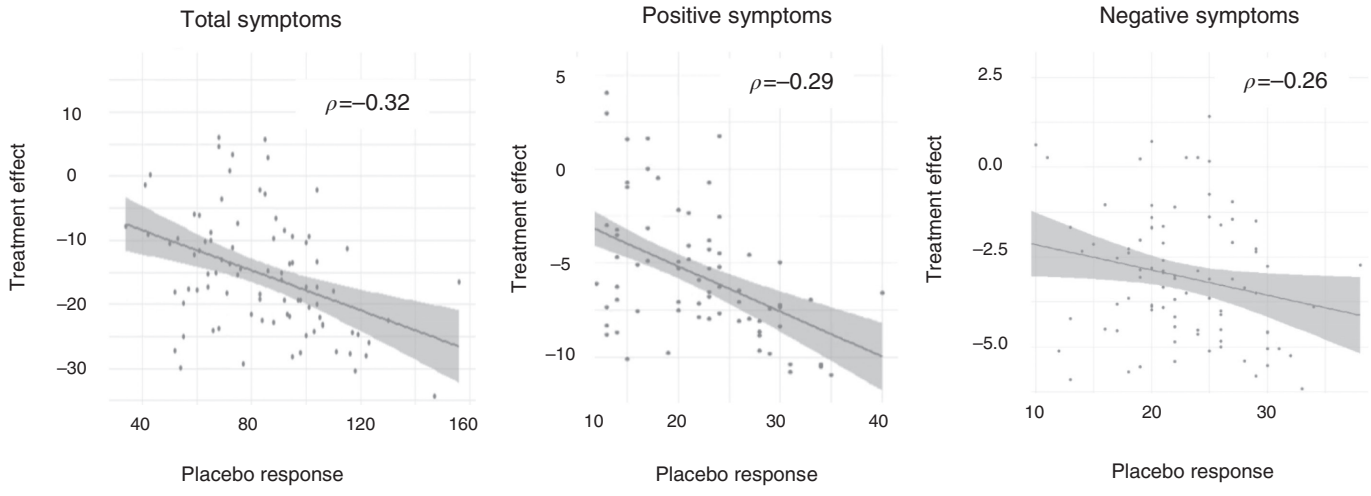

Figure 2 Correlation between treatment effects (estimated using the linear model method) and placebo response. Each point represents a participant.

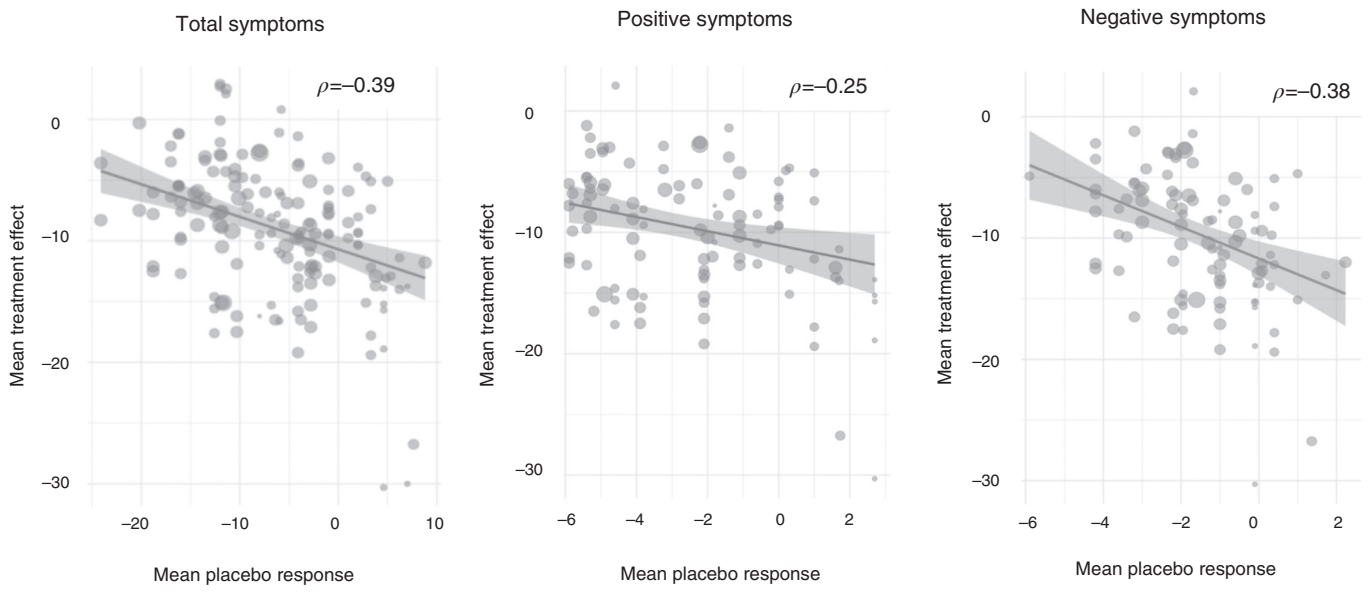

Figure 3 Relationship between study-level estimates of treatment effect and placebo response. Each point represents a clinical trial, with the size of the point proportional to the number of subjects in the trial.

values is illustrated in Figure 7. The figure is a density plot, effectively a smoothed histogram, which shows the distribution of expected treatment effects for a population of individuals with schizophrenia treated with antipsychotics. For total symptoms, the vertical lines denote the 25th and 75th percentile, located at –0.5 and 17.7 respectively. This means that 25% of the patients are expected to receive a benefit of at least 17.7 points on the PANSS, while another 25% are expected to experience a worsening of at least 0.5 points as compared to placebo. The remaining 50% are expected to receive a benefit between –0.5 and 17.7 on the PANSS. For positive symptoms, the 75th centile equates to an improvement of 5.4 points, and the 25th centile to a worsening of 0.05 points. For negative symptoms, the 75th centile equates to an improvement of 3.7 points, while the 25th centile equates to a deterioration of 0.1 points. The distribution suggests that 74%, 75% and 74% of patients will show a non-zero benefit in terms of total, positive and negative

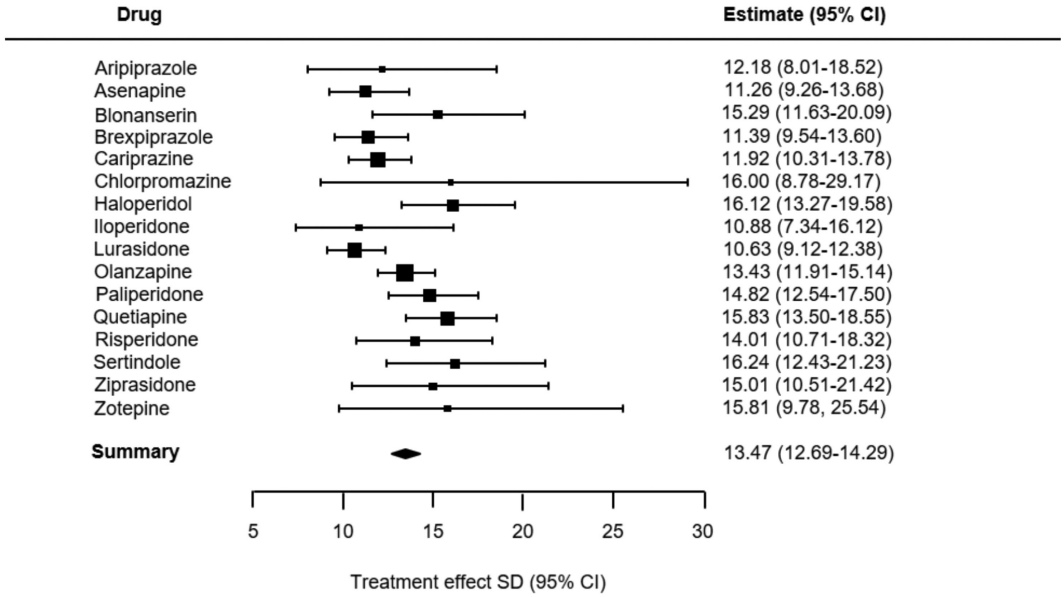

Figure 4 Total symptoms: meta-analysis of within-study estimates of the standard deviation (SD) of patient-level treatment effects of antipsychotics vs. placebo

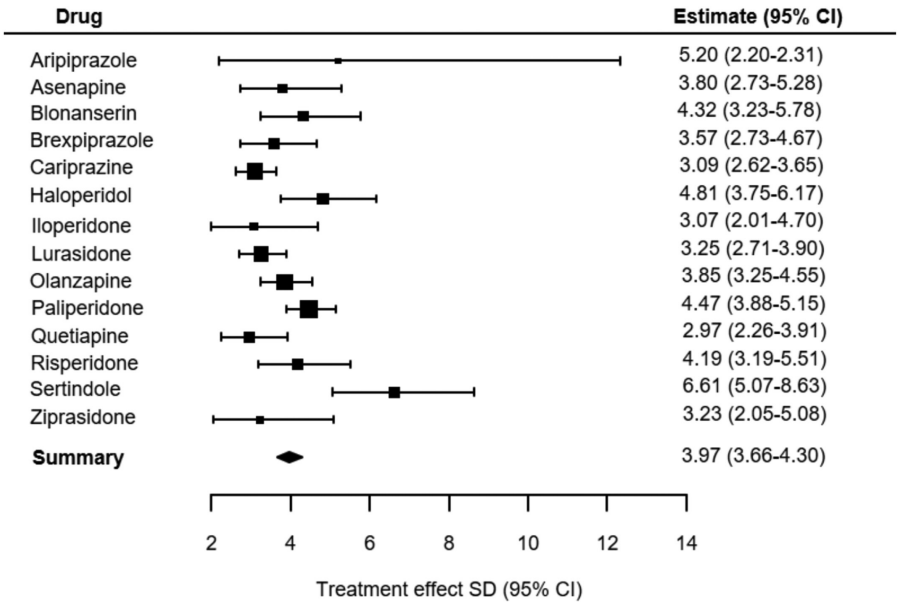

Figure 5 Positive symptoms: meta-analysis of within-study estimates of the standard deviation (SD) of patient-level treatment effects of antipsychotics vs. placebo

symptoms, respectively.

DISCUSSION

This study has found evidence of a marked variability in antipsychotic-specific effects between individuals with schizophrenia. According to our most conservative estimates, a quarter of individuals experience a substantial benefit of over 17 points on the PANSS total score, and a quarter present a detrimental effect relative to placebo. Clinically important treatment effect heterogeneity was also estimated for positive and negative symptom domains. These results suggest that the "one size fits all" approach to treating patients with a diagnosis of schizophrenia may be suboptimal, and provide support to efforts for developing personalized approaches to treatment[1,21-23]. The need for personalized approaches is apparent, since we have demonstrated that not only is treatment effect heterogeneity likely to exist, but that it may also

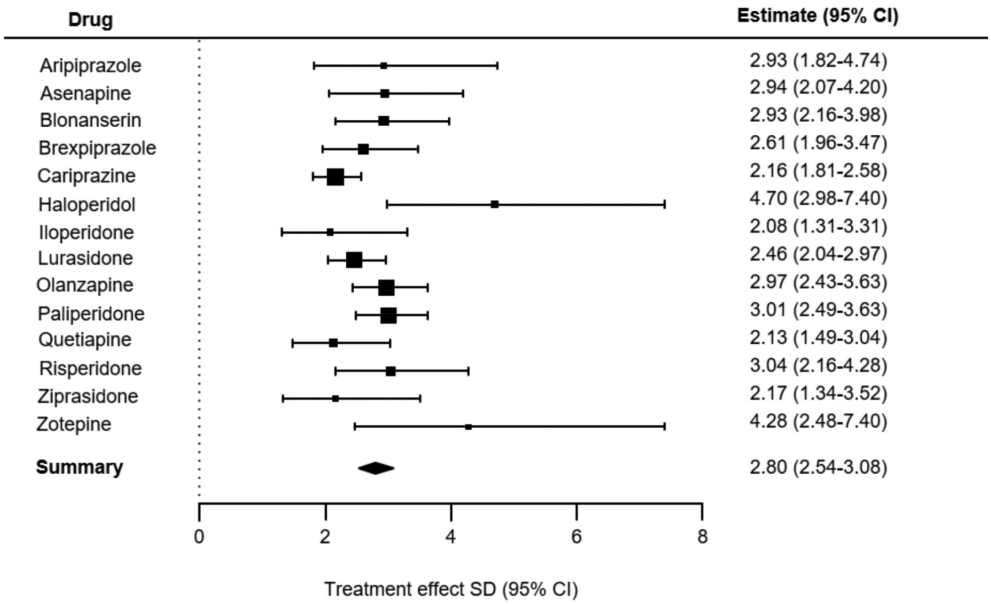

Figure 6 Negative symptoms: meta-analysis of within-study estimates of the standard deviation (SD) of patient-level treatment effects of antipsychotics vs. placebo

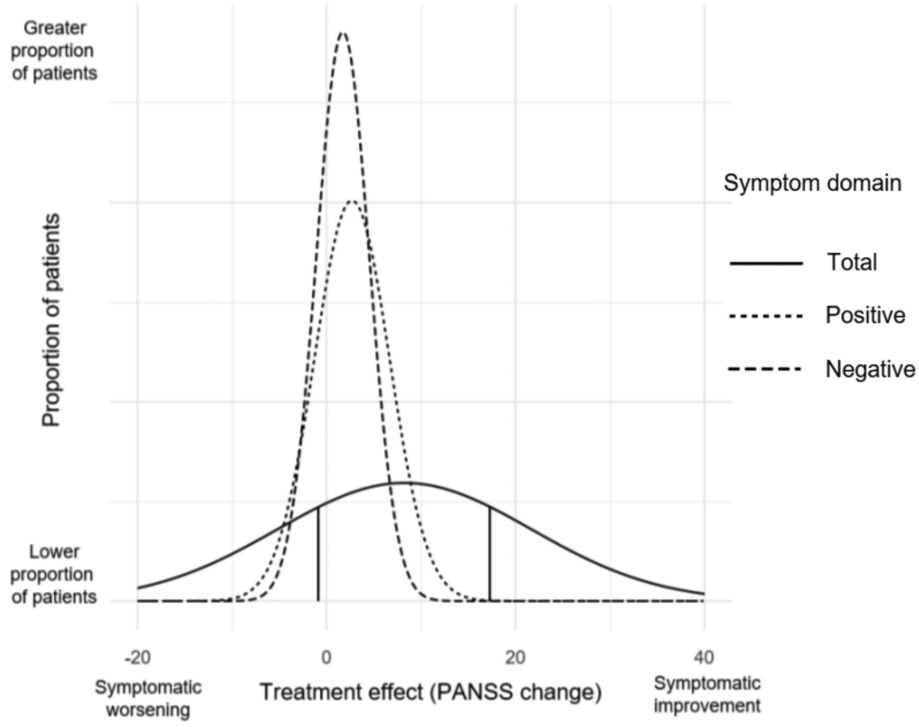

Figure 7 Distribution of treatment effects in the antipsychotic treatment of schizophrenia. The area under each curve equals 1, i.e. 100% of the patient population. In the case of total symptoms, solid vertical lines represent upper and lower quartiles. For total symptoms, 25% of individuals experience a treatment effect of at least 17.7 PANSS points, while 25% experience a negative effect of treatment of at least 0.5 points. PANSS – Positive and Negative Syndrome Scale.

be of a large and clinically meaningful magnitude.

Since individual patients differ from one another in terms of their overall response to antipsychotic treatment, it has long been assumed that they also differ in terms of the medication-specific benefit they get from the drug. This has been supported by findings from individual patient data meta-analyses[12-14]. This interpretation was recently challenged by meta-analyses which suggested that antipsychotics may in fact deliver relatively constant medication-specific effects, and that clinically observed variability was therefore secondary to variability of factors not directly related to medications, such as treatment-unrelated fluctuation in symptom severity or expectation effects, and measurement error[5,7].

In the present paper, we bridge the gap between the conclusions of variability meta-analyses and those of individual patient data analyses and clinical experience. We show that the evidence is consistent, with the discrepancy in conclusions resulting from a previously imprecise interpretation of the VR. Specifically, previous meta-analyses of variability did not formally tie the VR to the outcome of interest: the heterogeneity of treatment effects. To undertake this vital step, we estimated the correlation coefficient between placebo response and treatment effects with three different methods. We found this correlation to be consistently negative and, as a result, our findings reconciled inconsistencies in findings of variability meta-analyses, previous individual patient data meta-analyses, and clinical experience, suggesting that meaningful heterogeneity of antipsychotic treatment effects exists in adult patients with schizophrenia.

Our open-label method for estimating individual treatment effects involved calculating placebo responses in individuals who had previously received antipsychotic treatment. This is unavoidable, due to a lack of available trials of suitable design in antipsychotic-naïve individuals, but it has potential disadvantages. In addition to possible carry-over effects, withdrawal effects and placebo responses are enmeshed and, as a result, our estimates of variability may partly reflect the variability of withdrawal effects. To disentangle withdrawal and placebo responses in cross-over designs is complex but not impossible, and could be considered in studies aiming to further unpack individual variability of response[24]. The open-label method also assumes that the change in symptom severity with an active compound following a period of placebo treatment is a fair estimate of the treatment effect; whether this is fully justified is not known, although our group-level findings suggest that this may be a reasonable assumption.

The linear method for estimating treatment effects did not employ data from the open-label phase and so does not rely on the same assumptions. It does, however, estimate treatment effects and placebo response after assuming linear, non-interacting relations between symptom scores and the baseline covariates of age, gender, and symptom severity. Moreover, given that other covariates are likely to play a significant role in determining both placebo response and treatment effects, the estimates produced may not be entirely accurate.

The study-level calculation of the placebo-treatment effect cor-

relation circumvents shortcomings of the individual-level analyses. This analysis, however, runs the risk of aggregation bias ("ecological fallacy"), i.e. a correlation observed across studies at the study level may not reflect correlation at the individual level.

Nevertheless, concerns about the three approaches are mitigated by the consistency of findings between them. In addition, a negative correlation was *a priori* expected, as greater placebo response in an individual leaves less room for an additional treatment effect, and there are not reasons to believe that any of the methods would produce a bias towards a negative correlation. In addition, we believe that our estimate of the correlation coefficient is the best one currently available and, as such, its use is indicated, since the adoption of some form of coefficient is required to make any valid inference from VRs.

Other psychiatric treatments, including antidepressants[6,11] and brain stimulation[10], have also recently been examined in meta-analyses of VRs. As with the initial variability analyses of antipsychotic trials, the conclusion of these studies has been that minimal heterogeneity of treatment effects exists. However, this conclusion depends on the assumption of a positive correlation between placebo and treatment effects, which, as the results above demonstrate, may well not be the case.

Future work should seek to identify the correlation between treatment effects and placebo response in other disorders and with other treatments. The estimation of this correlation will then allow for determination as to whether interindividual heterogeneity of treatment effects also exists in these disorders. It would also be of interest to see if outcome measures other than symptom rating scales, such as functioning, adverse effects, and cognitive measures, show similar heterogeneity of treatment effects[25].

CONCLUSIONS

The current findings support the hypothesis that substantial interindividual heterogeneity exists in terms of symptomatic response to antipsychotic treatment in schizophrenia. In turn, these findings support efforts to provide treatment personalization[1]. Future work should aim to identify which medications and symptom domains are most likely to benefit from personalized precision approaches.

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Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum disorders: a network meta-analysis of 92 randomized trials including 22,645 participants

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According to current evidence and guidelines, continued antipsychotic treatment is key for preventing relapse in people with schizophrenia-spectrum disorders, but evidence-based recommendations for the choice of the individual antipsychotic for maintenance treatment are lacking. Although oral antipsychotics are often prescribed first line for practical reasons, long-acting injectable antipsychotics (LAIs) are a valuable resource to tackle adherence issues since the earliest phase of disease. Medline, EMBASE, PsycINFO, CENTRAL and CINAHL databases and online registers were searched to identify randomized controlled trials comparing LAIs or oral antipsychotics head-to-head or against placebo, published until June 2021. Relative risks and standardized mean differences were pooled using random-effects pairwise and network meta-analysis. The primary outcomes were relapse and dropout due to adverse events. We used the Cochrane Risk of Bias tool to assess study quality, and the CINeMA approach to assess the confidence of pooled estimates. Of 100 eligible trials, 92 (N=22,645) provided usable data for meta-analyses. Regarding relapse prevention, the vast majority of the 31 included treatments outperformed placebo. Compared to placebo, "high" confidence in the results was found for (in descending order of effect magnitude) amisulpride-oral (OS), olanzapine-OS, aripiprazole-LAI, olanzapine-LAI, aripiprazole-OS, paliperidone-OS, and ziprasidone-OS. "Moderate" confidence in the results was found for paliperidone-LAI 1-monthly, iloperidone-OS, fluphenazine-OS, brexpiprazole-OS, paliperidone-LAI 1-monthly, asenapine-OS, haloperidol-OS, quetiapine-OS, cariprazine-OS, and lurasidone-OS. Regarding tolerability, none of the antipsychotics was significantly worse than placebo, but confidence was poor, with only aripiprazole (both LAI and OS) showing "moderate" confidence levels. Based on these findings, olanzapine, aripiprazole and paliperidone are the best choices for the maintenance treatment of schizophrenia-spectrum disorders, considering that both LAI and oral formulations of these antipsychotics are among the best-performing treatments and have the highest confidence of evidence for relapse prevention. This finding is of particular relevance for low- and middle-income countries and constrained-resource settings, where few medications may be selected. Results from this network meta-analysis can inform clinical guidelines and national and international drug regulation policies.

Key words: Relapse prevention, maintenance treatment, schizophrenia-spectrum disorders, oral antipsychotics, long-acting antipsychotics, olanzapine, aripiprazole, paliperidone

(World Psychiatry 2022;21:295–307)

Schizophrenia-spectrum disorders are considered to be major drivers of the global burden of disease, as measured in prevalence, disability-adjusted life-years, and years lived with disability. More than 50% of diagnosed individuals have long-term, intermittent symptoms of psychosis, and around 20% have chronic symptoms and disability[1]. According to currently available evidence, regular pharmacological treatment since the early phases of disease may represent a key element for preserving neurocognitive abilities, preventing structural brain changes, and hindering the progression towards chronic functional deterioration[2-4].

Many randomized controlled trials (RCTs) have compared oral antipsychotics for the treatment of acute symptoms of schizophrenia and related disorders[5], while fewer studies are available for long-term, maintenance treatment[6-8]. According to a recent Cochrane review[9] and a network meta-analysis (NMA) on long-acting injectable antipsychotics (LAIs)[10], maintenance treatment with antipsychotics prevents relapse to a significantly greater extent than placebo for up to two years of follow-up, although long-term adverse effects must be carefully monitored over time[11,12].

Current guidelines agree in recommending maintenance treatment for at least one year after the first episode of psychosis, while intermittent treatment is discouraged[13,14]. However, it has been estimated that up to one half of individuals suffering from schizophrenia may not take their medications as prescribed and even less are fully adherent to antipsychotic treatment[15,16], and that non-adherence is among the most important predictors of relapse[17-19]. For this reason, an earlier and wider use of LAIs has been suggested in order to prevent discontinuation, relapse and hospitalization since the earliest phases of disease[10,20-22]. Still, individuals who begin antipsychotic treatment are usually prescribed oral formulations, as they allow easier titration, as well as more rapid tapering and discontinuation in case of adverse events. At such an early illness phase, future levels of adherence are difficult to predict, and switching to an LAI formulation might be needed without delay if the issue of non-adherence arises. Thus, it is of clinical relevance to identify which antipsychotics, including those available in both oral and LAI formulations, are the most tolerable, effective, and supported by the highest certainty of evidence.

Systematic reviews of studies assessing the comparative effectiveness and tolerability of both oral antipsychotics and LAIs vs. placebo and head-to-head for the prevention of relapse are relatively sparse. One systematic review and meta-analysis each compared the long-term effectiveness of first- vs. second-generation antipsychotics[8] and of second-generation antipsychotics between each other[7], and one NMA attempted to pool together both formulations[6]. However, several new studies have been conducted since then, and some existing studies were not included[9,10]. Furthermore, prior meta-analyses mixed together studies where patients were randomized during the acute exacerbation with studies where patients were randomized after clinical stabilization had occurred, which could have yielded biased results due to differential rates of stabilization across treatment arms.

This study aimed to assess the differential effectiveness and tolerability of oral antipsychotics and LAIs for the maintenance treatment of schizophrenia-spectrum disorders by applying a NMA approach, eliminating trials where randomization had occurred during the acute phase.

METHODS

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines specific for NMA[24]. The study protocol was registered in advance in the Open Science Forum (https://osf.io/3nb4s).

Study selection and data extraction

We searched for RCTs including adults (≥18 years old) diagnosed with schizophrenia-spectrum disorders (including schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and psychotic disorders not otherwise specified), according to validated diagnostic systems (DSM or ICD), and requiring antipsychotic maintenance treatment. We considered only studies randomizing clinically stable patients at baseline. Whenever this was not clearly stated by the study authors, clinical stability was ascertained on the basis of the mean score on a rating scale at baseline, according to validated cut-offs for severity – i.e., Brief Psychiatric Rating Scale (BPRS): ≤44; Positive and Negative Syndrome Scale (PANSS): ≤78; Clinical Global Impression-Severity (CGI-S): ≤4[25,26].

All available oral antipsychotics and LAIs, according to the Anatomical Therapeutic Chemical with Defined Daily Dose (ATC/DDD) classification (https://www.whocc.no/atc_ddd_index), were eligible. Studies comparing an antipsychotic with a mix of different antipsychotics were excluded. We excluded RCTs lasting <12 weeks, as previously suggested[27].

We searched without time or language restrictions the Medline, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) electronic databases. We performed additional searches in databases of regulatory agencies (e.g., US Food and Drug Administration, European Medicines Agency), online trial registers (e.g., clinicaltrials.gov; controlled-trials.com; World Health Organization (WHO)'s International Clinical Trials Registry Platform) and websites of pharmaceutical companies producing antipsychotics. We searched records from database inception to June 8, 2021 (for full search strategy, see supplementary information).

Two authors independently assessed titles, abstracts and full texts of potentially relevant articles, and two others extracted data following recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[28]. Two authors assessed the methodological quality of included studies using the Cochrane Risk of Bias version 2 (RoB2) tool[29]. Disagreements were resolved by discussion and consensus with a third author.

Outcomes

Two co-primary outcomes were analyzed: relapse (i.e., the number of participants experiencing at least one relapse by the end of the trial, as a proportion of the total of randomized participants) and tolerability (i.e., the number of participants who dropped out by the end of the trial because of an adverse event, as a proportion of the total of randomized participants). The definition of relapse provided by each study was considered. If data were not available, the number of relapses was imputed according to commonly used cut-off scores on validated rating scales measuring psychopathology (i.e., PANSS increase ≥25%; BPRS increase ≥30%; CGI-S increase ≥2 points)[30-32], using a validated methodology[33].

Secondary outcomes included: a) mean change score on validated rating scales measuring psychopathology at the end of the trials ("efficacy"); b) number of participants who dropped out by the end of the trial for any cause; c) number of participants who were admitted to hospital for psychiatric relapse by the end of the trial; d) mean change score on validated rating scales measuring quality of life at the end of the trial; e) mean change score on validated rating scales measuring the level of functioning at the end of the trial; f) common antipsychotic-related adverse events, including sedation, insomnia, QTc prolongation, anticholinergic symptoms, weight gain, hyperprolactinaemia, extrapyramidal symptoms, akathisia, and tardive dyskinesia.

Statistical analysis

We performed a standard pairwise, random-effects meta-analysis for every comparison, and, for each outcome, we also conducted a NMA with a random-effects model in a frequentist framework, using the R software[34] *netmeta* package and the Stata[35] *mvmeta* package. For dichotomous outcomes, we calculated and pooled relative risks (RRs) with 95% confidence intervals (CIs). For continuous outcomes, we pooled the mean differences (MDs) between treatment arms at the end of the study if all trials

used the same rating scale; otherwise, we pooled standardized mean differences (SMDs).

We calculated dichotomous data on a strict intention-to-treat (ITT) basis, considering the total number of randomized participants as the denominator. For continuous variables, we applied a modified ITT analysis, whereby participants with at least one post-baseline measurement were represented by their last observation carried forward (LOCF). When a study included different arms of the same antipsychotic (oral or LAI) at different doses, we pooled these arms into a single one[28], provided that they were administered within a therapeutic dose range[36,37]. Very low doses of antipsychotics were considered as pseudo-placebo, as endorsed by regulatory agencies[38], and pooled together with placebo in the analysis. Furthermore, following a pragmatic approach and considering their pharmacological similarity[39], fluphenazine enanthate and decanoate, as well as clopenthixol and zuclopenthixol decanoate, were pooled together in the analysis.

We asked trial authors to supply missing data or, alternatively, we imputed them with validated statistical methods[28]. Particularly, we calculated missing standard deviations (SDs) based on the standard error (SE), t-statistics or p values[40]. If this was not possible, we substituted missing SDs with a weighed mean of SDs reported in the other included trials[41]. As a last option, we used the SD of the mean baseline score.

For pairwise meta-analyses, we assessed heterogeneity by visual inspection of forest plots, and by the I-squared statistics. For the NMA, common heterogeneity across all comparisons was assumed and estimated in each network[42,43].

We assessed global heterogeneity by using the τ^2 and the I^2 statistics. As previously suggested[23], we compared the common τ^2 to the empirical distributions of heterogeneity found in meta-analyses of pharmacological treatments for mental health outcomes, showing a median of the τ^2 distribution of 0.049 and an inter-quartile range (IQR) of 0.010 to 0.242[44], and considered heterogeneity low when the estimated τ^2 was below the 25% quartile, moderate between the 25% and the 50% quartile, and high above 50% quartile. The I^2 statistics was interpreted according to the Cochrane handbook: 0-40%: might not be important; 30-60%: may represent moderate heterogeneity; 50-90%: may represent substantial heterogeneity; 75- 100%: considerable heterogeneity[29].

According to the assumption of transitivity, effect modifiers should be equally distributed across the comparisons. We extracted the key study characteristics judged to be potential effect modifiers, i.e. sample size, year of publication, follow-up duration, blinding (double-blind vs. open-label), industry sponsorship, placebo relapse rate, overall dropout rate, mean age, percentage of female participants, mean score of overall psychopathology at baseline, and dose of medication (expressed as a ratio between prescribed daily dose and defined daily dose)[45]. By comparing the distribution of these possible effect modifiers across treatments included in the NMA using the Kruskal-Wallis test, and assessing their actual impact on the treatment effect through meta-regression analyses, we formulated a judgment on whether distribution differences were large enough to threaten the validity of the analysis[46].

We evaluated the presence of inconsistency by comparing direct and indirect evidence within each closed loop by applying the separating indirect from direct evidence (SIDE) approach[47,48]. We further compared the goodness of fit for a NMA model assuming consistency with a model allowing for inconsistency in a "design-by-treatment interaction model" framework[49-51], using the *decompose.design* function in R package *netmeta*[52].

For the co-primary outcomes, we calculated the probability of each treatment of being at each possible rank, and produced a treatment hierarchy by means of surface under the cumulative ranking curve (SUCRA) and mean ranks with the R *gemtc* package[53].

If ≥10 studies were included in a primary outcome, we assessed publication bias by visually inspecting the funnel plot, testing for asymmetry with the Egger's regression test[54], and investigating possible reasons for funnel plot asymmetry.

For each co-primary outcome, we assessed the confidence of evidence by using the Confidence in Network Meta-Analysis (CINeMA) methodology[55,56] and its web-based application (http://cinema.ispm.ch).

For the co-primary outcomes, we conducted sensitivity analyses excluding trials: a) not employing double-blind design; b) with overall high risk of bias according to RoB2; c) for which information about clinical stability was assumed based on mean rating scale scores at baseline; d) with follow-up duration <1 year; e) where treatment effectiveness was not the primary outcome; and f) placebo-controlled.

We performed meta-regression analyses to assess if the following covariates acted as moderators of treatment effect: sample size, year of publication, follow-up duration, blinding (double-blind vs. open-label), industry sponsorship, placebo relapse rate, overall dropout rate, mean age, percentage of female participants, mean score of overall psychopathology at baseline, and dose of medication. In particular, for each potential effect modifier, we first tested the hypothesis of equality of parameters related to interaction terms between the covariate and treatment indicators; then, in case of non-rejection of such hypothesis, we evaluated statistical significance of the common covariate parameter; otherwise, we assessed the global significance of each covariate-treatment interaction.

RESULTS

We identified 3,418 records after database and hand-search. After removing duplicates and examining titles and abstracts, we selected 514 records for full-text assessment. Of these, 100 primary studies were eligible for inclusion (corresponding to 99 full-text articles[57-155], as one paper reported on two trials). Of these, 92 studies, including 22,645 participants, provided data for ≥1 outcome of interest (see Figure 1). The list of included and excluded studies, and the detailed characteristics of included studies, are provided in the supplementary information.

The mean sample size of included studies was 274 individuals (range: 49 to 1,098; median: 134), with 42 studies (45.6%) including

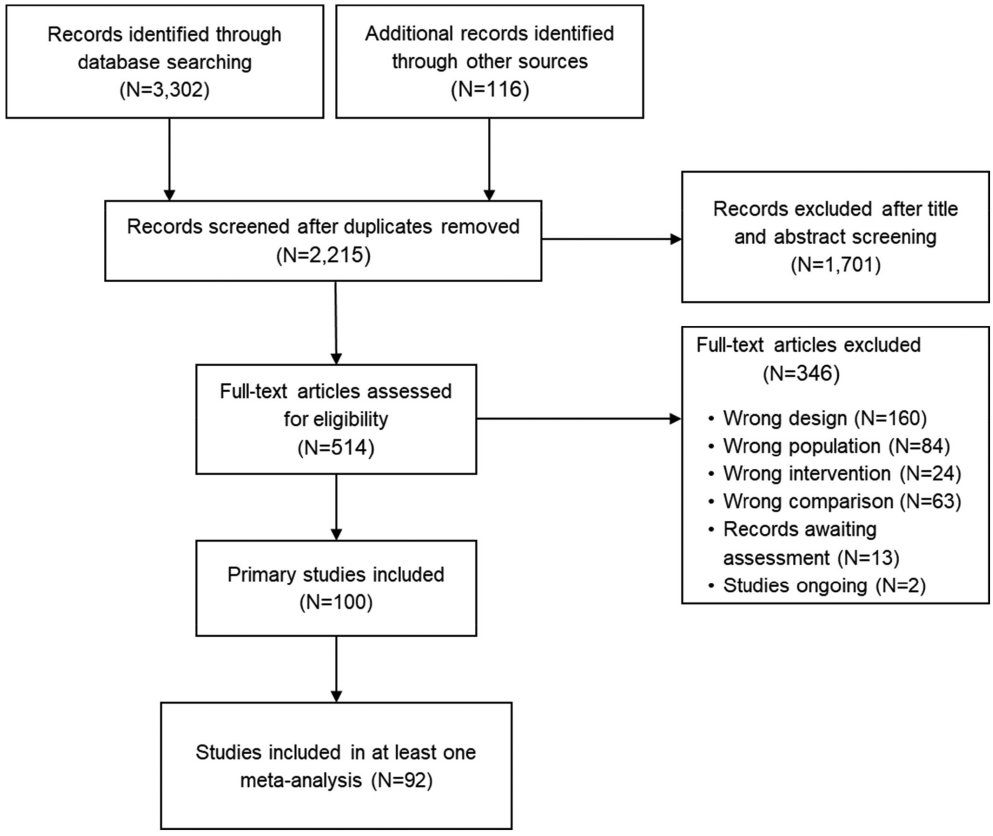

Figure 1 PRISMA flow chart

≤50 participants. The mean age of included participants was 39.2 years (range: 21.5 to 69.6; median: 39.7). Four studies included only males. In the remaining studies, the mean proportion of included women was 38.1% (range: 8 to 74%; median: 39%). According to the RoB2, 34.1% of the studies had an overall high risk of bias for the outcome relapse, and 16.7% for the outcome tolerability (see supplementary information).

Table 1 describes the characteristics of studies included in the two primary analyses, and Figures 2 and 3 show the corresponding network plots. Figures 4 and 5 show the forest plots comparing each antipsychotic with placebo for the two primary outcomes. Results were grouped according to the level of confidence as assessed by CINeMA. The transitivity assumption was not violated for any of the potential effect modifiers analyzed (see supplementary information).

In terms of relapse prevention, all antipsychotics – with the exception of clopenthixol-oral (OS), haloperidol-LAI and (zu) clopenthixol-LAI – were significantly more effective than placebo. "High" confidence was found for the following antipsychotics (ordered from the largest to the smallest point estimate): amisulpride-OS, olanzapine-OS, aripiprazole-LAI, olanzapine-LAI, aripiprazole-OS, paliperidone-OS, and ziprasidone-OS. "Moderate" confidence was found for the following antipsychotics (ordered from the largest to the smallest point estimate): paliperidone-LAI 1-monthly, iloperidone-OS, fluphenazine-OS, brexpiprazole-OS, paliperidone-LAI 1-monthly, asenapine-OS, haloperidol-OS, quetiapine-OS, cariprazine-OS, and lurasidone-OS. For the remaining antipsychotics, the confidence in the estimate was "low" or "very low" (see Figure 4).

Head-to-head comparisons showed relatively few statistically significant differences between antipsychotics. Among those with moderate-to-high confidence according to CINeMA, aripiprazole-LAI was more effective than lurasidone-OS; olanzapine-OS than cariprazine-OS, chlorpromazine-OS, haloperidol-OS and lurasidone-OS; paliperidone-LAI 3-monthly than cariprazine-OS, chlorpromazine-OS, lurasidone-OS and ziprasidone-OS; risperidone-LAI than lurasidone-OS (see supplementary information).

In the pairwise meta-analyses, moderate heterogeneity (i.e., I^2>50%) was detected for the following pairwise comparisons: aripiprazole-OS, olanzapine-OS, quetiapine-OS and trifluoperazine-OS vs. placebo; olanzapine-OS vs. asenapine-OS. Substantial heterogeneity (i.e., I^2>75%) was detected for risperidone-OS vs. quetiapine-OS. Overall, the NMA showed low-to-moderate heterogeneity (τ^2=0.056; I^2=32.8%, 95% CI: 9.8% to 49.9%), and no overall incoherence emerged according to the global approach (design-by-treatment test, p=0.089), while the local SIDE approach showed significant inconsistency of two comparisons (placebo vs. pimozide-OS; pimozide-OS vs. trifluoperazine-OS).

Fluphenazine-LAI, penfluridol-OS, paliperidone-LAI 3-monthly, flupenthixol-LAI, olanzapine-OS and amisulpride-OS

Table 1 Characteristics of randomized controlled trials included in each network of primary outcomes

	Relapse network	Tolerability network
Number of studies	89	81
Number of individuals included	22,275	21,504
Age (years, mean±SD)	39.0±11.9	38.9±11.9
Gender (% women)	36.4	37.7
Mean follow-up (% studies)		
12 to 26 weeks	37.1	37.0
27 to 52 weeks	44.9	44.4
53 weeks or more	18.0	18.6
Blinding (% studies)		
Double-blind	73.0	74.1
Open-label	27.0	25.9
Year of publication (% studies)		
Until 1989	28.1	25.9
1990 to 2009	33.7	34.6
2010 to 2019	38.2	39.5
Type of studies (% studies)		
Placebo-controlled	33.7	33.3
Only active comparator	66.3	66.7
Including oral formulation	73.0	72.8
Including LAI formulation	49.4	49.4
Setting (% studies)		
Inpatients	20.2	18.5
Outpatients	56.2	55.6
Mixed	23.6	25.9

LAI – long-acting injectable antipsychotic

ranked best according to the mean SUCRA. However, only for paliperidone-LAI 3-monthly, olanzapine-OS and amisulpride-OS the confidence in the evidence was "moderate" or "high" compared to placebo. In most cases, "low" or "very low" estimates were due to incoherence and within-study bias (see Figure 4 and supplementary information).

Sensitivity analyses suggested that placebo-controlled studies might have been responsible for most of the observed heterogeneity. Removing studies with high risk of bias, those for which stability was imputed, those with less than one year of follow-up, and placebo-controlled studies reduced the observed local and global inconsistency. Despite this, effect estimates from sensitivity analyses did not change significantly compared to the primary analysis (see supplementary information).

Meta-regression analyses showed that only the clinical severity at baseline was a statistically significant effect modifier, with studies randomizing more severely ill individuals showing a smaller effect size. However, results of a *post-hoc* sensitivity analysis excluding people who were markedly ill at baseline were not significantly different from the primary analysis (see supplementary information).

Compared to placebo, none of the antipsychotics included showed significant differences in terms of tolerability (dropouts due to adverse events), with the only exception of olanzapine-OS, which was more tolerable than placebo. However, only for aripiprazole-LAI and aripiprazole-OS the confidence according to the CINeMA assessment was "moderate", while it was "low" or "very low" for all remaining treatments (see Figure 5).

Head-to-head analyses showed olanzapine-OS to be more tolerable than haloperidol-OS, iloperidone-OS and lurasidone-OS; and olanzapine-LAI to be more tolerable than iloperidone-OS and fluphenazine-LAI.

Substantial heterogeneity (i.e., I^2>75%) was detected for two pairwise comparisons (olanzapine-OS vs. placebo; ziprasidone-OS vs. haloperidol-OS). Overall, the NMA showed moderate heterogeneity (τ^2=0.078; I^2=20.9%, 95% CI: 0% to 42.8%). Incoherence was detected according to the global approach (design-by-treatment test, p=0.01), while the local SIDE approach showed significant inconsistency between placebo and asenapine-OS, fluphenazine-LAI and haloperidol-OS, olanzapine-OS and quetiapine-OS. Pimozide-OS, flupenthixol-LAI, (zu)clopenthixol-LAI, olanzapine-OS and amisulpride-OS ranked best according to the mean SUCRA. However, for all of these comparisons, the confidence in the evidence was "low" or "very low". In most cases, "low" or "very low" estimates were due to incoherence, imprecision and within-study bias (see Figure 5 and supplementary information).

Sensitivity analyses suggested that placebo-controlled studies were the main source of the observed heterogeneity. Local and global inconsistency was notably reduced when removing studies with less than one year of follow-up (global approach: from p=0.09 to p=0.51; local SIDE approach: from two to zero inconsistent comparisons) and placebo-controlled studies (global approach: from p=0.09 to p=0.88; local SIDE approach: from two to zero inconsistent comparisons). Despite this, effect estimates from sensitivity analyses did not change significantly compared to the primary analysis (see supplementary information).

With regard to efficacy-related secondary outcomes, in descending ranking order of effect as compared to placebo, sertindole-OS, olanzapine-LAI, risperidone-LAI, olanzapine-OS, paliperidone-LAI 3-monthly, risperidone-LAI and fluphenazine-LAI showed lower risk of hospitalization for psychiatric relapse; brexpiprazole-OS, lurasidone-OS, pimozide-OS, sertindole-OS, ziprasidone-OS, iloperidone-OS, olanzapine-OS, asenapine-OS, risperidone-OS, cariprazine-OS, paliperidone-OS, risperidone-LAI, aripiprazole-OS, olanzapine-LAI, haloperidol-OS, aripiprazole-OS, paliperidone-LAI 3-monthly, paliperidone-LAI 1-monthly and quetiapine-OS showed larger reduction of mean rating scale scores at study endpoint; (zu)clopenthixol-LAI, pimozide-OS, olanzapine-OS, aripiprazole-LAI, trifluoperazine-OS, paliperidone-LAI 3-monthly, haloperidol-LAI, olanzapine-LAI, amisulpride-OS, asenapine-OS, aripiprazole-OS, fluphenazine-LAI, haloperidol-OS and risperidone-OS showed lower risk of total dropouts.

With regard to tolerability-related secondary outcomes, in descending ranking order of effect as compared to placebo, risperidone-LAI, paliperidone-OS, lurasidone-OS and risperidone-OS

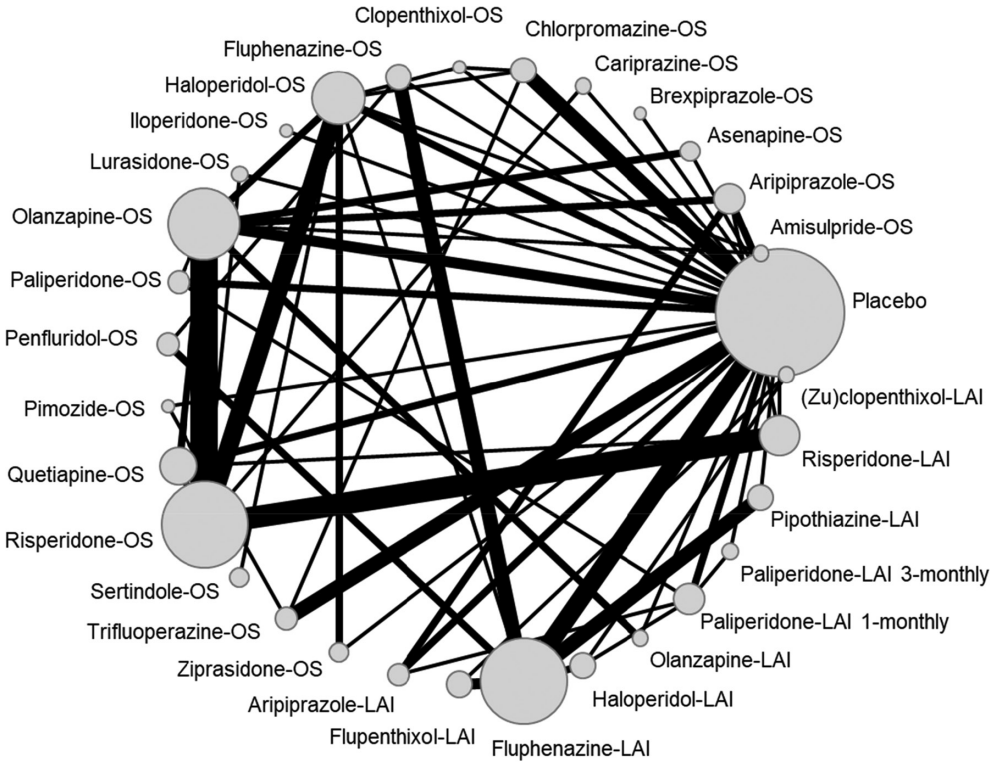

Figure 2 Network plot of evidence for relapse. The thickness of lines is proportional to the number of studies comparing the two treatments, and the size of circles is proportional to the number of individuals for each treatment. LAI – long-acting injectable antipsychotic, OS – oral antipsychotic

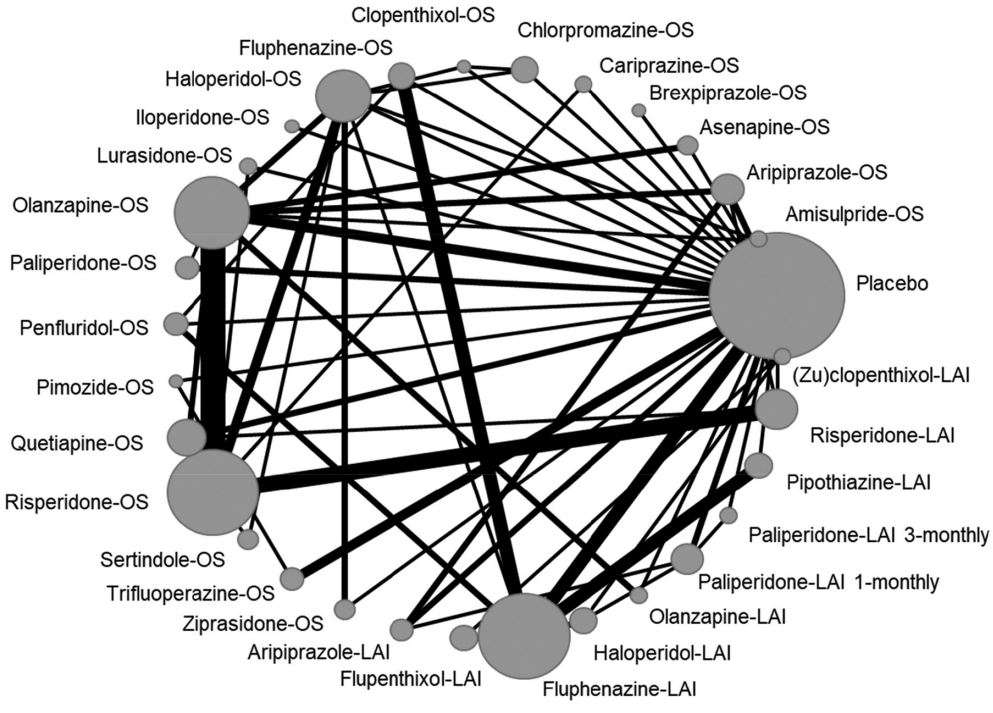

Figure 3 Network plot of evidence for tolerability. The thickness of lines is proportional to the number of studies comparing the two treatments, and the size of circles is proportional to the number of individuals for each treatment. LAI – long-acting injectable antipsychotic, OS – oral antipsychotic

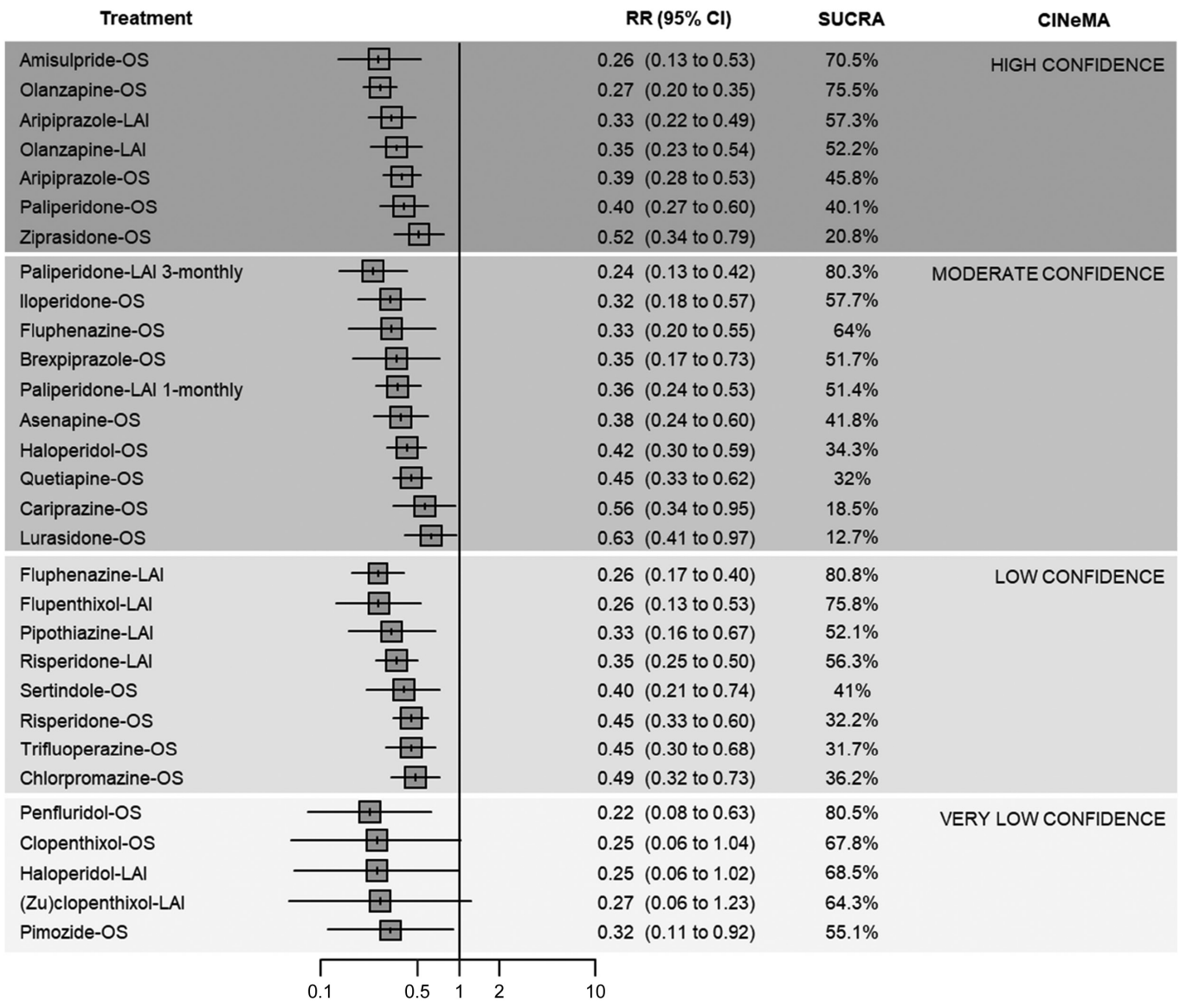

Figure 4 Forest plot comparing each antipsychotic with placebo for relapse, with the corresponding ranking probability (SUCRA) and certainty of evidence (CINeMA). LAI – long-acting injectable antipsychotic, OS – oral antipsychotic, RR – relative risk, SUCRA – surface under the cumulative ranking, CINeMA – Confidence In Network Meta-Analysis

showed significantly higher risk of sedation; aripiprazole-OS, olanzapine-LAI, olanzapine-OS, paliperidone-LAI 1-monthly and paliperidone-LAI 3-monthly showed significantly higher risk of weight gain; haloperidol-OS, fluphenazine-LAI and pipothiazine-LAI showed significantly higher risk of extrapyramidal symptoms; haloperidol-OS, haloperidol-LAI and trifluoperazine-OS showed significantly higher risk of akathisia; olanzapine-OS, olanzapine-LAI, paliperidone-LAI 1-monthly, paliperidone-LAI 3-monthly, risperidone-LAI, risperidone-OS and paliperidone-OS showed significantly higher risk of hyperprolactinaemia; olanzapine-OS, olanzapine-LAI, asenapine-OS, paliperidone-LAI 3-monthly and risperidone-OS showed significantly lower risk of insomnia. No antipsychotics showed higher risk of QTc prolongation and tardive dyskinesia as compared to placebo, although CIs were imprecise for most comparisons. For anticholinergic symptoms, a NMA could not be carried out, as data were relatively few and the network poorly connected (four sub-networks were identified); pairwise meta-analyses showed a higher risk for risperidone-LAI and quetiapine-OS as compared to placebo (see supplementary information).

Efficacy measured with rating scales, hospitalization rates and dropouts due to any cause was generally in line with findings from the primary analysis, while data on quality of life, functioning, and some common adverse events (particularly anticholinergic symptoms, QTc change, tardive dyskinesia) were relatively scarce. Significant incoherence and high heterogeneity were not detected for any of these outcomes, with the only exception of efficacy measured with rating scales (see supplementary information).

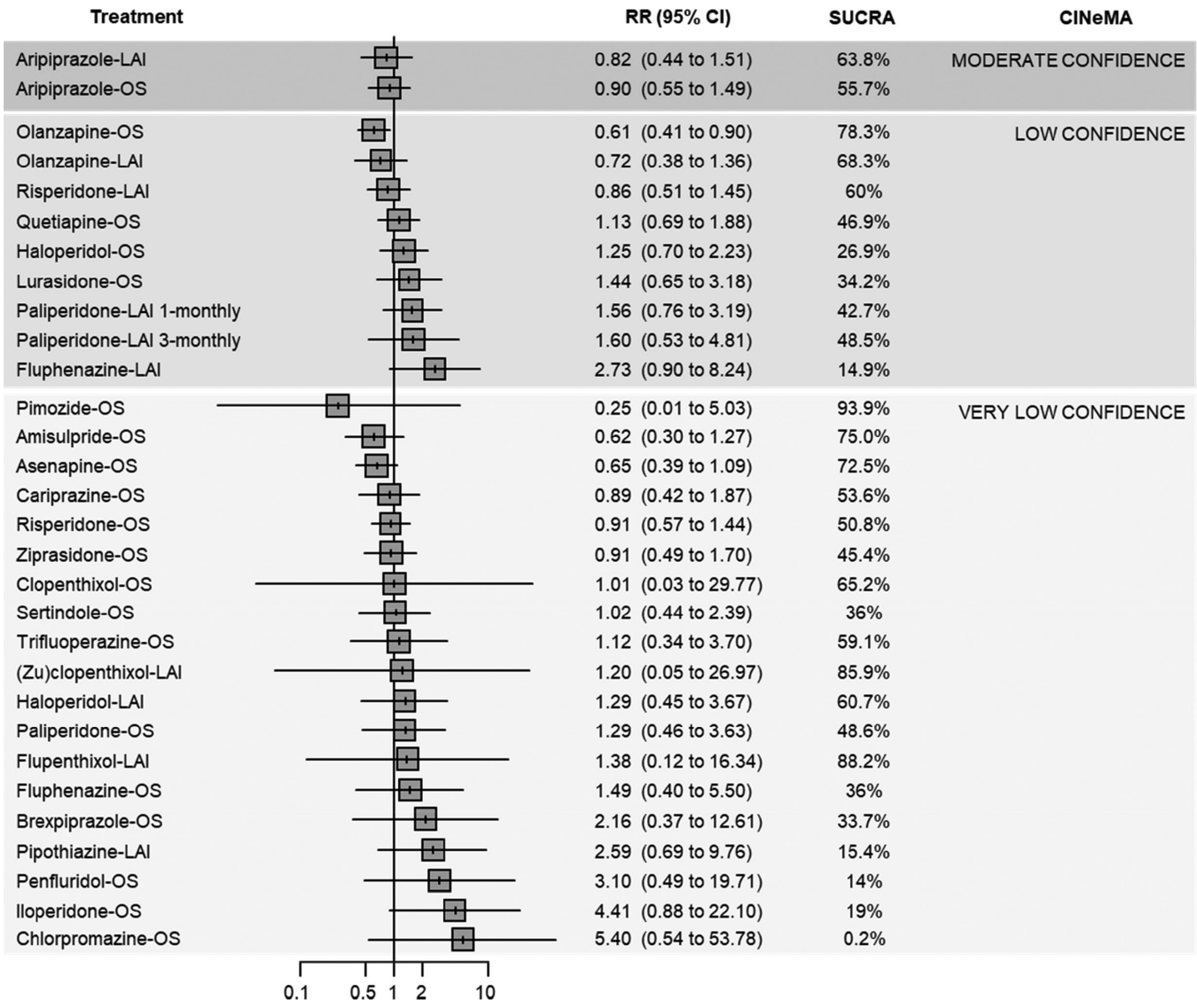

Figure 5 Forest plot comparing each antipsychotic with placebo for tolerability, with the corresponding ranking probability (SUCRA) and certainty of evidence (CINeMA). LAI – long-acting antipsychotic, OS – oral antipsychotic, RR – relative risk, SUCRA – surface under the cumulative ranking, CINeMA – Confidence In Network Meta-Analysis

DISCUSSION

To our knowledge, this is the largest and most updated systematic review and NMA comparing data on the maintenance treatment of individuals with schizophrenia-spectrum disorders.

Use of LAIs from the earliest phase of disease has been recommended[10,20,22]. However, in real-world practice, most individuals begin with an oral treatment for practical reasons. Thus, from a strictly clinical perspective, choosing an antipsychotic for which both oral and LAI formulation are available would be valuable, in order to facilitate a switch to the LAI when required. According to this viewpoint, our analyses suggest that olanzapine, aripiprazole and paliperidone are the most reasonable choices, as they are: a) among the best-performing treatments in terms of relapse prevention according to the effect estimate and the SUCRA ranking; b) supported by the highest confidence of evidence according to the CINeMA approach; and c) available in both oral and LAI formulation.

Regarding tolerability (dropouts due to adverse events), no antipsychotic was significantly worse than placebo, although the certainty of evidence was generally low, being "moderate" only for aripiprazole-OS and aripiprazole-LAI. Although dropouts due to intolerability reflect the overall burden of adverse events, this information alone cannot be exhaustive when tailoring the choice of antipsychotics to individual patients, for which detailed knowledge of specific adverse events might be more useful. However, analyses of common adverse events were limited and imprecise in many cases, calling for greater attention to measuring and reporting these adverse effects in maintenance/relapse prevention trials of antipsychotics.

Overall, the finding that most LAIs and oral antipsychotics are effective in preventing relapse and re-hospitalization as compared to inactive treatment (as in placebo-controlled trials) or no treatment/treatment "as usual" (as in observational studies) is consistent with existing large observational database studies[22,156] and with meta-analyses of observational and randomized studies[6,9,157] on the maintenance treatment of schizophrenia.

Our results are generally in line with those from a previous NMA on oral antipsychotics in acutely ill individuals[23]. Compared with placebo, the ranking and the magnitude of effect of treatments are roughly comparable between the two NMAs, with few exceptions, such as risperidone-OS, sertindole-OS and lurasidone-OS apparently performing better in the "acute" population, and fluphenazine-OS performing better in the "maintenance" population. However, these differences are of relatively small magnitude, and the confidence of evidence for these treatments was rated as "low" or "very low" in at least one of the two NMAs. Furthermore, it needs to be recognized that differences in populations and trial design across several decades when the acute and maintenance studies were conducted could also have affected the results, limiting the indirect comparability of antipsychotic effectiveness, both within and across illness stage (acute vs. maintenance).

This NMA did not detect clear advantages of LAIs over oral antipsychotic formulations in terms of relapse and re-hospitalization. This is in line with the observation that, in general, LAIs have shown clearer advantages over oral antipsychotics in observational studies[21,22,158,159] rather than in randomized trials[6,21,160]. As previously suggested, observational studies might have greater external validity because of less restrictive patient selection, although the lack of blinding might increase the risk of bias (e.g., detection, performance and prescribing bias)[161].

The results of this NMA should be interpreted in the light of some possible limitations. First, for some studies, clinical stability was not clearly described, and we imputed this information by using baseline scores of rating scales measuring psychopathology, according to validated cut-offs. This information can be considered as a valid proxy of clinical stabilization, although it may lack precision. However, after removing these studies in a sensitivity analysis, results did not change remarkably. Second, several studies lacked relevant information, and we used imputation techniques which have been empirically validated[41], but might nonetheless be imprecise.

Third, included RCTs employed different study designs and diagnostic criteria, and had different primary outcomes, settings of recruitment, and follow-up periods. Despite that, the overall coherence of the networks appeared to be preserved for the primary analyses and for most secondary outcomes. Fourth, we included placebo-controlled trials, which have possible limitations[162,163], and had probably a prominent role in introducing heterogeneity and incoherence, as shown by sensitivity analyses, which, however, did not show substantial changes of overall results.

Fifth, overall risk of bias was relevant for many studies. However, after removing these studies by means of sensitivity analyses, primary results did not change remarkably. Sixth, some secondary outcomes, such as quality of life and functioning, which might play a considerable role in helping clinicians to tailor their choice to individual patients, were insufficiently reported by the original studies, leading to poorly populated and connected networks, and imprecise results.

Seventh, effectiveness need to be put into the context of tolerability, especially during long-term treatment. However, adverse effect outcomes were only partially and inconsistently reported, not allowing a detailed benefit-to-risk assessment. Nevertheless, we used the outcome of intolerability-related discontinuation as a proxy of clinically relevant adverse effects and found similar performance of the meta-analyzable antipsychotics and no difference to placebo. Thus, although individual long-term adverse effects of antipsychotics can be potentially problematic[12,164], overall, patients do not seem to discontinue antipsychotic maintenance treatment more than those randomized to placebo. Moreover, effective long-term antipsychotic treatment facilitates healthier lifestyle choices and adherence to medical treatments prescribed to mitigate illness- and/or medication-related cardiometabolic burden[165,166].

Finally, as no comparison included ≥10 studies, the risk of publication bias could not be ruled out, although this is expected to be less relevant compared to other classes of psychotropic drugs[167].

Despite these limitations, to our knowledge, this is the largest and most comprehensive meta-analysis of antipsychotics for the maintenance treatment of people with schizophrenia. As such, findings of this NMA might have significant implications for clinical practice, policy and research. Current guidelines agree in recommending long-term maintenance treatment for at least one year after the first episode[13,14,168,169]. However, clear information on which antipsychotic to choose is lacking. According to the UK National Institute for Health and Care Excellence (NICE) guidelines, current evidence cannot guide the choice between antipsychotics in the maintenance phase[170], while the recently updated American Psychiatric Association guidelines suggest using the same treatment which provided benefit in the acute phase[168], as it is implicitly recommended also by the WHO mental health Gap Action Programme (mhGAP) guidelines[169]. Data from this NMA show that, although the magnitude of benefit is apparently similar between antipsychotics, they are not all equal, because the confidence in this estimate can largely vary, which is of paramount relevance for making evidence-based choices.

Both oral and LAI formulations of olanzapine, aripiprazole and paliperidone proved to be effective and are supported by moderate-to-high confidence of evidence, and should therefore be given priority when initiating a pharmacological maintenance treatment in people with schizophrenia-spectrum disorders, although differences in adverse effect profiles should also be considered in the decision-making process. Moreover, identifying antipsychotics allowing a switch between oral and LAI formulations might be particularly useful in low- and middle-income countries (LMICs), and in constrained-resource settings in general, where only a limited number of medications may be selected for inclusion in national formularies. Although costs might be an issue, this should not prevent the inclusion of

evidence-based treatments in such contexts. From this standpoint, these data call for an effort to produce more affordable second-generation LAIs, as it has been done for other treatments in LMICs[171].

Taken together, results from this NMA can inform clinical practice guidelines as well as national and international drug regulation policies, including the WHO Essential Medicines List.

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The alliance construct in psychotherapies: from evolution to revolution in theory and research

The construct of alliance (alternatively addressed as therapeutic, working or helping) was first formulated within psychoanalytic circles, before it was reconsidered in trans-theoretical terms and became recognized as an integrative variable, common factor, and generalizable change process or "principle of" change[1,2].

Much has been written over the years about the role of alliance in the adherence to various specific treatment tasks defined as critical to change (e.g., emotional insight and skill development), but also about alliance development as effecting change or "curative" in and of itself[3].

In the analytic literature, the evolution of the construct can be traced from Freud to Greenson, with a number of notable contributions in between. The construct was developed to highlight the importance of collaboration and the real and human aspects of the patient-therapist interaction. Interestingly, it did not receive much attention in the interpersonal and humanistic literatures, where these aspects were always central.

The construct complemented transferential considerations of patient-therapist relationship and provided a ground for technical flexibility, i.e., for departing from the idealized stance of therapist abstinence and neutrality. It did not come, however, without criticism and concern regarding its orientation towards patient identification or compliance with the analyst's agenda[3].

Bordin[4] broke boundaries with his seminal reformulation of the alliance as comprised of "purposeful collaboration" (patient-therapist agreement on the tasks and goals of treatment) and their "affective bond" (that is, mutual respect and trust, as well as emotional attunement), thus introducing the application of the construct to other orientations.

This coincided with or contributed to the psychotherapy integration movement that attempted to identify common change processes and that in turn adopted the alliance construct as its poster variable. With its emphasis on mutuality and orientation towards negotiation, Bordin's reformulation permitted greater attention to therapist participation and subjectivity.

Part of the post-modern turn or relational revolution that challenged the rigid demarcation between subjectivity and objectivity, and recognized the inextricable relationship between the observer and the observed, Safran and Muran[5] provided an intersubjective elaboration that concentrated on the person of the therapist and the negotiation of existential dialectics around agency/communion and subject/object in the alliance. According to this elaboration, the resolution of these dialectics in the context of the alliance represents an opportunity for change – that is, a new relational or corrective experience.

Beginning in the 1970s, the alliance construct became the focus of the psychotherapy research community, in large part due to Bordin's reformulation, which led to the development of many measures and a proliferation of research demonstrating the predictive relationship of alliance to outcome (see Norcross and Lambert[6] for a meta-analysis of 306 alliance studies, N=30,000).

This generation of research did not come without some controversy: multiple measures not surprisingly resulted in some definitional imprecision or confusion, and much of the research was observational and correlational, failing to address the question of causality. However, there have been more recent mediational analyses to establish the causal relationship of the alliance as a "change mechanism"[7]. There has also been some (though limited) research on patient and therapist factors or characteristics that moderate the quality of the alliance[1,6].

An extension of the research on the alliance-outcome relation included analyses of alliance patterns based on repeated post-session ratings to identify "v-episodes" (precipitous drops and then returns to recovery), and pre- to post-session ratings to identify "sudden gains" (significant increases) as proxies for alliance rupture repair. A meta-analysis of eleven such studies (N=180) has demonstrated that precipitous "drops" or ruptures are quite prevalent (15-80% of sessions) and subsequent "gains" or repairs predict outcome[6].

There is also research that directly assessed the presence of rupture, and found that patients report rupture in 20-40% of sessions, therapists in 40-60% of sessions, and third-party observers in 40-100% of sessions[6]. These direct assessments included self-reports (by patients or therapists) of any "tension or problem, misunderstanding, conflict or disagreement", and observations (by third parties) of "confrontation" (movements against other) and "withdrawal" (movements away from self or other) behaviors that mark ruptures. The prevalence of rupture that these studies demonstrate highlight the inherent messiness and conflict in human relations, including patient-therapist interactions[5,8].

These efforts (despite limitations in number and other methodological concerns) have been integral to a "second generation" of alliance research, particularly aimed at the construct of rupture (generally defined as deteriorations or breaches in relatedness) and the clarification of repair processes[3,6,9]. This second generation has included mixed method (quantitative and qualitative) efforts or task analyses (six small-scale studies) that have yielded clinically useful "when/then" data and defined stage-process models of rupture repair as a "change event".

More specifically, these efforts defined specific tasks to carry out in the face of rupture, beginning with an acknowledgement of the rupture and including an exploration of rupture experience and sometimes some renegotiation of the work of therapy and/or a formulation of the patient's presentation (all of which can be construed as resulting in a new or corrective experience). These efforts also led to experimentally designed studies that evaluated the effect of alliance-focused trainings aimed to advance therapist abilities to address ruptures (six studies, N=276), which provided limited but promising support[6,9].

Future directions for consideration regarding the alliance construct include the need for: a) more definitional clarification

and consensus on alliance and rupture (both suffer from too many definitions and methodological translations that seem too removed from the original conceptualization); b) more research on the causal relation of alliance development and rupture repair (more study of how each of these effect overall change); c) more research on patient (personal characteristics, intervention responsiveness) and therapist (personal characteristics, technical interventions) factors (specifically how these variables moderate alliance development and rupture repair).

In addition, there is a need for: d) more research on rupture repair processes, and more efforts to develop observer-based measures and to apply mixed method studies to explore what processes (i.e., specific patient and therapist behaviors and interactions) are essential to repair, and e) more experimental research on alliance-focused trainings (protocols designed to develop therapist abilities to negotiate alliance) and their potential effect on psychotherapy process and outcome.

These second-generation efforts could significantly address the risk of failure posed by alliance rupture and consequently redress the rates of failure in psychotherapy, including premature termination and poor adherence to treatment protocol.

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Effectiveness of currently available psychotherapies for post-traumatic stress disorder and future directions

Post-traumatic stress disorder (PTSD) entered the DSM just over 40 years ago. Since then, there have been more than 300 completed randomized controlled trials (RCTs) of therapies for this condition, about two thirds of which have included one or more psychotherapies[1]. It is therefore not surprising that there is a robust evidence base of effective psychotherapies for PTSD.

Trauma-focused psychotherapies, in which processing memories and emotions related to the traumatic event is a primary focus throughout the treatment, have emerged as the most effective[2]. Meta-analyses generally show large effect sizes for PTSD symptom reduction and high rates of loss of diagnosis or remission for these treatments[e.g.,2].

Among trauma-focused psychotherapies, prolonged exposure (PE) therapy, cognitive processing therapy (CPT), cognitive therapy, and eye movement desensitization and reprocessing stand out as having the strongest evidence, because they have been studied the most, by investigators different from those who developed the treatments, and with the broadest variety of populations and comorbidities. All involve manualized protocols usually completed in about 12 sessions, most often delivered weekly.

While there have been few direct comparisons of psychotherapies and pharmacotherapies for PTSD, a meta-analysis that compared effect sizes across studies found larger effects for psychotherapies (g=1.14) than medications (g=0.42)[3]. There is also evidence that PTSD can be treated effectively with non-trauma-focused psychotherapies, which generally aim to improve specific skills, but effect sizes are generally smaller than for trauma-focused psychotherapies[2].

The availability of effective treatments has fundamentally shifted our view of PTSD from a chronic condition that we can at best hope to manage, to a condition from which it is possible to recover. While this is tremendously good news, there is still a great deal of work left to do. Not everyone with PTSD is willing or able to engage in a trauma-focused psychotherapy; dropout from PTSD treatment remains high (this is true across PTSD treatment types, in part because a hallmark symptom of PTSD is avoidance); and a number of people who engage in these treatments remain partial responders or non-responders.

Ongoing work to further improve the effectiveness of psychotherapies for PTSD can be divided broadly into two categories: a) research to improve engagement in and outcomes of existing trauma-focused psychotherapies, and b) research to develop and evaluate novel psychotherapies.

A delivery adaptation that is promising in terms of improving engagement in existing psychotherapies is massed treatment, that is, psychotherapy sessions offered on consecutive days or multiple times per week. This format allows patients to complete treatment in 2-4 weeks, rather than in 3-4 months as is usually the case with weekly sessions. Field studies and a small number of RCTs show treatment completion rates upward of 85%, with effectiveness as good or better than weekly therapy[4].

Shorter versions of treatments are another promising direction. A preliminary RCT of PE for primary care (PE-PC), a 4-session version of PE where patients meet with their therapist for 30 min instead of 90 min, showed that over 80% of participants completed the treatment. The intervention resulted in a larger reduction in PTSD severity and general distress compared with

a minimal contact control, persisting at 6-month follow-up[5]. This version of PE is intended as part of a stepped care approach for those initiating PTSD treatment in primary care, and appears to be an adequate dose of treatment for some patients with PTSD.

The common thread between massed and shorter trauma-focused psychotherapies is that patients complete treatment in a shorter amount of time, which may contribute to the higher rates of completion compared to what we usually see with PTSD treatment.

Another improvement is that newer versions of PE and CPT manuals give more guidance to providers on how to help patients to process common, but sometimes challenging, non-fear based post-traumatic emotions such as guilt and shame, which may result in patients with such emotional reactions being more likely to benefit from these treatments. When more RCT results using the newer versions of these manuals become available, comparing within-group effect sizes between newer and earlier studies will shed light on whether these changes enhance treatment effectiveness.

Regarding research to develop and evaluate novel psychotherapies for PTSD, trauma-informed guilt reduction therapy, which focuses on reducing trauma-related guilt, has promising preliminary pre-post results with a fully powered trial underway[6]. Written exposure therapy, which asks patients to write about their traumatic event following scripted instruction, has been found in a randomized trial to be non-inferior to CPT in reducing PTSD symptoms and to be associated with significantly fewer dropouts[7]. Both of these psychotherapies are brief (5 and 6 sessions respectively), which, as noted above, may facilitate higher rates of treatment completion.

We still have a great deal to learn about PTSD and PTSD treatment to further improve psychotherapy treatment outcomes. For example, identity factors such as ethnicity and gender are still grossly underexamined in relation to PTSD treatment outcomes. Moreover, while a range of effective treatments now exists, little is known about how to optimally match patients to treatments. A recently completed Veterans Affairs 900-participant comparative effectiveness study of PE and CPT may help shed light on this[8], as may an in-progress meta-analysis of treatments for patients with co-occurring PTSD and substance use disorder that includes 42 trials and uses individual patient data[9].

For now, the best practice is to use shared decision making between patient and provider to inform treatment choice. Knowledge that would allow for more personalized or precision recommendations has the potential to be a force multiplier in enhancing outcomes.

In summary, we are fortunate to be in a time where over 40 years of research have given us a menu of effective PTSD psychotherapy options from which patients and their providers can choose. While gaps remain, more research is underway, allowing for optimism that we will be able to help more people recover more fully from PTSD in the coming years.

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Post-traumatic stress disorder as moderator of other mental health conditions

The comorbidity of post-traumatic stress disorder (PTSD) with a range of other mental disorders is common. This comorbidity is often attributed to either overlapping symptoms between PTSD and other disorders or to the variety of psychiatric conditions that can arise in the wake of exposure to a traumatic experience. However, this comorbidity may also be due to the fact that PTSD can moderate the onset or severity of other psychiatric symptoms or disorders. This is an important issue, because it has implications for how patients affected by the array of symptoms that can emerge after trauma may be most efficiently managed.

Our knowledge of how PTSD can impact other disorders rests on longitudinal studies that have assessed PTSD and other conditions, and have typically conducted cross-lagged or time-series analyses. This approach allows us to determine the extent to which each condition impacts other disorders at later assessments. Convergent evidence indicates that PTSD can precede or exacerbate depression, anxiety disorders, suicidality, substance abuse, eating disorders, and psychosis[1]. Furthermore, PTSD can precede a range of physical and behavioral indicators, including chronic pain and tobacco use.

There is also evidence from network analysis indicating how symptoms of PTSD may impact other psychiatric symptoms. Network analysis conceptualizes psychopathological states as resulting from causal paths between different symptoms – rather than emerging from an underlying disease state[2,3]. For example, the PTSD symptom of nightmares may play a causal role in contributing to sleep disturbance, which in turn leads to concentration deficits and irritability. Numerous studies using network analysis have shown that specific PTSD symptoms can influence problems across other conditions, including depression and anxiety disorders[4].

In explaining the role of PTSD as a mediator of the relation-

ship between trauma exposure and onset of other psychiatric disorders, there are several mechanisms that can be considered, and these arguably function in an interactive manner.

One key potential mechanism is the impact of PTSD on the capacity to down-regulate emotional distress. It is well documented that PTSD involves impaired emotion regulation, and it is possible that this impairment predisposes people to develop new psychiatric disorders or worsens others[5]. The capacity to regulate emotions in PTSD can be related to the well-documented deficits in executive functioning[6]. Deficient working memory and attentional capacity can limit the extent to which one can regulate emotions, which can result in greater risk for mental health problems.

Moreover, avoidance is a key symptom of PTSD, and this can trigger a cascade of strategies that can be maladaptive. Avoidance can involve situations or thoughts and memories related to the traumatic experience. This tendency can generalize to more pervasive avoidance of social networks, emotional states, and activities that promote good mental health. This can lead to a worsening of depression, anxiety and other psychiatric conditions.

Another common form of avoidance for people with PTSD is self-medicating with prescription or non-prescription substances to numb the distress that is experienced along with traumatic memories. This behaviour can not only lead to substance abuse, which has been documented in longitudinal studies of PTSD, but also facilitate other psychiatric problems, because issues may not be addressed in a constructive manner. Avoidance tendencies can also result in not seeking help from mental health services, which can impede early intervention or adequate treatment for other psychiatric disorders.

The DSM-5 explicitly recognizes the presence of harmful behaviors in PTSD, including such risk-taking behaviors as dangerous driving, severe alcohol use, and self-harm. These reactions are conceptualized as a result of the extreme arousal and the difficulties in impulse control that can be experienced by people with PTSD[7]. These behaviors can lead to a range of events and habits triggering repetitive cycles of exposure to trauma. This can compound the sensitization that has been reported in PTSD, in which the condition results in neural sensitivity to threats and stressors in one's environment, such that the person is more reactive to these events.

One of the strongest transdiagnostic predictors of risk for mental health problems is represented by maladaptive or catastrophic appraisals about oneself or the environment[8]. A key feature of PTSD is the tendency to engage in catastrophic appraisals after the traumatic experience, and these appraisals can generalize to many aspects of a person's life, such as one's self-esteem, trust in others, fears of negative evaluations, germs, or self-blame. These cognitive tendencies are major risk factors for an array of psychiatric conditions, including anxiety, depression, eating disorders, and obsessive-compulsive disorder. Relatedly, the tendency to ruminate is well documented after trauma, and this habit of repeatedly thinking about negative events is a major risk factor for many psychiatric conditions.

In considering these various mechanisms for how PTSD can moderate other psychiatric problems, it is worth noting that many of the risk factors reviewed here may be present prior to trauma exposure, and in fact predispose the person to developing PTSD. These elements can be intensified as PTSD develops, and then contribute to other psychiatric conditions which have a shared vulnerability. In this context, it is especially worth recognizing the emerging evidence on shared genetic vulnerabilities to a range of psychiatric disorders[9]. In the wake of trauma exposure and PTSD development, gene expression can predispose an individual to develop other psychiatric disorders by means of the shared genetic vulnerability.

Overall, this evidence reflects the interactive multifactorial nature of the processes explaining how PTSD can lead to the onset or worsening of other psychiatric conditions. Understanding how PTSD can impact on other psychological problems is an important area of future research, because it has important treatment implications. Targeting PTSD may have downstream benefits for many problems beyond the specific domain of that disorder.

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Intimate partner violence and mental health: lessons from the COVID-19 pandemic

Domestic violence and abuse is a global public health issue adversely impacting both physical and mental health. Intimate partner violence is one of the most common forms, and includes physical, sexual and emotional abuse (including technology-enabled abuse) and controlling or coercive behaviour from a partner or ex-partner.

Women and girls are particularly at risk for intimate partner violence. Globally, 27% of ever-partnered women aged 15 years

and older have experienced this violence, with the highest prevalence in low-income countries[1]. Risk factors can occur at four levels: a) individual (e.g., disability); b) relationship (e.g., partner exposure to parental violence, substance misuse); c) community (e.g., poverty, crime) and d) societal (e.g., inequitable gender roles, humanitarian and conflict settings, inadequate laws, such as those regarding marital rape, or inadequate law enforcement)[2]. The risk of intimate partner violence may increase during the perinatal period, particularly in unplanned pregnancies.

Public health restrictions during the COVID-19 pandemic have led to an increase in time at home with partners, with an associated rise in intimate partner violence, as evidenced by an increase in calls to helplines and contact with other support services[3]. In many countries, frequent lockdowns and quarantine rules have resulted in women having poor access to transport, shelters, safe houses and third sector services, compounding the problem. Remote delivery of health care has also presented new challenges for practitioners identifying and responding to intimate partner violence and addressing its effects on mental health.

While many of the studies in this area are cross-sectional, there is longitudinal evidence from high- and lower-income countries that exposure to violence and abuse across the life course can increase the risk of subsequent mental ill health[4]. Possible confounders of this association include socioeconomic adversity and early life exposure to violence and abuse.

However, the relationship between intimate partner violence and mental health is complex. There is also evidence that people with mental disorders across the diagnostic spectrum are disproportionately affected[4]. Evidence from meta-analyses suggests that women with depression and anxiety disorders are three to four times more likely to be exposed than those without, and exposure may affect up to 60% of women with severe mental illness[4]. Men with severe mental illness are also at increased risk.

While the majority of people with a mental disorder are not violent, there is some evidence for an association between being diagnosed with a mental disorder and violence perpetration, including intimate partner violence, although the absolute risk is low. This appears to be largely mediated by substance misuse. However, it may also be confounded by familial factors such as early exposure to family violence[4].

Clinical guidelines highlight the need to ask about experiences of intimate partner violence in people presenting with mental ill health, as part of any routine mental health assessment, but this practice is not uniformly followed. The World Health Organization (WHO) and the World Psychiatric Association (WPA), supported by qualitative meta-syntheses, recommend facilitating disclosure and response through a "LIVES" approach: *Listening* non-judgmentally and empathically, *Inquiring* about needs and concerns, *Validating* experiences, *Enhancing* safety for victim and family, and *Supporting* and connecting to information and services[5].

Risk assessment of violence perpetration is routine within mental health assessment, but has tended not to focus on risk to partners or ex-partners. A recent meta-synthesis of six studies found that barriers to disclosure of intimate partner violence perpetration to health care staff included perpetrators' negative emotions and attitudes towards their abusive behaviours and lack of trust in practitioners' abilities to address the problem[6]. Facilitators of disclosure included experiencing social consequences of abusive behaviours and receiving offers of emotional and practical support. However, there is only weak evidence for effectiveness of interventions in health care settings; early evidence suggests that cognitive behavioural and motivational interviewing interventions addressing alcohol use may reduce intimate partner violence.

Systematic reviews from both high- and lower-income settings report a range of psychological interventions that can improve mental health outcomes, including depression and anxiety, in women experiencing intimate partner violence and mental ill health[4]. However, there is little evidence on interventions for other disorders, such as post-traumatic stress disorder, or in male victims. It is also unclear the extent to which the effectiveness of the interventions is moderated by recent, current or historical abuse.

There is evidence that advocacy interventions reduce abuse. Where advocates also train mental health or primary care practitioners on domestic violence, with care pathways to deliver both advocacy and mental health interventions, both abuse can be reduced and mental health improved. However, the success of this may be moderated by the extent to which advocates are integrated within the clinical teams with whom they work. A recent meta-synthesis reported that practitioners perceive themselves to be more ready to address intimate partner violence when they collaborate both with expert team members internal to their organizations and with specialist professionals outside their team, and when supported by the health system[7].

The COVID-19 pandemic has emphasized the need for these collaborations. A reliance on online and tele-consultations has highlighted the need to assess abuse and deliver mental health interventions remotely in a manner that does not compromise safety[8]. Several organizations have produced guidance on how to provide mental health support by telephone, and in many parts of the world there has been an expansion in helplines alongside investment in shelters and other safe accommodation options.

A number of innovative interventions have been devised for those without access to mobile technology during the pandemic. These include utilizing existing public places such as pharmacies and shops by providing helpdesks or phone booth stations where support can be given. Other more discrete strategies include the use of code words, silent alarms or other signals that can be presented at the site of a support organization, or displayed outside the home[9]. Potentially these strategies could also be implemented by mental health facilities, although they have not been used to our knowledge to date.

The WPA has developed a curriculum and core competencies for psychiatrists focusing on intimate partner violence and sexual violence against women[5]. Similar undergraduate and postgraduate training initiatives are needed for other practitioners, including community health workers in low- and middle-income countries, with research to establish how best to intervene.

Moreover, mental health policies should recognize the need for trauma-informed approaches that support the identification and response to intimate partner violence. During the pandemic, the WPA, the International Association of Women's Mental Health and the International Marcé Society for Perinatal Mental Health have provided webinars to promote shared learning and discussion among health care professionals supporting those affected by intimate partner violence.

Services should provide routine data collection on intimate partner violence, and research should ensure measurement and analysis of the impact of this violence – in trials of (pharmacological and non-pharmacological) interventions, in observational cohort studies, and in the evaluation of public health interventions that have the potential to reduce the extent of the problem (e.g., minimum alcohol pricing). Finally, through the WHO, United Nations and national bodies, psychiatrists could also be advocates for wider changes that focus on tackling the social and structural drivers of intimate partner violence, and in doing so reduce its burden on mental health.

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Repurposing fluvoxamine, and other psychiatric medications, for COVID-19 and other conditions

Early in the COVID-19 pandemic, repurposing some already-approved drugs was proposed for reducing the morbidity and mortality risk of those who were infected. For example, the UK RECOVERY trial demonstrated the benefits of dexamethasone for severe respiratory illness, leading to its widespread adoption by mid-2020. Many psychiatric drugs have antiviral and immune modulatory effects, and are candidates for repurposing for COVID-19 and other non-psychiatric conditions.

Fluvoxamine is a potent activator of the sigma-1 receptor (S1R), dampening cellular stress responses and leading to anti-inflammatory effects[1]. In 2020, we conducted a randomized placebo-controlled trial which demonstrated that fluvoxamine prevented clinical deterioration from COVID-19[2]. These findings were replicated in a larger study, the TOGETHER trial, which randomized 1,497 patients to fluvoxamine 100 mg twice daily or placebo for 10 days. The trial found a 32% reduction in risk for severe disease progression with fluvoxamine. Among patients who were compliant with their treatment regimen, taking at least 80% of their pills, there was a 66% reduction in risk for hospitalization with fluvoxamine, and only one death in the fluvoxamine group compared to 12 in the placebo group[3]. Fluvoxamine has now been recommended for use by several organizations, including the Ontario province in Canada. Two ongoing trials are testing fluvoxamine at a lower dose of 50 mg twice daily: the ACTIV-6 trial and the COVID OUT trial.

Based on this growing scientific evidence, as well as its safety profile and availability, we believe that fluvoxamine should be used in COVID-19 for outpatients at high risk for morbidity and mortality from complications of the infection. The recommended dose is 100 mg twice daily for 10-15 days, which can be adjusted based on tolerability. No laboratory monitoring is needed, but co-prescribed drugs should be evaluated for potential interactions, because of fluvoxamine's inhibition of cytochromes P450 (CYP) 1A2 and 2C19. Patients taking theophylline, clozapine, olanzapine and tizanidine, which are CYP1A2 substrates, should not be administered fluvoxamine in most cases. Caffeine, a CYP-1A2 substrate, should be eliminated or greatly reduced during fluvoxamine treatment. Also, for patients already taking a serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), we would discourage adding fluvoxamine or switching to it for COVID-19 treatment.

Other potential mechanisms have been suggested for the effects of SSRIs, beyond fluvoxamine alone, including inhibition of hypercoagulable states or excess serotonin release by platelets, and functional inhibition of acid sphingomyelinase, leading to inhibition of entry and propagation of SARS-CoV-2 into cells[1]. For example, a study of adults hospitalized for severe COVID-19 found that those who were taking a medication which was a functional inhibitor of acid sphingomyelinase (including all SSRIs) were less likely to be intubated or die[4].

A study of psychiatric inpatients in New York state during the first wave of the pandemic in 2020 found that SSRIs and SNRIs, and specifically fluoxetine, showed a protective effect against COVID-19 infection[5]. Also, a study of 83,584 patients found that those who were taking SSRIs, and in particular those who were on fluoxetine or fluvoxamine, had a reduced mortality[6].

Given the time and costs of conducting large randomized controlled trials, it is tempting to use the data from these observational studies as sufficient evidence for drug repurposing. Yet, observational studies are known to suffer from biases, including confounding by indication. Although techniques exist to reduce these biases, it remains controversial to assert a drug's benefit for a new indication based purely on observational data. For example, a drug or drug class might appear to be protective against COVID-19, yet be a proxy for some other patient characteristic or behavior (e.g., social isolation because of depression). Thus, promising observational study findings will still require corroboration in randomized trials, and accomplishments such as the UK RECOVERY trial show that rapid clinical innovations are possible.

SSRIs and other antidepressants might also help with the longer-term neuropsychiatric manifestations of COVID-19. "Neuropsychiatric long COVID" refers to the fact that cognitive and psychiatric symptoms are a large proportion of the constellation of post-acute COVID-19 symptoms that are either chronic or intermittent, and are bothersome, painful and disabling. For example, the Patient-Led Research Collaborative assessed the prevalence of symptoms in 3,762 persons over 7 months post-COVID[7]. They found a preponderance of neuropsychiatric symptoms, particularly memory and cognitive dysfunction, which were experienced by over 85% of respondents, with negative impacts on daily functioning. Other common neuropsychiatric symptoms were insomnia, anxiety, depression, and occasionally hallucinations (olfactory and other).

The etiological factors involved in neuropsychiatric long COVID may include persistent SARS-CoV-2 infection and a prolonged hyper-inflammatory state, compounded by psychosocial stress. Unfortunately, there is little research to-date on the treatment of neuropsychiatric long COVID. One recent report in post-COVID depressive illness[8] found that 55/60 (92%) patients showed a clinical response after 4 weeks of SSRI treatment. This strong antidepressant benefit was seen irrespective of gender, previous psychiatric history, and SSRI type. The authors speculated that this rapid response to SSRIs could be due to their direct action on neuroinflammation, in addition to their typical antidepressant mechanisms (which remain unclear). This was a single-site, open-label study, and more research is needed regarding the efficacy of various treatments. But this study also shows an important role for psychiatrists in managing, and supervising, the long-term neuropsychiatric effects of COVID-19.

With the pandemic continuing to evolve, it will be critical to keep on answering key questions about the role of SSRIs in the treatment of acute COVID-19 illness. What is the best dose and timing of fluvoxamine, and how effective is it in combination with other treatments against COVID-19 (such as monoclonal antibodies)? Is fluoxetine, which has lower S1R affinity compared to fluvoxamine but has shown promise in preclinical and observational studies, also an effective treatment, considering that it is more widely available and easier to use? And what are the best treatments for neuropsychiatric manifestations of long COVID, and in which patients?

Given that many psychotropics are now appreciated to have widespread molecular, cellular and physiological effects, including anti-inflammatory, neuroprotective and cardioprotective, and antiproliferative, we can expect that lessons learned in testing these medications for COVID-19 will be important for other drug repurposing efforts, ranging from infectious and inflammatory diseases, to neurodegenerative diseases such as Alzheimer's disease, and cancer[9].

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Empirical severity benchmarks for obsessive-compulsive disorder across the lifespan

Obsessive-compulsive disorder (OCD) is characterized by time-consuming obsessions and compulsions that cause distress and impairment[1]. It can affect people of all ages and has a lifetime prevalence of 1-2%[2,3]. The severity of OCD is assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[4,5]. Despite extensive use of this scale for several decades, there is still uncertainty about what constitutes subclinical, mild, moderate and severe OCD.

To our knowledge, only two previous studies have attempted to calculate Y-BOCS severity benchmarks[6,7], yielding inconsistent results. Both studies were underpowered, as they included a small number of individuals in the lower and higher severity ends of the distribution, and only recruited participants from a single country or single age group.

To provide definitive severity benchmarks for OCD that can be used across the lifespan and different cultures, large multinational samples are required. Empirically supported severity benchmarks would facilitate clinical decision making, trial design, and communication between professionals, the patient community and policy makers.

The OCD Severity Benchmark Consortium collected Y-BOCS data from 5,140 individuals with a lifetime diagnosis of OCD from Sweden, Brazil, South Africa, US and India (47/53% male/female, 21/79% children/adults, age range: 5-82 years). Data were collected as part of various research projects; each of the individual studies was approved by the local ethical review board, and all participants provided written informed consent (or assent if under the age of 18) for participation.

Data from four countries were used for model development (Sweden, N=1,697; Brazil, N=936; South Africa, N=552; US, N=599; total N=3,784). Data from India (N=1,356) were used for external model validation. Experienced clinicians administered the child or adult versions of the Y-BOCS, and the Clinical Global Impression-Severity (CGI-S) scale, which constituted the benchmark measure in this study. The CGI-S is a single-item measure (score range: 1-7) of global disorder severity (in this case, OCD) that synthesizes all available information about the patient, including but not limited to current symptoms, impairment and general function[8].

An ordinal logistic regression model was trained in 80% of the data from the four countries used for model development (training dataset, N=3,027) and accuracy of the best severity benchmarks was separately evaluated in the remaining 20% of these data (holdout dataset, N=757) and in the external dataset from India. To compensate for the unevenly distributed severity classes during model development, oversampling was performed by drawing 2,500 samples, with replacement, from each severity class.

A large proportion of all participants in the training and holdout datasets were classified as having moderately severe OCD (CGI-S score of 4 or 5; N=2,577, 68.1%). The next most common severity class was mild OCD (CGI-S score of 3; N=580, 15.3%), followed by severe OCD (CGI-S score of 6 or 7; N=408, 10.8%), and subclinical OCD (CGI-S score of 1 or 2; N=219, 5.8%). In the external Indian dataset, moderately severe OCD was most common (N=502, 37.0%), followed by severe OCD (N=352, 26.0%), mild OCD (N=341, 25.1%), and subclinical OCD (N=161, 11.9%).

Spearman's rho indicated that severity class and Y-BOCS severity correlated moderately to strongly ($r=.61$, $p<0.00001$). An ordinal regression model with severity class as the dependent

variable and Y-BOCS score as the independent variable was statistically significant ($p<0.00001$), and the Nagelkerke's pseudo R^2 estimate of the model indicated that variation in Y-BOCS severity accounted for 47.9% of the variation in the CGI-S severity classification.

Using the training dataset, the ordinal regression model indicated that subclinical OCD corresponded to scores of 0-13 points on the Y-BOCS, mild OCD to 14-21 points, moderate OCD to 22-29 points, and severe OCD to 30-40 points. These benchmarks classified individuals in the holdout and external datasets with modest accuracy (holdout: 57%, external: 55%). When we allowed the severity levels to overlap three points, accuracy increased to 79% in both datasets. This indicates that roughly half of misclassifications appeared around the breakpoints, which is expected since OCD severity is a dimensional construct[9].

A Y-BOCS score of 14 points separated clinical from subclinical individuals with excellent sensitivity (holdout: 94%, external: 91%) and adequate specificity (62% and 78%, respectively). The positive predictive value (PPV), or proportion of participants classified as having clinical OCD who truly had clinical OCD, was excellent in both the holdout (98%) and the external (99%) datasets. The negative predictive value (NPV), or proportion of participants classified as having subclinical OCD that truly had subclinical OCD, was lower (40% and 28%, respectively).

Interestingly, 14 is two points lower than the 16 points that are typically used as inclusion criteria for entry in most clinical trials of OCD. To the best of our knowledge, the 16-point cut-off used in clinical trials is arbitrary and could be revised in light of the current findings.

A Y-BOCS score of 30 points separated severe from non-severe OCD with adequate sensitivity (holdout: 70%, external: 82%), good specificity (89% and 84%), a low PPV (43% and 49%), and a high NPV (96% and 96%). Thus, a score of 30 may work best to screen out individuals with severe OCD rather than identifying a pure group above a certain severity level. Therefore, decisions to ration access to certain intensive specialist treatments to individuals with Y-BOCS scores above 30 should be questioned.

Largely consistent classification performance (total accuracy, sensitivity, specificity, PPV and NPV) of the general benchmarks was found across countries, genders and age groups, and overall benchmarks were similar in accuracy to subgroup-derived benchmarks (i.e., benchmarks that were based on only subgroups of the training dataset). This indicates that the provided benchmarks are largely invariant across national settings and individuals, and can therefore be used globally and across the lifespan.

In summary, we provide the field with empirically derived Y-BOCS severity benchmarks across the lifespan which will be useful in research and clinical settings (subclinical OCD: 0-13 points; mild OCD: 14-21 points; moderate OCD: 22-29 points; severe OCD: 30-40 points).

However, due to the modest accuracy of the classifications, we caution against the exclusive use of these benchmarks to guide important clinical decisions regarding individual patients, such as offering access to specialist treatment. Other relevant variables should be used, together with Y-BOCS scores, to guide clinical decision making and resource allocation, such as duration of the disorder, time without adequate treatment, psychiatric and somatic comorbidities, family accommodation, socioeconomic circumstances, and personal treatment history.

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Further information on this study can be found at https://osf.io/yu3xd/. The OCD Severity Benchmark Consortium includes, in addition to the authors, S.S. Arumugham (India), C. Lochner (South Africa), O. Cervin (Sweden), J.J. Crowley (US and Sweden), M.C. do Rosário (Brazil), T.S. Jaisoorya (India), M.C. Batistuzzo (Brazil), J. Wallert (Sweden), M.A. de Mathis (Brazil), S. Balachander (India), W.K. Goodman (US), D.L.C. Costa (Brazil), E. de Schipper (Sweden), S. Wilhelm (US), A. Palo (US), J.C. Narayanaswamy (India), R.G. Shavitt (Brazil), Y.A. Ferrão (Brazil), Y. Omar (US), J. Boberg (Sweden), T.K. Murphy (US), A. Tendler (US and Israel), E. Ivanova (Sweden), S.C. Schneider (US), D.A. Geller (US), C. Rück (Sweden), D.J. Stein (South Africa), E.C. Miguel (Brazil), E.A. Storch (US) and Y.C.J. Reddy (India).

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Twelve rather than three waves of cognitive behavior therapy allow a personalized treatment

The expression "third-wave cognitive behavior therapy (CBT)" has become a trade mark. It has been argued that it represents a new "process-based therapy", which targets the relationship of the client to his/her own experiences in a transdiagnostic approach[1]. However, a look at both history and present practice suggests that modern CBT encompasses at least a dozen "waves", or basic theoretical concepts and treatment approaches. We summarize them herein.

First wave: classical learning theory. The development of CBT started with classical learning theory, including conditioning, habituation and systematic desensitization[2]. Since then, dozens of technical variations of "exposure treatments" have been developed

for transdiagnostic purposes, which show more or less the same therapeutic efficacy and are all part of this first theoretical framework, that can be summarized as the "first wave" of CBT.

Second wave: operant learning theory. Subsequently, it was recognized that behavior is also shaped by reinforcers, as described in operant learning theory, which can be called the "second wave" of CBT. Corresponding new treatment approaches were reinforcement schedules and behavioral activation, that have been used transdiagnostically with many technical variations until today[3].

Third wave: coping and social learning theory. Reinforcers depend to some extent upon the coping skills of the individual, which is especially true in social encounters, as described in social learning and coping theories, including model learning theory. Relevant treatment approaches include many technical variations of social skills and assertiveness training[4]. Historically, "interpersonal therapy", which also refers to social interaction models, was introduced at the same time.

Fourth wave: self-control. Coping and social competence require that the person has a sufficient capacity for self-control, which means to control oneself in the presence of adverse outer conditions under the influence of long-term reinforcers. Relevant treatment techniques are self-monitoring, self-instruction, internal dialogues, idealized self-imagination, and cognitive rehearsal, that are used transdiagnostically in anxiety, pain or "stress inoculation"[5].

Fifth wave: attribution theory and cognitive theory. Even if a person has the capacity to control oneself, there is still the problem of when and why this is happening. Persons may have many skills, but may not use them because of dysfunctional expectations. This can be explained by "cognitive" models and attribution theories, which assume that it is not the environment *per se* that causes problems, but the person's interpretation of the world. This may depend on cognitive schemata (content: e.g., belief in a just world) or processes (attribution style: e.g., generalization, magnification, minimization, emotional reasoning, worrying). "Cognitive therapy", which has encompassed a large variety of techniques, aims to promote functional cognitions and cognitive processes[6].

Sixth wave: emotion theory. Cognitions and behavior are also reversely shaped by emotions, as shown in experiments on motivation and state-dependent memory and reasoning. Relevant treatment strategies aim to promote development of various emotion regulation skills[7].

Seventh wave: therapeutic relationship. While at the beginning of CBT the patient-therapist relationship did not play a major role, it became subsequently apparent that, also in this psychotherapy, patient participation, trust and relationship to the therapist are essential. There is not one uniform, but many types of relationships in CBT, depending on the needs of the person – i.e., warm or rational, demanding or permissive, structured or flexible. Therefore, mandatory self-experience has been introduced as part of training in CBT.

Eighth wave: disorder-specific therapy. As psychotherapy became more widely used, and health insurance began to be involved, proof of efficacy was needed with regard to specific disorders. This was not only supported by clinicians, but also demanded by the US Congress Office of Technology Assessment[8]. A wave of new studies referring to DSM criteria and using "disorder-specific therapy manuals" then emerged. Several alternative treatment methods were sometimes proposed for a given disorder.

Ninth wave: acceptance theory. As there was no remission or cure in many disorders, further treatment goals were to help the patient accept what could not be changed and make the best of the situation. Treatments were developed such as mindfulness based cognitive therapy, or acceptance and commitment therapy[1], using strategies such as cognitive defusion, directing the attention to the present, value clarification, or action orientation.

Tenth wave: positive psychology and salutotherapy. A next step in dealing with chronic ailments came from positive psychology and salutogenesis. Relevant treatment approaches are euthymia therapy, well-being therapy, and salutotherapy. Patients are encouraged to identify moments of well-being, in contrast to negative states, and learn that well-being is not the result of external factors, but something that one is able to influence.

Eleventh wave: life span development and individual constitution. The "diathesis-stress model" showed that various individuals have different susceptibility to environmental influences. Thus, somatic and psychological constitution became a topic in CBT. This includes the assessment, by means of a "macro-analysis", of the precursors and contingencies of the disorder from early childhood across the life span.

Twelfth wave: culture-sensitive psychotherapy. Therapists see patients with different cultural and religious backgrounds, which influence how they see the world, are controlled by their environment, and express mental distress. Recommendations for a culture-sensitive CBT include explicitly acknowledging the culture of the patient, developing disease concepts that fit into his/her culture, using metaphors from the patient's world, and involving relatives or clergymen in decision-making.

The many theoretical foundations of CBT are integrated in a coherent type of psychotherapy through "behavior analysis"[9]. This looks at precursors and stimuli, cognitions, attributions, expectations, physiological and psychological constitution and skills, emotions, behavior, and consequences, which are all interrelated. All this results in a personalized appraisal of the patient's problems, which then guides an individually tailored treatment process, independent of diagnostic labels. CBT can be therefore considered a "precision therapy". All techniques of all "waves" are used depending on the results of the behavior analysis, which distinguishes CBT from other types of psychotherapy.

Thus, a cognitive behavior therapist is somebody who is well versed in all theories which underlie CBT, masters the spectrum of therapeutic techniques derived thereof, and can integrate them in an individual model, after having conducted a competent behavior analysis.

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The efficacy of complicated grief therapy for DSM-5-TR prolonged grief disorder

The American Psychiatric Association recently announced the inclusion in the DSM-5-TR of a new category for prolonged grief disorder (PGD)[1,2], following introduction of this category in the ICD-11. Our group previously demonstrated the efficacy of a targeted treatment (complicated grief therapy, CGT) for complicated grief, a condition corresponding in many respects to PGD. We examined now the performance of that treatment among people who met the DSM-5-TR criteria for PGD.

CGT is a manualized 16-session intervention developed when we observed that treatments for depression did not appear to be effective for complicated grief[3]. We considered loss of a loved one to be a major life stressor[4] and understood grief from an attachment theory perspective[5]. We conceptualized grief after attachment loss as typically emerging in an acute form and becoming integrated over time as the reality of the loss is accepted and the capacity for well-being is restored. We understood complicated grief as a condition in which the initial intense form of grief persisted and interfered with functioning. A body of research informed our understanding of impediments to adapting to the loss. We developed a treatment that focused on facilitating adaptation to loss and addressing impediments, drawing upon strategies and techniques from prolonged exposure, motivational interviewing, positive psychology, interpersonal psychotherapy, and psychodynamic psychotherapy.

CGT was tested in three randomized controlled trials funded by the US National Institute of Mental Health[6-8]. For the present report, we analyzed data from one of these trials[6], in which participants (N=395) were people with a score of 30 or higher on the Inventory of Complicated Grief (ICG) who underwent a clinical interview confirming that grief was the primary problem. People with current substance use disorder, or a lifetime history of psychotic disorder, bipolar I disorder, active suicidal plans requiring hospitalization, or a Montreal Cognitive Assessment score less than 21 were excluded.

These patients were evaluated through the Structured Clinical Interview for Complicated Grief (SCI-CG), an instrument that can be used to identify DSM-5-TR criteria for PGD[9]. The evaluation was available for 307 study participants, 77 (25.1%) of whom were bereaved between 6 and 12 months and therefore did not meet the DSM-5-TR criteria solely due to time considerations. Of the remaining 230, 194 (84.3%) met DSM-5-TR criteria for PGD and 36 (15.7%) did not. All patients recruited for the parent study were randomized either to citalopram or to placebo, with or without CGT[6].

Among patients meeting criteria for PGD (N=194), we compared study outcomes at endpoint (week 20) for those who received CGT (N=96) versus those who did not receive it (N=98). The main outcome was treatment response measured as a rating of "much improved" or "very much improved" on the Clinical Global Impression (CGI) Improvement. We further used several grief symptom measures: the ICG, the Grief-Related Avoidance Questionnaire (GRAQ), the Typical Beliefs Questionnaire (TBQ), and the Grief-Related Work and Social Adjustment Scale (WSAS). Chi-squared tests were used for binary outcomes and two sample t-tests for continuous outcomes. All hypothesis tests were two-sided with a 5% level of significance. All analyses were performed in R (v1.4.1717). The parent study had been approved by the relevant institutional review board[6]. Written informed consent had been obtained from all participants before baseline assessment.

The sample of patients with PGD was not significantly different with respect to demographic and clinical variables from the parent study sample. Most patients were female (79.9%), white (80.9%), completed at least partial college (90.2%), and were bereaved of a parent or spouse (68.6%) by illness (65.5%) for 4-5 years on average. The sample had an average age of 52.7±14.2 years. Patients had high rates of current depression (69.6%), current post-traumatic stress disorder (46.4%), and suicidal ideation since the loss (61.9%) (see also supplementary information).

Treatment response for the sample with PGD closely reflected that of the parent study. Specifically, response rates for those randomized to CGT vs. no CGT were 88.2% vs. 60.9% ($p<0.001$) for the DSM-5-TR PGD group compared to 82.9% vs. 63.4% for all participants in the parent study. Also comparable to the parent study, average post-treatment scores on grief-related symptoms and impairment were significantly lower for those who received CGT vs. no CGT (ICG: 17.7 vs. 25.4, $p<0.001$; WSAS: 7.9 vs. 13.4, $p=0.001$; GRAQ: 9.4 vs. 14.6, $p=0.01$; TBQ: 3.9 vs. 7.1, $p<0.001$) (see also supplementary information).

Our results indicate that study participants who met DSM-5-TR criteria for PGD showed no significant demographic or clinical differences from the full parent study sample. Those diagnosed with PGD showed significantly greater response rates to CGT vs. no CGT, with results nearly identical to the parent study.

These findings are limited by the need to apply retrospectively the DSM-5-TR criteria for PGD, and diagnosis may have been less accurate than if made using a validated instrument[1]. Additionally, those diagnosed with PGD for these analyses represented only

half of the originally randomized sample. However, almost half (43.8%) of the omitted participants simply did not receive the assessment needed to diagnose PGD, and another 38% were excluded because it was too soon (six months to one year since the loss) to receive a PGD diagnosis. Further, those assessed showed no differences in demographic or clinical characteristics from participants in the parent study.

We endorse continued study of effective treatments for PGD. In the meantime, we believe that clinicians will benefit from knowing that CGT, a strongly validated intervention[6-8], can be appropriately re-labeled as prolonged grief disorder therapy (PGDT).

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Supplementary information on the study is available at http://christinemauro.com/downloads/tables_17.02.2022.pdf.

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Risk of new-onset psychiatric sequelae of COVID-19 in the early and late post-acute phase

Recent publications have documented that a proportion of COVID-19 patients develop psychiatric symptoms during or after acute infection[1]. We investigated this risk in the context of the National COVID Cohort Collaborative (N3C) – a centralized, harmonized, high-granularity electronic health record (EHR) repository[2] – using the largest retrospective cohort reported to date.

Two previous large-scale EHR studies examined psychiatric sequelae 90 and 180 days after COVID-19 diagnosis. A cohort of 44,779 individuals with COVID-19 was propensity score-matched to control cohorts with conditions such as influenza and other respiratory tract infections (RTI). In the 90 days following the initial presentation, the incidence proportion of new-onset psychiatric conditions was 5.8% in the COVID-19 group vs. 2.5% to 3.4% in the control groups[3]. A follow-up study also included individuals with a prior history of mental illness and similarly showed an increased risk of psychiatric conditions in the six months following initial presentation[4].

To validate these findings, we leveraged data from N3C, which at our cutoff date of October 20, 2021 had 1,834,913 COVID-19 positive patients and 5,006,352 comparable controls. Our data set was drawn from 51 distinct clinical organizations. We included patients in the COVID-19 cohort if they had a confirmed diagnosis of SARS-CoV-2 infection by polymerase chain reaction or antigen test after January 1, 2020. Controls were selected from patients with a diagnosis of a RTI other than COVID-19. We excluded from this analysis patients with a history of any mental illness prior to 21 days after COVID-19 diagnosis, as well as patients without a medical record extending back a year prior to COVID-19. There were 245,027 COVID-19 positive individuals available for propensity matching.

Each COVID-19 patient was matched with a control patient from the same institution whose age differed by no more than 5 years. Propensity score matching was done on 34 factors using a logistic regression model including main effect terms, resulting in 46,610 matched patient pairs. Multivariable Cox regression was performed to compare the incidence of new-onset mental illness for all psychiatric conditions, mood disorders and anxiety disorders for 21 to 365 days following initial presentation. We additionally considered dyspnea as a positive control.

We tested the Cox regression proportional hazard assumption for comparisons of COVID-19 patients and controls[5]. Schoenfeld residual analysis yielded a significant p-value and led us to reject the null hypothesis of a constant proportional hazard over the full time period of 21-365 days. We therefore separated the cohort into two time intervals (before and after 120 days) in which the proportional hazard assumption was not violated.

We identified a statistically significant difference in the hazard rate of new-onset psychiatric sequelae between COVID-19 and RTI in the early post-acute phase (from 21 to 120 days), but not in the late post-acute phase (from 121 to 365 days). The estimated incidence proportion (as modeled on the log-hazard scale over time) of a new-onset psychiatric diagnosis in the early post-acute phase for the COVID-19 group was 3.8% (95% CI: 3.6-4.0), significantly higher than the 3.0% (95% CI: 2.8-3.2) for the RTI group, with a hazard ratio (HR) of 1.3 (95% CI: 1.2-1.4). The HR for new-onset mental illness in the late post-acute phase was not significant in the COVID-19 compared to the RTI group (HR: 1.0; 95% CI: 0.97-1.1).

Similar findings were obtained for anxiety disorders, but not for mood disorders. The estimated incidence proportion of a new-onset anxiety disorder diagnosis was significantly increased for COVID-19 patients (2.0%; 95% CI: 1.8-2.1) compared to RTI patients (1.6%; 95% CI: 1.5-1.7) in the early post-acute phase (HR: 1.3; 95% CI: 1.1-1.4). However, the estimated incidence proportion

of a new-onset mood disorder diagnosis in the same period was not significantly increased for COVID-19 patients (1.2%; 95% CI: 1.1-1.3) in comparison to RTI patients (1.1%; 95% CI: 1.0-1.2).

New-onset anxiety and mood disorders were not significantly increased in the interval of 121-365 days following initial presentation (HR: 1.0, 95% CI: 0.91-1.1; and HR: 1.1, 95% CI: 0.97-1.2, respectively). In contrast, the HR for dyspnea, a known post-acute COVID-19 sequela[1], increased in both time periods (1.4, 95% CI: 1.2-1.5; and 1.2, 95% CI: 1.0-1.3, respectively).

We reasoned that patients might be followed more closely after COVID-19 as compared with other RTIs, and that a higher visit frequency might increase the probability of a mental illness being recorded in the EHR. To assess this, we repeated our analysis but added the frequency of visits 21 days or more after initial presentation as a factor to the Cox regression. The HR for any mental illness in the early post-acute phase was still significant ($p<0.0001$), but reduced to 1.2 (95% CI: 1.1-1.3).

Our results confirm the conclusion of the above-cited study[3] that patients are at significantly increased risk of psychiatric conditions after a COVID-19 diagnosis. However, the degree of increased risk documented in our study is substantially lower than previously found.

There are several potential reasons for the differences between our results and those of the above-mentioned study. The previous study included data from January 20, 2020 (first recorded COVID-19 case in the US) to August 1, 2020, while our study includes data through October 20, 2021. It is conceivable that perceptions of COVID-19 by patients have shifted or that clinical practice has changed in the intervening time. It is possible that improved treatment options available later in the pandemic have reduced the risk of psychiatric illness. Finally, COVID-19 vaccination may reduce rates of anxiety and depression and alleviate symptoms in persons with post-acute sequelae[6,7]. Thus, the increasing availability of vaccines might have reduced the rate of mental illness following COVID-19. The data available in N3C do not include comprehensive information about vaccination status, so we could not test this hypothesis.

Many cohort studies have documented a high prevalence of mental illness in individuals with long COVID. For instance, in our recent analysis, the prevalence of depression was 21.1% (median reported percentage in 25 studies) and that of anxiety was 22.2% (median over 24 studies)[1]. However, it is possible that the reported prevalence of these and other conditions was inflated by a sampling bias toward long COVID patients who joined support groups or chose to participate in cohort studies[8]. This, and the fact that inclusion criteria for long COVID studies vary, has made it difficult to characterize the natural history of psychiatric manifestations of long COVID. Our study did not focus specifically on long COVID, but instead investigated a cohort of patients following a diagnosis of acute COVID-19. It is difficult to know what proportion of these patients went on to develop long COVID; the recent introduction of ICD-10 codes for long COVID[9] may enable studies on this topic in the future.

In summary, we support previously published reports of an increased risk of new-onset psychiatric illness following acute COVID-19 infection. In contrast to the nearly doubled risk identified by the earlier study, we found the relative risk to be increased by only about 25% (3.8% vs. 3.0% following other RTI). We did not find a significant difference in risk in the late post-acute phase, suggesting that the increased risk of new-onset psychiatric illness is concentrated in the early post-acute phase.

Our results have important implications for understanding the natural history of psychiatric manifestations of COVID-19. If confirmed by independent studies, our findings suggest that health services should consider mental health screening efforts early in the post-COVID clinical course.

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Evidence-informed is not enough: digital therapeutics also need to be evidence-based

We are witnessing exponential growth in a heavily capitalized digital health industry which promises to transform behavioral and mental health care[1,2]. Consequently, it is critical that there is no ambiguity about the evidence standards necessary for the safe and effective treatment of psychiatric disorders through digital approaches. In our opinion, these standards should be essentially the same as for any other form of treatment, or even arguably higher, given the intrinsic likelihood of placebo effects in software

products that are specifically designed for user engagement[3].

These standards are all the more necessary as user engagement is often far less than reported, in clinical studies but especially in the real world, where it hovers at less than 5% after two weeks[4,5]. The nascent digital industry, therefore, must resist marketing and investor pressures in favor of sound clinical governance when developing "software as a medical device" (SaMD) where the declared purpose is "treatment or alleviation of disease"[6]; a modality increasingly referred to as "digital therapeutics" (DTx)[2].

If the industry unequivocally adopts evidence-based gold standards, there is opportunity for great good, and this need not be a complex undertaking, because the treatment evaluation template is well established. The randomized controlled trial (RCT), despite its focus on internal validity and inherent limitations to generalizability, has been the mainstay of evidence-based medicine for many decades, and the solution to the crucial matter of external validity may be found in real-world data (RWD), which is best regarded as complementary, rather than alternative, to clinical trials data[7].

We are concerned, however, that it may be tempting to utilize the near-hand available RWD associated with SaMD to supplant the need for robust clinical trials. We do not believe that this is the US Food and Drug Administration (FDA)'s intention when they require RWD as part of their Pre-Cert model, but rather that the combination of RCT and RWD offers a compelling safety and effectiveness argument. This combination is necessary as, while an RCT can establish efficacy, the very nature of DTx, as compared to pharmaceuticals, requires their clinical effectiveness to be studied. With mounting data that real-world longitudinal engagement with many of these apps is minimal, the need for this clinical "pipeline" of studies has become critical[5].

The risks of ignoring this rigorous pathway are substantial. There is already a parallel concern relating to neurotechnology devices being marketed to consumers as aids to cognitive and mental health without sufficient oversight[8]. We are mindful of a history of what has been termed "stealth research"[9] in the digital sector, which has already caused reputational damage, and are wary of reliance on an "evidence-informed" company rhetoric that is not consistent with evidence-based standards.

Although we absolutely do recognize that clinical trials research should be combined with other inputs to ensure evidence-informed decision-making in clinical practice, our point is that it is spurious to regard evidence-informed as a substitute for evidence-based. The requirement to generate clinically meaningful evidence on a DTx should be related to the product itself being evidence-based. However, one becomes familiar with an unhelpful form of "inductive reasoning" along the lines of: "1. X treats Y effectively; 2. This new product contains X; 3. Therefore, this new product treats Y effectively". No novel selective serotonin reuptake inhibitor (SSRI) would ever be approved or offered to patients without testing just because other SSRIs have established effects.

Of course, DTx are likely to contain behavioral elements, but the fallacious argument equally applies. Indeed, 14 out of the 25 FDA-cleared DTx products utilize cognitive-behavioral therapy (CBT) to treat the conditions they target[1]. Simply having content that is drawn from an evidence-based field, or endorsed by subject experts, does not demonstrate clinical efficacy of a novel DTx. Our argument is that any candidate DTx product itself, with its integrated content fields and software algorithms, needs to be subjected to rigorous evaluation in a clinical trial program as well as in real-world use cases, in order to be regarded as a safe and evidence-based treatment. Consequently, a candidate DTx should not be made available to treat a medical condition until it has proven benefits, because the intention to become a therapeutic does not make any intervention a therapeutic.

The most obvious danger of treating evidence-informed as evidence-based in DTx is the potential for adverse effects, reckless inefficacy, and devaluation of the entire space. Along with this, however, there is an additional danger stemming from any perceived equivalence of evidence-informed and evidence-based. Specifically, treating evidence-informed DTx as though they are evidence-based creates an environment in which actual evidence-based interventions (e.g., in-person CBT) could be easily replaced by DTx, which claim to have the same evidence as those existing interventions, but in reality could lack the efficacy of those genuinely evidence-based approaches. Thus, in a worst-case scenario, blind substitutions of evidence-based care with evidence-informed DTx could deprive patients of effective interventions, while providing them with a time-wasting or even adverse alternative.

Although our analogies to drugs and to in-person therapeutics may be imperfect, we strongly urge that it is prudent to apply the same standards, if not even higher, to the DTx clinical research pipeline. Some may say that the emergence of a novel, disruptive approach like DTx presents the opportunity to "break the mould". However, surely the counterbalance to that is that the greater the novelty, the greater the need for caution.

There is much at stake where treatment of psychiatric conditions is concerned, and the duty to be evidence-based should not be taken lightly. The popular phrase attributed to astronomer Carl Sagan, "Extraordinary claims require extraordinary evidence", is a fitting end to this piece, and a beginning to the journey towards a higher standard for evidence.

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Prenatal exposure to antidepressants or antipsychotics and the risk of seizure in children

Perinatal mental health problems account for a substantial health burden across the world. Almost one in two women aged under 25 report some form of common mental disorders during pregnancy[1]. The use of psychotropic medications, especially antidepressants and antipsychotics, has doubled in the past two decades, with a disproportionate increase amongst women at childbearing age and during pregnancy[2,3].

Despite increased prescribing, there is insufficient evidence supporting the safety of psychotropic drug use during pregnancy[1], in particular regarding seizure in offspring, one of the most common neurological conditions in early childhood and an important predictor of mortality, long-term disability, and poor prognosis[4]. This may lead to hesitations in perinatal psychiatric treatment: indeed, high rates of discontinuation of psychotropic medications have been observed in pregnant women with mental disorders[5,6]. There can be significant adverse effects to both maternal and foetal health when stopping medications abruptly or withholding treatment during pregnancy[5,6].

We used the Hong Kong Clinical Data Analysis and Reporting System (CDARS)[7] to examine the risk of seizure in offspring (ICD-9-CM diagnosis codes 333, 345, 779 and 780, with the exception of febrile convulsion, ICD-9-CM codes 780.31 and 780.32) associated with prenatal exposure to an antidepressant (British National Formulary, BNF chapter 4.3) or an antipsychotic medication (BNF chapter 4.2.1). We included all pregnant women aged 15-50 years who delivered a live birth between January 1, 2001 and December 31, 2015. All children had at least one-year follow-up by the end of the study period (December 31, 2016). Children without valid mother-child linkage or with incomplete birth information were excluded.

Children were considered as exposed prenatally if their mothers received any antidepressant or antipsychotic medication during the pregnancy period ("maternal gestational use"). Separate exposure cohorts were created for antidepressant and antipsychotic use. Mothers with epilepsy or prenatal lithium treatment may have an increased risk of having a child with seizure[8]; we therefore excluded pregnant women who had a diagnosis of epilepsy, and those treated with lithium during pregnancy. We also excluded mothers with antipsychotic or antidepressant prescriptions in the analyses of antidepressants or antipsychotics, respectively. We restricted the analyses to mothers who received at least two prescriptions of interest.

Based on maternal antidepressant/antipsychotic use in different risk periods, we classified the children into three comparator groups: a) those whose mothers did not use antidepressants/antipsychotics during pregnancy ("maternal gestational non-use"); b) those whose mothers used these drugs any time before pregnancy but stopped treatment when pregnant ("maternal past use"); and c) those whose mothers had never used the drugs before and during pregnancy ("maternal non-use ever"), who were further classified into those with and without maternal psychiatric disorders (ICD-9-CM codes 290-319).

To explore the impact of confounding by indication, we compared children with "maternal past use" to those with "maternal non-use ever". An increased risk of seizure among children with "maternal past use" indicates confounding by indication, as the infant was not exposed to antidepressants/antipsychotics. Similarly, children with "maternal gestational use" were compared to children with "maternal past use". Secondly, to evaluate the role of maternal psychiatric disorders, we restricted comparison cohorts to children with "maternal non-use ever".

Sibling-matched analysis was conducted to control for shared genetic and social confounding at the family level. Covariates for confounding adjustment were maternal age at delivery, calendar year at delivery, birth hospital, infant gender, parity, maternal underlying medical conditions and socioeconomic status. Cox proportional hazard regression models with propensity score fine-stratification weighting[9] was used to estimate the hazard ratios with a 95% confidence interval (CI) to assess the association.

This study included 412,796 and 410,587 pairs of mother-child records in the antidepressant and antipsychotic analyses, with a mean follow-up time of 6.59±3.91 and 6.60±3.91 years, respectively. For antidepressants, the proportion of children diagnosed with seizure among those with "maternal gestational use" and "maternal gestational non-use" was 6.75% and 4.46%, respectively. For antipsychotics, the corresponding figures were 9.31% and 4.46%.

Thus, the prenatal use of antidepressants and antipsychotics was associated, respectively, with a 23% (propensity score weighted hazard ratio, wHR=1.23, 95% CI: 1.02-1.48) and 49% (wHR=1.49, 95% CI: 1.11-1.99) increased risk of seizure in children, when compared with unexposed children. However, the increased risk was not observed when children with "maternal gestational use" were compared to those with "maternal past use" (wHR=1.01, 95% CI: 0.79-1.28 for antidepressants; wHR=0.98, 95% CI: 0.64-1.50 for antipsychotics), as well as to those with "maternal non-use ever" and maternal psychiatric disorder (wHR=1.13, 95% CI: 0.88-1.44 for antidepressants; wHR=1.32, 95% CI: 0.93-1.89 for antipsychotics).

Moreover, when the analyses were restricted to children with "maternal non-use ever" of antidepressants or antipsychotics, the risk of seizure was consistently higher in children whose mothers had a psychiatric disorder, compared to those whose mothers had no psychiatric disorder (wHR=1.44, 95% CI: 1.25-1.67 for antidepressants; wHR=1.41, 95% CI: 1.20-1.66 for antipsychotics). Comparisons between children with "maternal gestational use" and the sibling-matched children with "maternal gestational non-use" also showed no statistically significant difference (wHR=1.16, 95% CI: 0.75-1.77 for antidepressants; wHR=1.19, 95% CI: 0.29-4.82 for antipsychotics).

The results of our study, therefore, do not support a causal

relationship between prenatal exposure to antidepressants or antipsychotics and the risk of seizure in children.

Since the first report of a possible association between psychotropic drug exposure *in utero* and childhood neurological disorders, clinicians have faced a dilemma regarding the management of women with mental disorders during both the time that they are trying to conceive and pregnancy. Ongoing efforts have been made to enhance perinatal psychiatric drug management, such as the European regulatory ban of valproate use in women of childbearing potential due to clear evidence of teratogenic and neurodevelopmental harm. However, current guidance on gestational antidepressant and antipsychotic use remains unclear due to the lack of strong clinical evidence.

When generating evidence, methodological considerations such as adequate adjustment for known confounders and increase in precision of estimates should be considered wherever possible, to minimize uncertainties of the results. Sustained efforts in ascertaining the specific benefits and harms of prenatal psychotropic medication exposure are pivotal towards individualized risk-benefit analyses of psychiatric treatment to safeguard both maternal and foetal health.

We cannot completely exclude the possibility that prenatal exposure to antidepressants or antipsychotics is related to risk for childhood seizure, but our study suggests that the association might be explained by confounding factors. Further studies stratifying antidepressants/antipsychotics by different drug classes, exposure time in different trimesters, and first-time seizure diagnosed at different developmental timepoints are needed.

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Prevention, treatment and care of substance use disorders in times of COVID-19

Since 2015, the United Nations Office on Drugs and Crime (UNODC) – World Health Organization (WHO) Informal Scientific Network (ISN) has brought the voice of science to international drug policy discussions, especially at the Commission on Narcotic Drugs, the prime policy-making body of the United Nations (UN) for drug control matters. In recent years, the public health dimensions of the world drug problem, including prevention and treatment of substance use disorders (SUDs), have become prominent in policy debates within the UN system[1].

Individuals with SUDs are at increased risk of contracting COVID-19 and, if infected, are more likely to experience negative outcomes[2-4]. This vulnerability reflects both the adverse effects of the non-medical use of psychoactive substances on health[5], compounded by high rates of non-attended medical comorbidities[3,4], as well as associated psychosocial and structural factors. These may include situations of homelessness and incarceration, which increase the risk of acquiring COVID-19 through intermediate and direct factors (e.g., poverty, stigma, overcrowded settings) and decrease access to adequate care, ultimately worsening outcomes[6]. Several surveys have identified disruptions of services for people with SUDs during the COVID-19 pandemic[7]. Providing services for population groups with increased vulnerabilities is a key public health principle especially during a pandemic, also benefitting the general population as a whole[4].

Evidence-based and human rights-based treatment of SUDs, including mental health and physical comorbidities, should be considered essential and integrated into existing health care services. The provision of remote services and digital health solutions for the treatment and care of SUDs, and medications to treat SUD and prevent overdose, should be accessible to those in need. Due to overlapping vulnerabilities, people who use substances with special treatment and care needs carry a disproportionate risk and require special attention[8]. Investment in evidence-based prevention and treatment of SUDs and comorbid health conditions, and attention to the impact of social determinants on the health of all age groups are now more necessary than ever. Global actions are needed to build health systems resilience for universal health coverage and health security during the COVID-19 pandemic and beyond[9].

The ISN shares the following recommendations in its 2021 statement:

- Support the timely collection and analysis of data to monitor the impact of the COVID-19 pandemic, including the role of

policies and interventions targeting demand and supply of psychoactive substances. Also, on the unintended consequences of "lockdowns" on substance use, SUDs, overdoses, and treatment and care services.
- During the COVID-19 pandemic, ensure the ongoing provision of evidence-based treatment of SUDs along an integrated continuum of care in line with the UNODC-WHO International Standards for the Treatment of Drug Use Disorders.
- Ensure the meaningful inclusion of mental health and SUD experts in COVID-19 task forces and promote multi-stakeholder, integrated approaches to trainings that facilitate innovations in the health system by bringing together the scientific community, the private sector and international and civil society organizations.
- Increase resources, including trained workforce, to secure continued access to SUD prevention and treatment and care services, including for those infected with COVID-19.
- Populations in especially vulnerable circumstances with special needs (such as women, children, victims of violence, ethnic minorities and indigenous populations, refugees and migrants, the unhoused, the economically disadvantaged, those with mental illnesses, the elderly, socially isolated people, and people in contact with the justice system) should be provided adequate services in accordance with local resources, and especially in light of the COVID-19 pandemic.
- During the COVID-19 pandemic, existing socioeconomic disadvantages have increased. Recalling the ISN statement from 2019, the ISN recommends including people who use substances in priority strategies and interventions that minimize inequalities.
- Develop policies that promote and evaluate the use of information technologies, including mobile devices, to support digital health solutions for substance use screening, treatment and recovery, and develop solutions to address the existing digital divide. Every effort must be taken to ensure the confidentiality, privacy and safety of those who use remote/online services.
- Ensure that COVID-19 information, prevention, testing and vaccination is available for individuals with SUDs, and SUD treatment professionals.
- Give special consideration to addressing communicable and non-communicable disorder prevention and treatment, including prevention of the negative health and social consequences of substance use, as well as mortality due to overdose, and comorbid mental and physical health conditions, even when resources and attention are primarily focused on COVID-19.
- Stigma and discrimination are among the biggest challenges for people with SUDs, including those in contact with the criminal justice system, and they have been exacerbated during the COVID-19 pandemic. Strategies should be developed to ensure that SUDs are treated like any other chronic medical condition during this crisis and beyond, and that people with SUDs are not left behind.
- The ISN, especially now and in view of the increased risk for COVID-19 in closed settings, joins the global call for increased consideration of alternatives to conviction or punishment for people with SUDs and comorbid mental health conditions, in line with the UN Standard Minimum Rules for Non-Custodial Measures and the International Drug Control Conventions.
- Strengthen research on the impact of COVID-19 on substance use, SUDs and comorbid mental health conditions, and barriers to treatment during the pandemic, including ongoing monitoring and evaluation of policies that affect people who use substances and with SUDs.

Investments in evidence-based prevention for all age groups (especially children, teenagers, and young adults), including support to parents, carers and families, are now more necessary than ever.

The ISN recommends to ensure that, during and beyond the COVID-19 pandemic, people with drug use disorders are not left behind, and that quality substance use prevention, treatment and care services are accessible to those in need, including to those in most vulnerable circumstances.

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Implementation of the WPA Action Plan 2020-2023: an update

The year 2021 has been another tough one for us all. Uncertainty about the COVID situation, restrictions about travel, and difficulties in getting connected have been the major issues that have affected our professional work and personal lives during that year. The WPA has also struggled coping with these limitations. However, that period has given us some motivation and new insight to work under difficult circumstances and to continue with the implementation of our Action Plan 2020-2023[1,2].

The WPA Executive Committee and Standing Committees, along with the Secretariat staff, remained committed to fulfil their responsibilities[3-8]. The WPA's drive to encourage and inspire learning among colleagues and trainees around the world led to offering more online educational activities during 2021. We were delighted to organize, support and promote several new educational modules, courses, teaching sessions and online programmes[9].

The accelerated development of the WPA education portal and learning management system (LMS) has promoted the launch of new education and training modules to support our young professionals, especially for the emergency response measures during the pandemic period. The first of these modules supports psychiatrists in using e-mental health tools. The portal also gives ready access to WPA's existing training materials available in several languages. Available programmes also include ICD-11 and Yoga courses, free webinars on Early Intervention in Psychosis, updates in Psychopharmacology and courses on Telepsychiatry, Psychotherapy and Child and Adolescent Psychiatry.

We continued with our projects outlined in the Action Plan. Various Working Groups offered a number of activities in areas of training, research and clinical updates. The Working Groups on Co-morbidity in Mental Illnesses, Early Intervention in Psychosis, Public Mental Health, and Promotion of Psychiatry among Medical Students highlighted their contributions in various activities[10-12]. I am pleased that we also completed some unfinished projects started in the previous triennium[13]. The WPA Scientific Sections likewise supported the scientific work of the Association in an inspiring way[14-16].

Since the start of the network of WPA Collaborating Centres in 2016, these centres are providing practical advice on teaching, policy, research and clinical activities in psychiatry worldwide. During 2021, the network, now including eight sites, supported the implementation of the WPA's strategic plan to build a global alliance for better mental health[17].

In addition to the pandemic, unfortunately, we saw many adversities in 2021 in several parts of the world. Following WPA's mission to help and support our membership during disasters, we established an Advisory Committee for Responses to Emergencies (ACRE), that brought together the leaders of the larger Member Societies to facilitate practical and concrete aid to Member Societies in need. This work continued mobilizing and fostering education, information collection, and development of local, national and international strategies to cope with the mental health consequences of emergencies throughout 2020-21.

The WPA recently formed a sub-committee of the ACRE for Afghanistan's deteriorating conditions, that are not only causing an humanitarian crisis but also adding concerns about provisions and delivery of health care for the general population. We, at the WPA, as a part of our ACRE project, are working with our fellow Afghan mental health professionals to offer ongoing support through the provision of medicines, patient assessments and training.

With the start of the WPA eNewsletter in 2021, we are facilitating sharing of activities and reports from our membership. The Newsletter has emerged as a strong medium for our visibility on the social media platform and a better communication among different components of the Association.

World Psychiatry, the WPA official journal, achieved an impact factor of 49.548. It was reaffirmed that it is ranked as the number one in the list of psychiatric journals and in the Social Science Citation Index, and number five among all the journals in the Clinical Medicine category. The journal is published regularly in three languages (English, Spanish and Russian), with individual issues or articles also available on the WPA website in other languages (Chinese, French, Arabic, Turkish, Japanese, Romanian and Polish). More than 60,000 mental health professionals regularly receive the electronic or the print version of the journal. All the back issues can be freely downloaded from the PubMed system and the WPA website.

We very much enjoyed our successful virtual World Congress of Psychiatry that took place in October 2021. As always, the current pandemic is all about adapting and innovating, and we feel that we were able to redesign the event from the ground up to ensure that we could bring the most timely clinical, academic and research topics to our membership. I am also pleased that we are actively working for our next World Congress to be held in Bangkok on August 3-6, 2022.

We are optimistic that the new challenges that will undoubtedly come, as the full impact on mental health following this pandemic becomes evident, will be addressed effectively. Like many, the WPA is learning fast with the changes and looks forward with confidence to its future, remaining fully committed to fulfilling its triennium's goals.

Let's shape the future of psychiatry and mental health together.

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The "Meet the WPA Council" Panel at the 21st World Congress of Psychiatry

The WPA Council is the organ including the Past Presidents of the WPA, which has the mandate to offer recommendations and advice to the WPA Executive Committee about any matters affecting the mission and strategy of the Association. It is currently chaired by me, and its other members are Profs. J.A. Costa e Silva, F. Lieh-Mak, N. Sartorius, J.E. Mezzich, M. Maj, P. Ruiz, D. Bhugra and H. Herrman.

Within the 21st World Congress of Psychiatry, a "Meet the WPA Council" Panel took place virtually on October 21, 2021. It included presentations by Profs. N. Sartorius, J.E. Mezzich, M. Maj, H. Herrman, J.A. Costa e Silva, D. Bhugra and myself, plus a speech by the WPA President Elect, Prof. D. Wasserman.

I welcomed the participants, and offered a brief presentation about the risks in the future of digital psychiatry. How will digital psychiatry reach those most in need in community settings? How will it reach children in low-income households and their parents, who disproportionately lack access to devices and high-speed Internet? Moreover, confidentiality breaches might seriously impair public cooperation in big data projects. There is the risk of being unable to respond to psychiatric emergencies in a timely manner. Patients with schizophrenia are known to have cognitive impairment, which may hinder their ability to engage with telepsychiatry. People experiencing homelessness may also be disproportionally excluded from accessing appropriate care and interventions if largely delivered virtually. How we can proceed with telepsychiatry for legal implications and involuntary admission, forensic psychiatry and confirmation of identity? Lastly, can we practice rehabilitation by digital psychiatry?

N. Sartorius' presentation dealt with comorbidity of mental and physical disorders as a priority issue for psychiatry. The prediction that this comorbidity will continue to be a major problem rests on the examination of two trends. The first is the increasing expectancy of life of people with noncommunicable diseases, for which we have treatments that prolong life but no treatments that cure them. The second is the increasing fragmentation of medicine into ever finer specialties, with practitioners who are willing to deal with the diseases of their specialty but not with others[1]. The various efforts to develop collaborative care, involving action of several specialists in the management of the person with several diseases, were successful in some settings due to the presence of exceptionally committed physicians linked in a well functioning system. This is unlikely to be developed in less endowed situations. The resolution of the problems of comorbidity will require changes in the education of medical practitioners and in the organization of health services.

J. Mezzich's speech focused on the future of person-centered medicine and psychiatry. He reported that, as a reaction to modern medicine's hyperbolic emphasis on organs and diseases and its accompanying neglect of the doctor-patient relationship, a worldwide programmatic movement has evolved to re-humanize medicine and public health. The epistemological definition of person-centered medicine proposes a holistic and collaborative medicine that is informed by evidence, experience and values, and aimed to health restauration and promotion of the whole person. The WPA has actively contributed to the increasing centrality of the person in medicine and health. In 2005, an Institutional Program on Psychiatry for the Person was established by the WPA General Assembly, which engaged many Member Societies and Scientific Sections in symposia and publications. The WPA Section on Classification developed the Person-centered Integrative Diagnosis model[2], which was applied by the Latin American Psychiatric Association for its Latin American Guide for Psychiatric Diagnosis. So, the person centered approach is emerging as a widely recognized and respected core feature of psychiatry and medicine.

M. Maj's presentation dealt with some current trends in psychiatry emerging from the latest issues of *World Psychiatry*. He focused on four topics. First, the structural and attitudinal barriers to the access of evidence-based psychotherapies, which have to be actively addressed worldwide, ensuring that these therapies are not only available in the private offices of psychologists and psychiatrists, but also in public mental health services, in order to avoid an unacceptable socioeconomic divide. Second, the importance of listening to patient preferences when making mental health care decisions, since users have a lot to say about the choice of pharmacotherapies (having often had a previous experience with medications), the decision to implement a psychotherapy and its choice, and their unmet social, practical and emotional needs to be addressed by psychosocial interventions. Third, the increasingly acknowledged need for a further clinical characterization of the patient who has received a given psychiatric diagnosis, in order to guide the formulation of a more personalized management plan[3-5]. Fourth, the participation of psychiatrists in the promotion of mental health in the community. This requires new competencies, which should however be added to psychiatrists' skills as clinicians, rather than replacing them. Unfortunately, there are some contexts in which the clinical skills of psychiatrists are being depreciated, trivialized or marginalized. These skills should be defended and cultivated worldwide.

H. Herrman's speech dealt with future prospects for women in psychiatry. She emphasized that deep-seated gender biases persist across the world. The Lancet Commission on Gender and Global Health 2020 [6] contends that gender intersects with other social factors to drive health inequities. It notes that, whereas 70% of health workers globally are female, 70% of health-care leaders are male. In psychiatry, women are still relatively scarce in the leadership of the profession, even though they are entering in higher numbers. The full involvement of women is critical for psychiatry[7]. Women can bring a special contribution and different perspectives. However, professional barriers and problems for women persist. Mentoring and support of various kinds, flexible career paths, monitoring needs and experiences, and working with educators, employers, professional societies and policy makers are all needed. The WPA has worked to ensure that women colleagues are invited to participate fully and equally in the Association's activities. It supports women in different places to share experiences and work together. Above all, it aims to foster an open and optimistic view among women of working in the profession.

D. Bhugra's presentation summarized the outcome of the work of the WPA-Lancet Psychiatry Commission on the future of psychiatry. In six potential themes, the Commission suggested that patients' needs and treatments are likely to change. Laws supporting patients also need to change, as a survey of laws of 193 countries showed widespread discrimination[8]. The use of digital technology has been successfully demonstrated in the COVID-19 pandemic and this is likely to continue. However, ethical, confidentiality and privacy issues need to be addressed by the profession. Societal expectations will need to be taken into account when training the psychiatrists of the future.

D. Wasserman's speech dealt with suicidal behaviours during the COVID-19 pandemic. She reported that, compared to previous years, suicide rates have remained largely unchanged globally or declined in the early phase of the pandemic. However, increased suicide rates have been reported among non-white residents and Afro-American groups in the US, as well as among adolescents in China. Among adolescents, there have been no significant changes in suicide rates during the period of school closure, but an increase has been observed in the period after coming back to schools. No change in the number of suicide-related emergency department visits has been reported in many countries in the early phase of the pandemic. However, an increase in suicide-related emergency visits by females and youths has been identified since the summer of 2020 in the US. The assessment of suicidal thoughts and attempts during the pandemic showed significant increases, particularly in females and the young. As suicide attempts are the foremost predictor of completed suicides, vigorous preventive measures should be taken, including both health care and public mental health initiatives[9].

Despite its brevity, the session was lively and informative. I hope that similar panels will be regularly organized within the World Congresses of Psychiatry in the future.

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The WPA Working Group on Intellectual Developmental Disorders: the need for a second paradigm shift

The WPA Action Plan 2020-2023[1-3] coincides with a much-needed focus on the mental health needs of people with intellectual disabilities/intellectual developmental disorders (IDD). A Working Group on IDD has been formed and has met for the first time at a Presidential Symposium during the 19th World Congress of Psychiatry in Lisbon, Portugal in August 2019[4].

A recent international review of service models for IDD[5] has highlighted that some countries rely on high-quality specialist services that are however difficult to reach, while only few countries use trained volunteers to work with family networks to provide care and support, education, training and employment to affected people. It is evident that very few low- and middle-income countries (LMICs) have any significant services for persons with IDD across the lifespan. Furthermore, any mental health care provided entails untrained staff practicing in segregated facilities. Factors that impact the quality of services in LMICs include cultural barriers, social stigma, geography, transport links, poorly developed legislative frameworks, and poor government spending.

The activities of the WPA Working Group on IDD have been envisioned under the World Health Organization (WHO) framework recommended by the ICD-11 relevant Work Group[6]. That framework has been widely acknowledged as the impetus for the paradigm shift in the classification of IDD as a neurodevelopmental condition in both the DSM-5 and ICD-11. This approach recognizes that functional limitations often coexist alongside strengths, and that both are to be considered during the individuals' assessment; and that descriptions of limitations should be aimed to develop a profile of needed supports. It also underscores the need to identify the underlying etiologies, consistent with the

WPA public health mission to emphasize the importance of risk factors and to adopt evidence-based preventive and rehabilitative interventions.

The WPA Working Group on IDD has participated this year in the initiative called Rehabilitation 2030, sponsored by the WHO Department of Noncommunicable Diseases, Disability, Violence, and Injury Prevention, aiming to develop a package of rehabilitative interventions[7] along with specified resource requirements for their delivery. The overarching goal is the improved care of persons with IDD across the lifespan, with a particular emphasis on LMICs.

Following on these ground-breaking approaches in classification and evidence-based interventions, the Working Group is now promoting a second paradigm shift aiming to include training on IDD within mainstream psychiatry, once again with a particular emphasis on LMICs.

Three important arguments justify this call. First, when polled about their knowledge on the impact of IDD, many trainees in psychiatry recognize the disproportionately high burden of co-occurring mental disorders in persons with IDD[8]. Second, when offered opportunities to interact with persons with IDD during rotations, many trainees in psychiatry regard such experiences as highly formative and inspiring. Third, and most important, psychiatry as a profession has the potential to improve significantly the care for persons with IDD.

Furthermore, the gap in mental health services for persons with IDD is too significant to be compensated by an *ad hoc* reliance on individual providers and families, and their resilience is not limitless. Moreover, within the context of the COVID-19 pandemic, persons with IDD are facing the utmost intensification of inequities in term of underlying medical liabilities, inability to socially distance, increased infection and mortality risks, challenges to participate in telehealth services, and ensuing social isolation and adverse mental health outcomes[9].

The Working Group and the WPA leadership invite Member Societies to work collectively to enhance efforts for the development of inclusive training models in the mental care of persons with IDD. The Working Group is ready to provide awareness raising, training, and research collaboration to promote and disseminate effective services and thereby improve the lives and outcomes for persons with IDD. For this purpose, the Working Group is developing an open access handbook focusing on global aspects of the psychiatry of IDD, with authorship from both LMICs and high-income countries. In parallel, the Working Group is developing online educational materials summarizing the key aspects of psychiatric care in people with IDD. These resources will be accessible through the WPA educational portal in 2022.

The WPA Working Group on IDD encourages systematic exposure to and experience in this area for all psychiatrists, so that they can adjust treatments for co-occurring mental disorders and avoid diagnostic overshadowing in which IDD may be wrongly considered the cause of all behavioural problems, and psychiatric, physical as well as environmental factors may be overlooked. Since relatives remain key partners as well as co-providers of services for people with IDD throughout their lives, the Working Group encourages provision of support to families by using local networks, with access to specialists for training and supervision as well as to more intensive forms of treatment for co-occurring problems (e.g., autism spectrum and seizure disorders)[7]. Third, the Working Group calls for the development of targeted mental health services including psychiatrists and allied professionals, who will need additional training to improve their diagnostic and therapeutic skills relevant to IDD. Finally, the Working Group emphasizes the need for person-centered care tailored on abilities and aspirations of affected persons, blending the social and medical models of development and disability within a human rights framework to improve access to health care, education and employment.

These themes have been the subject of presentations in Presidential and State-of-the-Art Symposia at the World Congress in Lisbon, and subsequently at the World Congresses in Bangkok, Thailand in March 2021, and Cartagena, Colombia in October 2021, and will continue to be addressed by the Working Group at forthcoming WPA congresses and conferences.

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WPA Working Group on Medical Students: current initiatives and future priorities

Psychiatric issues impact individuals of all ages globally. Shortage of mental health professionals is a major concern especially in low- and middle-income countries. Further, the COVID-19 pandemic has led to downsizing and even closure of various mental health services worldwide[1-4]. In the WPA Action Plan 2020-2023, capacity building and promotion of psychiatry among medical students is an important pillar[5,6]. To this aim, a WPA Working Group on Medical Students has been created. The inau-

gural meeting of this group was held on December 21, 2020, attended by the WPA President. This was followed by regular meetings.

The remit of this Working Group includes four components: to identify opportunities for promoting psychiatry as a career among medical students; to identify organizations and individuals interested in participating and promoting WPA's Action Plan in nurturing psychiatry among medical students; to liaise with other WPA Working Groups regarding medical students; and to support medical students around the world.

Since the beginning of 2019, COVID-19 has caused significant disruptions in the day-to-day lives of millions of people around the world. Medical education is not an exception in this regard. The pandemic has impacted on in-person learning, medical school examinations, clinical rotations, faculty availability for supervision and future placements[7].

The pandemic has also impacted on the emotional well-being of medical students. A study done by members of our Working Group among 1,100 medical students from five medical schools in Pakistan found high rates of anxiety (48.6%) and depressive symptoms (48.1%) during the COVID-19 pandemic. The study included 69% female and 31% male medical students, with approximately 25% reporting past psychiatric issues. One of the most concerning observations was that one in five medical students thought that it would be better if they were dead and 8% often thought about suicide during the past 2 weeks[8]. It is imperative that medical schools develop strategies and support systems to maintain medical student well-being.

A major highlight of the activity of our Working Group has been the release of a promotional video for medical students entitled *Why Psychiatry*. This video was created to share perspectives from seasoned faculty, psychiatry trainees and medical students on the importance of supporting the psychiatry workforce around the world. Interviews included key themes encompassing medical student mental health, the diversity of psychiatric subspecialties, the interface of mental health with social determinants of health, and opportunities to partner with primary care providers. A consistent message was the critical shortage of psychiatrists and the need to support workforce development to address mental health needs. This video is available in English, French, Spanish and Russian for medical educators to share with their trainees and medical students (www.wpanet.org/post/why-psychiatry-medical-student-group-video-now-available-online).

In addition to the video, the Working Group is developing a set of online tools for psychiatric educators. The first of these tools is an interactive self-learning module on the well-being of medical students, which is now available on the WPA educational portal. Self-care and wellness are often ignored in the formal medical school curricula[9]. The current pandemic has increased the visibility of burnout and depression in the health care workforce. This module plans to encourage educators and policy makers to implement student wellness policies and to support a learning environment which nurtures emotional and physical well-being.

In order to augment the virtual resources, the Working Group has organized three in-person events to promote psychiatry among medical students and address burnout. These inaugural events were held in Pakistan, India and Qatar, with active participation from local medical students, who provided input on core topics. These events also served as a platform to support and mentor medical students interested in psychiatry.

The Working Group is active in publishing peer-reviewed articles, covering areas such as promoting psychiatry among medical students and the impact of COVID-19 on medical students[10,11]. Additional research articles are planned and underway. All of the activities and initiatives of the Working Group are accessible on the dedicated section of the WPA website (www.wpanet.org/wg-on-medicalstudents).

The Working Group has been active in presenting invited and peer-reviewed abstracts and symposia around the world. This included presidential and other symposia on psychiatry capacity building and medical education themes at the World Congresses in Bangkok, Thailand in March 2021, and Cartagena, Colombia in October 2021. Abstracts on the promotion of psychiatry were presented at the annual conferences of the Association of University Teachers of Psychiatry Annual Conference, UK in February 2021; at the WPA Regional Conference, Russia in May 2021; and at the 67th Virtual American Academy of Child and Adolescent Psychiatry Conference in October 2021. An innovative contest was held among medical students in Mexico to submit papers on "The Role of Psychiatry after the Pandemic". The top three papers were recognized during the 27th Congress of the Mexican Psychiatric Association in September 2021.

Future directions include: a) to create online self-learning modules on "stigma" and "burnout" for medical students; b) to conduct a survey about psychiatry curriculum in medical education across medical schools in different countries; c) virtual and in-person activities to promote psychiatry among medical students and to address burnout among students; d) to liaison with regional and international organizations to promote psychiatry; e) presentations at the WPA congresses and other national and international conferences; and f) social media and video campaigns to promote psychiatry.

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WPA Working Group on Public Mental Health: objectives and recommended actions

Mental disorder is reported to account for almost a third of global disease burden as measured by years lived with disability (YLDs)[1]. On the other hand, mental well-being results in broad positive impacts[2]. Effective public mental health interventions exist to treat mental disorder, prevent associated impacts, prevent mental disorder from arising, and promote mental well-being and resilience[2,3].

However, only a minority of those with mental disorder receive treatment, with far lower coverage in low- and middle-income countries (LMICs)[4]. There is even less coverage of interventions to prevent associated impacts of mental disorder, and negligible coverage of interventions to prevent mental disorder, or promote mental well-being and resilience. This implementation gap represents a breach of the right to health, and results in population-scale suffering and associated economic costs[3]. The gap has further widened during the COVID-19 pandemic[5-7].

The United Nations (UN) Sustainable Developmental Goals have set a target of universal coverage by 2030 which includes treatment and prevention of mental disorder and promotion of mental well-being. The most recent World Health Organization (WHO) Mental Health Atlas highlighted that "global targets can be reached in 2030 only if there is a collective global commitment over the next 10 years across Member States to make massive investments and expanded efforts at the country level relating to mental health policies, laws, programmes and services"[4].

Public mental health involves a population approach to improve coverage, outcomes and coordination of interventions to treat mental disorder, prevent associated impacts, prevent mental disorder from arising, and promote mental well-being and resilience. This aims to support efficient, equitable and sustainable reduction in mental disorder, promotion of population mental well-being, and achievement of the UN Sustainable Developmental Goals target of universal coverage by 2030[3].

The WPA Action Plan 2020-2023 promotes public mental health as a guiding principle[8,9]. A Working Group on Public Mental Health has been then established, including experts such as J. Allan, F.K. Baingana, J. Campion, Y. Huang, A. Javed, N. Lamb, S. Levin, C. Lund, M. Marmot, S. Saxena, T. Schulze, E. Sorel, H. Tu, P. Udomratn, and M. van Ommeren (observer).

The Working Group highlighted that public mental health is not well defined or understood, with some languages having no terms for it. This contributes to lack of action on relevant issues. The Group agreed upon the definition outlined above, which is reported on the Group webpage of the WPA website (www.wpanet.org/public-mental-health) and in a recent publication[3].

The main objective of the Working Group is to improve implementation of public mental health interventions in four ways. The first is to raise awareness, value, acceptance and prioritization of this area in national health policies. The second is to promote national assessments of public mental health unmet need and required actions which can then inform policy development and implementation. The third is to promote public mental health training, including through digital platforms, which can support psychiatrists and other professionals to address the public mental health implementation gap, particularly in LMICs, through identification of required actions by different sectors as well as clarification of a core curriculum, training targets and milestones. Examples of public mental health training are highlighted on the above-mentioned Group webpage. The fourth way is to support development of integrated public mental health approaches to disease management and prevention including through engagement with primary and general health systems.

Further objectives include: a) work with interested countries in order to facilitate these approaches with identified funding; b) engagement with other organizations on the public mental health agenda – thus far, these have included the Organization for Economic Co-operation and Development (OECD), the UN International Children's Emergency Fund (UNICEF), and the WHO; c) disseminating work relevant to public mental health through publications, presentations and training, also delivered online; d) supporting a public mental health approach in other areas of the WPA Action Plan 2020-2023, including child, adolescent and youth mental health, the management of comorbidities, and partnership with other organizations.

Publications already produced by the Working Group include an editorial on the field as a whole[10], articles dealing with the public mental health approach to the COVID-19 pandemic[11-13], and papers about required actions to address public mental health implementation failure[3,14]. Members of the Working Group have given and will give presentations at World Congresses of Psychiatry in 2021 and 2022, and will present in a public mental health symposium at the 2022 International Congress of the UK Royal College of Psychiatrists.

In order to achieve consensus on required actions to address the public mental health implementation gap, the members of the Working Group were invited to contribute to a health policy article[3], which recommends the following six actions: a) making the public mental health case through assessment of unmet need, estimation of impact and associated economic benefits from improved coverage, as well as collabo-

rative advocacy and leadership; b) public mental health practice; c) public mental health training and improving population knowledge; d) improving coverage of public mental health interventions through settings-based approaches, integrated approaches, digital technology, maximizing existing resources, and focus on high-return interventions; e) a rights approach, legislation and regulation; f) public mental health research, including that focused on implementation.

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The ICD-11 is now officially in effect

The 11th revision of the International Classification of Diseases (ICD-11) has come into effect on January 1, 2022. All the Member States of the World Health Organization (WHO) will now be asked to use this new version of the classification to report their morbidity and mortality statistics. An implementation package has been made available to facilitate the transition from the ICD-10 to the ICD-11.

The ICD-11 consists of 26 chapters corresponding to groups of diseases, plus a supplementary section (Chapter V) for functioning assessment. Chapter 6 is on Mental, Behavioural or Neurodevelopmental Disorders. Separate chapters are provided for Sleep-Wake Disorders (Chapter 7) and for Conditions Related to Sexual Health (Chapter 17). In addition to chapters on Injury, Poisoning or Certain Other Consequences of External Causes (Chapter 22) and on Factors Influencing Health Status or Contact with Health Services (Chapter 24), already available in the ICD-10, a new Supplementary Chapter on Traditional Medicine Conditions (Chapter 26) has been added.

The main uses for which the classification is designed include: certification and reporting of causes of death; morbidity coding and reporting, including primary care; casemix and diagnosis-related grouping (DRG); assessing and monitoring the safety, efficacy and quality of care; research and performance of clinical trials and epidemiological studies; assessing functioning; and clinical documentation (https://icd.who.int).

The ICD-11 has 17,000 codes and more than 120,000 codable terms. It is entirely digital and accessible to everybody. It is available (by now) in English, Spanish, Chinese, Arabic and French.

The Clinical Descriptions and Diagnostic Requirements (CDDR) for mental health, corresponding to the Clinical Descriptions and Diagnostic Guidelines (CDDG) of the ICD-10, are an integral part of the ICD-11. They cover 20 groupings of disorders: Neurodevelopmental Disorders, Schizophrenia or Other Primary Psychotic Disorders, Catatonia, Mood Disorders, Anxiety or Fear-Related Disorders, Obsessive-Compulsive or Related Disorders, Disorders Specifically Associated with Stress, Dissociative Disorders, Feeding or Eating Disorders, Elimination Disorders, Disorders of Bodily Distress or Bodily Experience, Disorders Due to Substance Use or Addictive Behaviours, Impulse Control Disorders, Disruptive Behaviour or Dissocial Disorders, Personality Disorders and Related Traits, Paraphilic Disorders, Factitious Disorders, Neurocognitive Disorders, Psychological or Behavioural Factors Affecting Disorders or Diseases Classified Elsewhere, and Secondary Mental or Behavioural Syndromes Associated with Disorders or Diseases Classified Elsewhere.

For each category included in each of these groupings, there are sections on Essential (Required) Features, Additional Clinical Features, Boundary with Normality (Threshold), Course Features, Developmental Presentations, Culture-Related Features, Sex- and/or Gender-Related Features, and Boundaries with Other Disorders and Conditions (Differential Diagnosis).

The development of the CDDR, to which WPA experts have extensively contributed (including through chairmanship of several Workgroups), is regarded as the most broadly international and participative process ever implemented for a classification of mental disorders[1]. The main differences between the CDDR and the DSM-5 diagnostic criteria, and the main contentious issues that have been debated in the development of the CDDR, have been extensively dealt with in this journal[2-13].

The finalization of the CDDR has been preceded by a vast programme of international field studies. These included Internet-based and clinic-based studies. The Internet-based field studies were implemented through the WHO Global Clinical Practice Network (https://gcp.network). This now includes more than 16,000 clinicians from 159 countries (51% psychiatrists, 30% psychologists; 40% from Europe, 25% from Western Pacific, 24% from the Americas, 5% from Southeast Asia, 3% from Eastern Mediterranean, and 3% from Africa; 63% from high-income countries, 37% from middle- and low-income countries).

The clinic-based field studies were conducted with the participation of WHO Collaborating Centres. An Internet-based field study[14] in a sample of 928 health professionals from all WHO regions found that, on average, the ICD-11 CDDR for ten selected mental disorders displayed significantly higher diagnostic accuracy (71.9% vs. 53.2%), as well as higher ease of use, higher clarity, better goodness of fit, and lower time required for diagnosis, compared to ICD-10 CDDG.

An international training programme focusing on the CDDR is now being implemented. A first comprehensive online 20-hr training course was organized by the Naples WHO Collaborating Centre on Research and Training in Mental Health and the European Psychiatric Association from 9 to 30 April, 2021. The course was coordinated by G.M. Reed and M. Maj, and covered several sections of the CDDR (Schizophrenia or Other Primary Psychotic Disorders, Mood Disorders, Anxiety or Fear-Related Disorders, Obsessive-Compulsive or Related Disorders, Disorders Specifically Associated with Stress, Feeding or Eating Disorders, Disorders Due to Substance Use or Addictive Behaviours, and Personality Disorders). W. Gaebel, M. Cloitre, M. Maj, C.S. Kogan, P. Monteleone, M. Swales, J.B. Saunders and N.A. Fineberg composed the Faculty. The live course was attended by 120 psychiatrists, selected from almost 500 applicants, representing 78 different countries. A further group of 250 psychiatrists had access to the course on demand.

A training course with exclusive access to the members of the WHO Global Clinical Practice Network has been set up by the WHO Collaborating Centre at Columbia University, in collaboration with the WHO Department of Mental Health and Substance Use. The course consists of 15 online training units, each focusing on a different disorder grouping and taking from 1 to 1.5 hours. Each unit provides a description of the relevant diagnostic grouping and the main innovations with respect to the ICD-10. Knowledge check questions are provided to ensure comprehension. Participants have the opportunity to practice by applying diagnostic guidelines to clinical case examples.

A training course co-organized by the WPA and the Global Mental Health Academy, with a structure similar to the course organized by the Naples WHO Collaborating Centre and the European Psychiatric Association, but with access also to psychologists and primary care practitioners, took place online from 8 to 29 November, 2021.

A WHO International Advisory Group on Training and Implementation for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders has been established to develop and evaluate educational, training and implementation processes related to the ICD-11 in various countries. WPA former officers who contributed to the development of the CDDR – such as M. Maj, W. Gaebel and D. Stein – are members of this Advisory Group.

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