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World Psychiatry

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The neurodevelopmental origins of schizophrenia in the penumbra of genomic medicine

The notion that schizophrenia has its origins long before the emergence of the clinical syndrome dates back at least to Kraepelin, who proffered that behavior peculiarities in children who later manifest dementia praecox were an expression of the "morbid pathology" at that time of life. In the 1920s, E. Southard, Harvard Professor of Psychiatry and Neuropathology, interpreted his neuropathological findings in brain tissue from patients with schizophrenia as being of developmental origin. L. Bender, an influential Boston psychiatrist and neuropathologist of the 1940s, labeled schizophrenia a "congenital encephalopathy". B. Fish of the University of California at Los Angeles started in the 1960s a series of landmark studies of high risk children and described neurological "dysmaturation" as a hallmark of these individuals during early childhood.

In 1986, in a paper entitled *The pathogenesis of schizophrenia: a neurodevelopmental theory*[1], I elaborated on these earlier ideas in the context of two traditional neurological principles: neuroanatomical localization of function and the implications of the state of brain maturation for clinical translation. I argued that the "lesion" in schizophrenia occurred early in development and involved distributed neural circuitries, that no single etiology had a monopoly on the underlying pathology, and that clinical and biological heterogeneity reflects interindividual variation in the extent of this pathology.

I attempted to espouse a further amplification of these principles a year later in the paper *Implications of normal brain development for the pathogenesis of schizophrenia*[2], by arguing that, while the pathology associated with schizophrenia may occur during early brain development, it was not a sufficient explanation for the condition. I highlighted the deterministic role of brain maturation for the clinical expression of psychosis and suggested that what is unique about schizophrenia is neither its pathology nor its cause, but the interaction of the pathology with the normal course of maturation of the brain systems affected by it.

I also raised the provocative possibility that the pathology in schizophrenia "may not reflect a discrete event or illness process at all, but rather one end of the developmental spectrum that for genetic and/or other reasons 0.5% of the population will fall into". In other words, rather than being an illness in a traditional sense, schizophrenia may reflect a quantitative developmental physiological deficit, a "liability factor that seems to be inherited".

The association of specific genes with schizophrenia allowed for a more detailed approach to this story, which P. Levitt and I discussed in 2011[3]. Studies of structural chromosomal defects, such as velocardiofacial syndrome, Klinefelter's syndrome and NRXN1 deletions, illustrated the variable clinical expressivity ("pleiotropy") of these genetic factors, such that cases of schizophrenia, autism and intellectual disability were associated with each of them. We proffered that, as schizophrenia is not something someone has, but a diagnosis that someone is given, it made sense to consider the syndrome not as a disease, but rather as a state of brain development and function based on an altered developmental trajectory with changing repercussions throughout life, much like autism and intellectual disability.

The more granular insights about genetics and epigenetics prompted us to observe that schizophrenia appears to be on a developmental continuum with other behavioral disorders with onset in childhood, including autism, intellectual disability and epilepsy, arising perhaps from overlapping biological risk factors that may each have distinct covariates. Schizophrenia reflects the relatively least "noise" burden of this group of developmental disturbances. We expropriated the concepts of C. Waddington in further suggesting that, as individuals on a particular developmental trajectory move forward, "the subtle course corrections from early cell differentiation and circuit construction become increasingly amplified and compounded as the phenotypic endpoint becomes increasingly mature and the circuits involved take on increasingly complex functions". Schizophrenia, we suggested, involved alterations in molecular trajectories that converge on relatively late maturating mechanisms for tuning cortical microcircuitry, involving the interplay between glutamate and GABA neurons (now popularly referred to as "excitatory-inhibitory balance").

From the background of this perspective, I found the paper by Owen and O'Donovan[4] appearing in this issue of the journal to be most timely and informative. These investigators have been at the leading edge of a generation of landmark genetic studies, based on rapidly developing molecular techniques for surveying genetic variation across the genome and the availability of large samples of case and control subjects generated by teams of investigators sharing data across many international research centers. The results of this work have permanently transformed the landscape of psychiatric research, from its long history principally of phenomenology into a mainstream scientific discipline with objective insights about basic causative mechanisms.

At the core of their discussion is the notion of a neurodevelopmental gradient, with genetic and biological overlap between schizophrenia and other neurodevelopmental disorders, including autism, attention-deficit/hyperactivity disorder, intellectual disability and epilepsy. This evolving idea is now strengthened by evidence which they review of relatively rare, but putatively deleterious, variations in the same genes and genomic regions being associated with each of these syndromes, and the burden of deleterious variation being greater in intellectual disability than autism, which is greater than in schizophrenia.

These are potentially seminal insights. It is also noteworthy that the shared genetic associations in each of these disorders span large fractions of the genome, implicating many and diverse pathways to risk. Overall, consistent with their conclusions, these findings would seem to implicate a relative burden of developmental "noise" that is a common factor in neurodevelopmental disorders, in which more "noise" has a greater impact on function and adaptation. Less consistent with this notion, however, is the overlap between common variants and this spectrum of developmental disorders. Current data suggest that most genetic risk for schizophrenia is accounted for by common variants, and the overlap here with more traditional neurodevelopmental disorders, such as intellectual disability and autism, is less strong[5].

It is also important to note that sharing genetic components with disorders that arise early in development, while suggestive, does not establish a neurodevelopmental origin for schizophrenia. A more direct test of this possibility is differential expression analysis in fetal and postnatal brain of genes associated with schizophrenia and other neurodevelopmental disorders. Jaffe et al[6] have shown that genes associated with schizophrenia, autism and intellectual disability are preferentially expressed during fetal life, in contrast to genes associated with bipolar disorder and neurodegenerative disorders, which are preferentially expressed after birth.

Surprisingly, these authors also found that epigenetic changes associated with fetal life are enriched for positive schizophrenia genome-wide association study (GWAS) loci and that epigenetic changes in brain associated with the manifest illness also are enriched for fetal epigenetic marks[7]. Epigenetic changes around the time of onset of schizophrenia were surprisingly not enriched for GWAS loci and were not enriched in the brains of deceased individuals who had schizophrenia at the time of their death. These surprising results suggest that both genetic and environmental events related to schizophrenia risk, at least those that leave epigenetic marks in the brains of patients with schizophrenia, are related principally to fetal life.

However, these data are still circumstantial support for a neurodevelopmental origin of schizophrenia. Perhaps the strongest evidence to date for a "smoking gun" are recent data showing that a sizable fraction of the genes in the schizophrenia GWAS significant loci directly influence placental biology and placental health and can predict complicated pregnancy, a well-recognized risk factor for schizophrenia[8]. This may offer new opportunities for developing primary prevention strategies early in life.

Finally, a recent highly provocative and influential publication by Boyle et al[9] argues that "many complex traits are driven by enormously large numbers of variants of small effects, potentially implicating most regulatory variants that are active in disease-relevant tissue". The authors go on to suggest that disease risk is driven mostly by genes with no direct relevance to disease, but which act as modifiers of more fundamental biologic processes, perhaps related to individual genetic backgrounds and environmental experience. This proposal echoes the question of whether psychiatric disorders are really "diseases" rather than varying states of brain development that have a particular way of expressing difficulties in particular environmental contexts, based on genomic background, development and experience.

If this is so, the primary public health challenge may not be in defining the genetics, but in defining the functional state of the brain when it matters most.

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Schizophrenia and the neurodevelopmental continuum: evidence from genomics

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The idea that disturbances occurring early in brain development contribute to the pathogenesis of schizophrenia, often referred to as the neurodevelopmental hypothesis, has become widely accepted. Despite this, the disorder is viewed as being distinct nosologically, and by implication pathophysiologically and clinically, from syndromes such as autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD) and intellectual disability, which typically present in childhood and are grouped together as "neurodevelopmental disorders". An alternative view is that neurodevelopmental disorders, including schizophrenia, rather than being etiologically discrete entities, are better conceptualized as lying on an etiological and neurodevelopmental continuum, with the major clinical syndromes reflecting the severity, timing and predominant pattern of abnormal brain development and resulting functional abnormalities. It has also been suggested that, within the neurodevelopmental continuum, severe mental illnesses occupy a gradient of decreasing neurodevelopmental impairment as follows: intellectual disability, autism spectrum disorders, ADHD, schizophrenia and bipolar disorder. Recent genomic studies have identified large numbers of specific risk DNA changes and offer a direct and robust test of the predictions of the neurodevelopmental continuum model and gradient hypothesis. These findings are reviewed in detail. They not only support the view that schizophrenia is a disorder whose origins lie in disturbances of brain development, but also that it shares genetic risk and pathogenic mechanisms with the early onset neurodevelopmental disorders (intellectual disability, autism spectrum disorders and ADHD). They also support the idea that these disorders lie on a gradient of severity, implying that they differ to some extent quantitatively as well as qualitatively. These findings have important implications for nosology, clinical practice and research.

Key words: Schizophrenia, neurodevelopment, autism, ADHD, intellectual disability, bipolar disorder, genomics, copy number variants

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The neurodevelopmental hypothesis has been the dominant framework within which research on schizophrenia has been conducted since the influential papers of Weinberger[1] and Murray and Lewis[2] thirty years ago.

The crucial conceptual advance was the proposal that the emergence of schizophrenia in adolescence or early adulthood could be explained by the interaction between an early "lesion" to the developing brain, arising from genetic and environmental factors, and normal developmental processes. According to this view, as the brain develops and takes on new and more complex functions, the impact of early neurodevelopmental pathology can become apparent.

The idea that schizophrenia might have its origins in disturbances of early neurodevelopment was not new, and both Kraepelin and Bleuler were aware that the developmental histories of those with schizophrenia could be abnormal[3]. However, the neurodevelopmental hypothesis brought together findings implicating early environmental exposures, such as obstetric injury, with those from clinical and basic neuroscience implicating cognitive impairment and cortical dysfunction, and evidence for "premorbid" developmental deviance. Crucially, it provided a framework to explain how early developmental abnormalities might be manifest as psychosis in late adolescence and early adulthood when schizophrenia typically presents, and explained the failure to identify neurodegenerative, traumatic or neurotoxic mechanisms in *post mortem* studies[1].

THE NEURODEVELOPMENTAL CONTINUUM

While the neurodevelopmental hypothesis has been hugely influential within the confines of schizophrenia research, its broader implications for nosology, diagnosis, management, research and prevention remain largely overlooked[4].

Despite general acceptance that schizophrenia has a substantial neurodevelopmental basis, the disorder remains widely regarded as being distinct nosologically, and by implication pathophysiologically and clinically, from syndromes such as autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD) and intellectual disability, which typically present in childhood and are grouped together as "neurodevelopmental disorders"[5].

This separation overlooks several key observations[4,6-9]. First, there are many clinical and other phenotypic similarities between schizophrenia and childhood neurodevelopmental syndromes[7,9]. These have tended to be overlooked because of the prominence given to psychotic symptoms in schizophrenia by researchers and clinicians. This focus on symptoms that typically present after childhood has drawn attention from the fact that schizophrenia shares with childhood neurodevelopmental disorders impairments of cognition, which are often present before psychotic breakdown, a greater frequency in males, and associations with varying degrees of developmental delay, neurological soft signs and motor abnormalities. Second, there are no clear diagnostic boundaries between these

disorders, and there is a significant comorbidity between them that is obscured by the use of diagnostic hierarchies or exclusions, developmental change in predominant symptom type, and service configurations[4]. Third, a number of environmental risk factors, particularly those impacting on early brain development, are shared across these disorders[4,9]. Finally, and most tellingly, evidence began to emerge about ten years ago, particularly from studies of rare copy number variants, that childhood neurodevelopmental disorders such as intellectual disability, autism spectrum disorders and ADHD share specific genetic risk alleles with each other and with schizophrenia[4,6].

Consideration of these issues led us to reappraise the neurodevelopmental hypothesis of schizophrenia and propose a new model, the neurodevelopmental continuum[4,6], in which neurodevelopmental disorders, including schizophrenia, are seen as representing the diverse range of outcomes that follow from disrupted or deviant brain development. This model was based on the emerging evidence for shared genetic and environmental risk factors and predicts that there are also likely to be overlapping pathogenic mechanisms.

Thus, childhood neurodevelopmental disorders (such as intellectual disability, autism spectrum disorders and ADHD) and adult psychiatric disorders (including both schizophrenia and bipolar disorder), rather than being etiologically discrete entities, could better be conceptualized as lying on an etiological and neurodevelopmental continuum or spectrum, with the major clinical syndromes reflecting the severity, timing and predominant pattern of abnormal brain development and resulting functional abnormalities, as well as the modifying effects of other genetic and environmental factors[4,6].

This approach accepts that current diagnostic systems have some utility in defining groups of cases that are more closely related than by chance, but it regards current categorical diagnoses as arbitrary divisions of what is essentially a continuous etiological, pathogenic, developmental and clinical landscape. The implications of this for research and practice are substantial[4,8].

The notion of a spectrum or continuum in childhood neurodevelopmental disorders was not a new one[10,11], but we expanded this further across the hitherto deep nosological divide between childhood neurodevelopmental disorders and psychiatric disorders that present in adulthood, such as schizophrenia and bipolar disorder. Subsequently, others have made a similar suggestion[12].

THE NEURODEVELOPMENTAL GRADIENT

We have also proposed a more refined, and testable, conceptualization: the neurodevelopmental gradient hypothesis. This suggests that, within the neurodevelopmental continuum, severe mental illnesses occupy a gradient of decreasing neurodevelopmental impairment as follows: intellectual disability, autism spectrum disorders, ADHD, schizophrenia and bipolar disorder[4,6,8]. The severity of neurodevelopmental impairment is indexed by a number of features. These include typical age at onset (congenital for intellectual disability, early childhood for autism spectrum disorders, adolescence for schizophrenia) as well as the severity of associated cognitive impairment and the persistence of functional impairment (see Figure 1).

Like all models, that of a neurodevelopmental gradient is certainly an oversimplification. Neurodevelopmental disorders clearly differ along a number of additional clinical dimensions, and presumably there are mechanistic differences as well, but it posits that the degree of neurodevelopmental impairment is currently the most recognizable of these features. It makes clear predictions about the relative importance across the neurodevelopmental spectrum of the most damaging classes of rare mutations, such as large copy number variants and rare coding variants. It also makes predictions about the relative extent of brain dysfunction (number of structures and circuits affected) in the various clinical syndromes and the relationships and likely similarities between disorders according to their relative position on the gradient.

In recent years, there has been increasing evidence from family studies for shared, as well as independent, genetic risk between different adult psychiatric disorders, and between adult disorders and childhood neurodevelopmental disorders[7,13-16]. There has also been an accumulation of evidence that schizophrenia shares environmental risk factors with childhood neurodevelopmental disorders, particularly those likely to index early neurodevelopmental impairment[17-21]. At the same time, there has been a profusion of large, increasingly well-powered genomic studies of childhood neurodevelopmental disorders, particularly autism spectrum disorders and intellectual disability, and of adult psychiatric disorders, in particular schizophrenia.

In contrast to the environmental exposures, which generally are risk indicators rather than factors known to be causal, the identification of large numbers of specific risk DNA changes offers a direct and robust test of the predictions of the continuum model and gradient hypothesis, and for this reason it is considered in detail in this paper.

GENETICS OF SCHIZOPHRENIA

Genetic risk for schizophrenia is conferred by both rare and common alleles distributed across the genome[22]. The largest published analysis of genome-wide association study data (up to 36,989 cases and 113,075 controls including replication data) identified a total of 108 conservatively defined loci that contain common risk alleles, and which met genome-wide significance[23].

These robustly implicated loci access only a small fraction of the total number of common alleles involved in conferring risk to schizophrenia, and studies of the *en masse* effects of common variants have suggested that between a half to a third of the genetic risk of schizophrenia is indexed by common

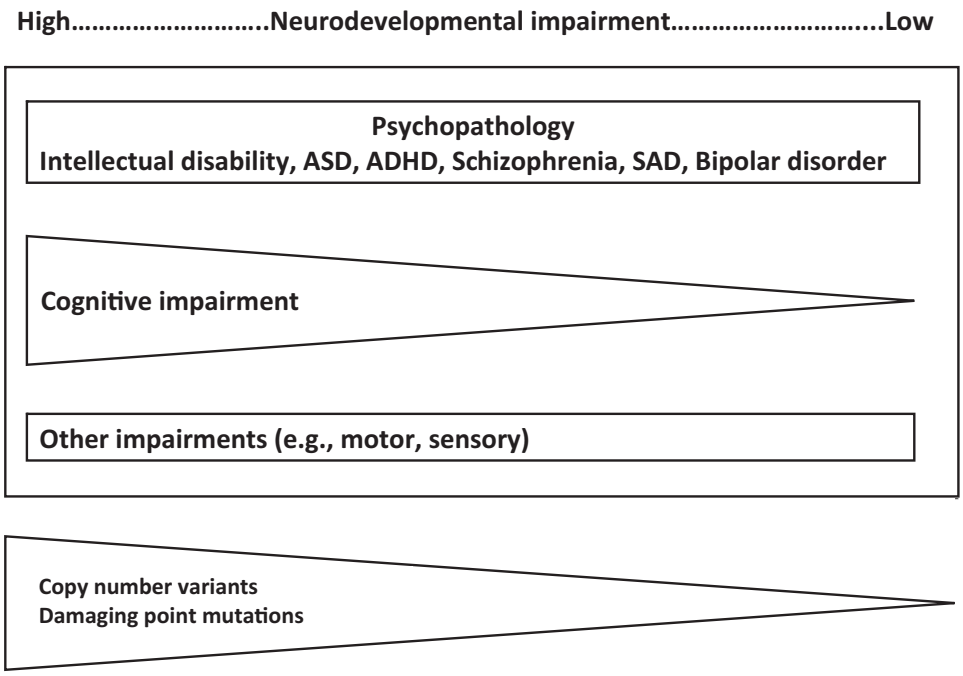

Figure 1 The neurodevelopmental continuum. This shows the different domains of outcome of neurodevelopmental impairment. It also shows the hypothesized relationship between the severity of neurodevelopmental impairment and psychiatric syndromes and degree of associated cognitive impairment. The relative impact of copy number variants and damaging point mutations is also shown. ASD – autism spectrum disorders, ADHD – attention-deficit/hyperactivity disorder, SAD – schizoaffective disorder

alleles genotyped by current genome-wide association study arrays[24,25]. Recent estimates suggest that there may be many thousands of common risk alleles for schizophrenia, with 71-100% of 1 Mb regions containing a schizophrenia locus[26].

In addition to common alleles, each of which confers only a small increase in individual risk (odds ratio, OR < 1.2), a relatively small number of copy number variants are associated with substantial increases in individual risk, with ORs of 1.5 to >50[27,28]. A recent meta-analysis of previously implicated candidate copy number variants robustly identified eleven specific variants as schizophrenia risk factors[28]. These schizophrenia-associated copy number variants are extremely rare, being found in 1 in 200 to 1 in several thousand people with the disorder, and have required large sample sizes to confidently implicate them[28].

The genome-wide burden of >500kb copy number variants has been shown to be significantly increased in schizophrenia compared with controls even after excluding known risk loci[29], suggesting the existence of further schizophrenia risk variants. More recently, a genome-wide investigation applying a centralized analysis pipeline to a schizophrenia cohort of 21,094 cases and 20,227 controls[30] reported a global enrichment of copy number variants burden in cases, which persisted after excluding loci implicated in previous studies. Genome-wide significant evidence was obtained for eight loci, and suggestive support was found for eight additional candidate susceptibility and protective loci.

Most of the specific copy number variants definitively associated with schizophrenia impact on multiple genes. The exception to this is deletions of NRXN1[28,31], the gene that encodes the presynaptic cell adhesion protein neurexin1. In order to infer the biological mechanism(s) through which multigenic copy number variants contribute to disease, researchers have sought to determine whether the genes impacted by schizophrenia-related variants are enriched for functionally related sets of genes. This is often termed pathway analysis. Studies using this approach have yielded remarkably consistent findings. Schizophrenia-related variants are enriched for synaptic genes[30,32-36], and particularly those encoding members of N-methyl-D-aspartate receptor and neuronal activity regulated cytoskeleton-associated protein complexes, both of which are known to be important for glutamatergic signaling and synaptic plasticity[30,34,36]. A recent large case-control study showed that case copy number variants are also enriched for genes involved in GABAergic neurotransmission[36].

Finally, recent large-scale work using new generation sequencing approaches, predominantly exome sequencing to date, has shown that rare coding variants that change the DNA sequence at one or a few nucleotides are enriched in specific gene pathways, particularly those involved in synaptic function, including many of those implicated in studies of copy number variants[37-39], and that ultra-rare, gene-disruptive and putatively protein damaging variants are more abundant in schizophrenia than among controls[39]. Finally, loss-of-function rare coding variants in a gene that encodes the histone methyltransferase SETD1A have been shown to be associated with schizophrenia[40]. This is the first gene to be implicated in

schizophrenia by exome sequencing at Bonferroni corrected genome-wide levels of statistical significance and, when combined with previous common variant evidence[41], points to chromatin remodelling, specifically histone H3K4 methylation, as an important mechanism in the pathogenesis of schizophrenia.

COMPARATIVE GENETIC ARCHITECTURE OF SCHIZOPHRENIA AND OTHER NEURODEVELOPMENTAL DISORDERS

Copy number variants

A major impetus for the continuum model and gradient hypothesis came from the observation that specific rare copy number variants that are significantly associated with schizophrenia are also associated with a range of other neurodevelopmental disorders, such as autism spectrum disorders, ADHD and intellectual disability[31,42,43].

Although there have been no unbiased population studies conducted to date, it is apparent that the severity of the neurodevelopmental outcome associated with such copy number variants is highly variable, with phenotypes ranging from mild cognitive impairment in some individuals[44,45] through to schizophrenia, autism, ADHD or intellectual disability in others[42,46]. Moreover, the evidence suggests that this reflects true pleiotropy rather than heterogeneity resulting from the multigenic nature of most copy number variants[47].

Support for the neurodevelopmental gradient hypothesis has come from a number of observations. First, Girirajan et al[48] showed that, in children, the burden of large copy number variants is positively correlated with the severity of childhood neurodevelopmental disorders, being greater in intellectual disability than in autism spectrum disorders, and greater in autism spectrum disorders with intellectual disability than in those without. Second, Kirov et al[46] found that the burden of large rare copy number variants implicated in neurodevelopmental disorders is greater in cases with developmental delay, autism or congenital malformations than in schizophrenia. For most variants, penetrance for the early onset developmental disorders was greater than for schizophrenia; importantly, this was not only true for variants robustly identified first in the childhood disorders, but also for variants identified initially in schizophrenia, thus minimizing bias.

Furthermore, studies of patients with autism spectrum disorders, intellectual disability and congenital neurodevelopmental disorders referred to clinical genetics clinics for chromosomal microarray analysis have highlighted ninety loci enriched for copy number variants in these disorders, albeit not all are definitively implicated. Emphasizing the overlap between these disorders and schizophrenia, every schizophrenia-associated variant is in this set of ninety childhood neurodevelopmental disorder copy number variants. Moreover, in a recent study of over 20,000 cases of schizophrenia, even after excluding known schizophrenia loci, copy number variations associated with intellectual disability were *en masse* significantly enriched in patients in schizophrenia[49], supporting the view that many additional intellectual disability-related variants also confer risk to schizophrenia, but at reduced penetrance.

The evidence suggests that large copy number variants are less strongly associated with bipolar disorder than schizophrenia[50] and, where direct comparisons have been made, large rare variants were indeed found to be significantly less common in bipolar disorder than schizophrenia[51-54]. These findings do not exclude the involvement of copy number variants at specific loci in susceptibility to bipolar disorder[53]: actually, there is strong evidence that duplications of 16p11.2 that are associated with schizophrenia are also associated with bipolar disorder[53]. However, it is now clear that relatively large copy number variants contributing to childhood neurodevelopmental disorders, and to impaired cognition in non-clinical populations, contribute less to susceptibility for bipolar disorder than they do for schizophrenia. This is in keeping with the generally higher level of cognitive function and less persistent impairment seen in bipolar disorder, and supports the view that this disorder lies between schizophrenia and controls on the neurodevelopmental gradient (see Figure 1).

The neurodevelopmental gradient hypothesis further predicts that, among bipolar cases, those with cognitive impairments or earlier onsets would show a higher burden of large copy number variants. There is already some evidence, albeit not definitive, to support this[55,56].

Neurodevelopmental disorders, including schizophrenia, are associated with reduced fecundity[57]. Mutations that confer very high risk for those disorders should, therefore, be rare in the population due to strong negative selection, and the frequency in the population should, hypothetically, be a function of that selection pressure versus the rate of replacement by *de novo* mutation. Such a postulated relationship between selection pressure and *de novo* mutation rate has recently been empirically demonstrated for neurodevelopmental disorder-associated copy number variants[46]. Assuming neurodevelopmental impairment to be a major driver of loss of fecundity, this leads to the prediction that the relative contribution of *de novo* mutations to different neurodevelopmental disorders should correlate with their position on the proposed neurodevelopmental gradient.

Unfortunately, precise comparisons of the *de novo* mutation rate between diagnoses are difficult, because there have been no direct tests based on identical arrays, mutation size cut-offs, and epidemiologically ascertained samples fully representative of each diagnosis. However, the findings to date are broadly in line with the predictions of the neurodevelopmental gradient hypothesis. For example, it has been reported[58] that the frequency of large (>100kb) *de novo* mutations in bipolar disorder (2.2%) is intermediate between schizophrenia (4.3%) and controls (1.5%). A recent large study of autism[59] found a *de novo* mutation rate of 5.2% in cases and 1.6% in unaffected siblings. Finally, a recent large study of intellectual disability reported a *de novo* rate of 11.5% for rare mutations[60].

Rare coding variants

As we have seen, specific mutations conferring high individual risk to neurodevelopmental disorders are likely to be rare, and large samples will be required to implicate them in case-control studies. However, as is the case for copy number variants, in people with neurodevelopmental disorders, very high risk rare coding variants are likely to be enriched among mutations occurring *de novo*.

A higher than expected burden of mutations predicted to be functionally deleterious, loss of function and missense *de novo* mutations predicted by algorithms to be damaging, is clearly seen in intellectual disability and autism spectrum disorders[40,59,61]. The *de novo* burden in schizophrenia is much less pronounced, but it is nevertheless clearly present with respect to loss of function mutations[40], especially in genes that are highly constrained by natural selection and in which loss of function mutations are more likely to be damaging[62]. When the relative enrichment of *de novo* mutations is compared across disorders, the rates are higher in intellectual disability than autism spectrum disorders, and higher in autism spectrum disorders than schizophrenia[37,40,61,62], in line with the predictions of the gradient hypothesis.

Moreover, there is evidence that schizophrenia patients with intellectual disability have a greater enrichment of rare damaging variants in highly constrained genes and developmental disorder genes, but that a weaker but significant enrichment exists throughout the larger schizophrenia population[62]. Also, even amongst those with schizophrenia who do not have intellectual disability, the rate of *de novo* loss of function mutations is higher in those with poorer educational attainment[37]. These findings are consistent with those in autism spectrum disorders, in which the burden of *de novo* mutations is positively correlated with the degree of cognitive impairment[63].

We can also explore whether the same genes, or sets of functionally related genes, tend to be implicated across neurodevelopmental disorders, and this would appear to be the case. Genes affected by loss of functioning *de novo* mutations in schizophrenia are enriched for those affected by this same class of mutation in people with autism spectrum disorders and intellectual disability[37]. Genes and mutation sites were most highly conserved in intellectual disability, then autism spectrum disorders, with those in schizophrenia least conserved. When loss of function mutations in highly constrained genes are considered, a similar pattern is seen, with enrichment in schizophrenia concentrated in known autism spectrum disorder and intellectual disability genes[62]. At an even finer level of resolution, the same loss of function mutation in SETD1A gene that contributes high risk for schizophrenia also does so for severe intellectual disability and developmental delay[40].

Finally, there is also evidence that the burden of rare variation found in schizophrenia, autism and intellectual disability is concentrated in functionally related sets of genes, particularly those involved in synaptic function and histone remodelling and other neurodevelopmental gene sets[37,62,64,65]. These findings all converge on the conclusion that at least some of the risk to schizophrenia conferred by rare mutations of large effect is shared with childhood neurodevelopmental disorders and impacts on synaptic development and function. They also support the prediction of the neurodevelopmental gradient hypothesis that the burden of such mutations is greatest in intellectual disability, then in autism spectrum disorders and then in schizophrenia.

Bipolar disorder has been much less extensively studied by exome sequencing. Consistent with the picture that is more clearly emerging from studies of intellectual disability, autism spectrum disorders and schizophrenia, one small study found an excess of *de novo* loss of function and protein altering variants in mutation intolerant genes, and an association with early onset[66], while a second study found that damaging variants were enriched for genes previously found to contain *de novo* mutations in autism and schizophrenia[67].

Common variants

The evidence for shared genetic risk across psychiatric disorders arising from common alleles detected by genome-wide association studies is strong. This was first demonstrated by the International Schizophrenia Consortium[24] using a polygenic risk score approach. A highly robust evidence for genetic overlap between schizophrenia and bipolar disorder was found. Subsequent work has shown that common alleles that confer risk for schizophrenia also do so for major depressive disorder and to a lesser extent autism spectrum disorders, ADHD, anorexia nervosa and obsessive-compulsive disorder[47,68].

A note of caution should be sounded here, in that the sample sizes subjected to genome-wide association studies for a number of these disorders, including autism spectrum disorders and ADHD, are relatively small compared to those studied in schizophrenia, and the estimates of shared risk may well change as larger samples are studied[69].

At the level of individual loci, there is evidence that those implicated in schizophrenia genome-wide association studies are enriched for genes in which *de novo* non-synonymous mutations have been observed in schizophrenia, autism spectrum disorders and intellectual disability, pointing to shared biological mechanisms across the common and rare variant signals and between disorders[23]. There is also emerging evidence that some of the genes and gene pathways implicated by common variants overlap with those enriched for rare variants in autism spectrum disorders and intellectual disability[70].

That there is at least a partial convergence of the common and rare variant signals is also supported by the observation that carriers of pathogenic copy number variants who develop schizophrenia have a higher load of common risk variants than carriers who do not[71], suggesting that the outcome of rare variants is to some extent determined by the complement of common risk alleles present in the carrier and supporting the liability threshold model of schizophrenia.

A number of studies have used a polygenic risk score or similar approaches to show overlap in common genetic variation between schizophrenia and developmental outcomes in the general population, and have shown that alleles which increase risk for schizophrenia also associate with, for example, poorer cognitive function and impaired social and communication difficulties, similar to those seen in people with autism spectrum disorders[72-74]. While the overlaps are not large, neither are they trivial (genetic correlations between 0.18 and 0.37) and support the involvement of alleles that increase risk for schizophrenia in a wider set of developmental traits.

PLEIOTROPY, PSYCHOPATHOLOGY AND COGNITION

We have seen that a large amount of recent genomic data point to shared genetic risk across childhood neurodevelopmental and adult psychiatric disorders. But do the findings allow us to be more specific about the relationship between shared risk and variable outcome? The term "pleiotropy" is used to describe the phenomenon of an individual gene influencing two or more distinct traits[47]. Genetic pleiotropy is said to occur when the altered function of a gene influences multiple traits, whereas allelic pleiotropy, a subtype of genetic pleiotropy, occurs when the same gene variant influences multiple traits. It should also be noted that "pseudo-pleiotropy" can arise as a result of imprecision in gene mapping, whereby two phenotypes are influenced by different genes in close proximity, but it can also arise from poor study design, or associations that are due to chance or publication bias[47].

The evidence in relation to pleiotropy in psychiatric disorders has been reviewed in detail elsewhere[47]. It suggests that, in the majority of instances, the pleiotropy observed between different psychiatric diagnoses and between psychiatric disorders and cognitive impairment is a true allelic pleiotropy rather than a pseudo-pleiotropy[47]. The data from rare variants (copy number variations and rare coding variants) are also largely inconsistent with the view that the findings reflect mediated pleiotropy, in which an allele influences two traits, but its effects on one are secondary to more direct effects on the other[47]. In other words, the findings suggest that intellectual disability, autism spectrum disorders, ADHD and schizophrenia represent direct outcomes of the same rare pathogenic mutations. Moreover, the risk of psychiatric disorders does not appear to be mediated by cognitive impairment, which itself seems to be an additional pleiotropic outcome of the same genetic risk[47].

However, the concept of pleiotropy requires a phenotype to be linked directly to a particular gene or mutation, and this is not an easy test to perform for psychiatric disorders, for a number of reasons. First, these are highly polygenic disorders, and the relationship between risk alleles and specific phenotypic outcomes is complex and combinatorial. One clear example of this is that an individual's burden of common risk alleles can influence psychiatric outcome in copy number variants carriers[71]. Second, despite our use of categorical diagnoses, the boundaries between disorders are not clear-cut, and comorbidity frequently occurs.

While more work is needed, considering all these elements together leads to the conclusion that what we perceive as pleiotropic manifestations of a particular mutation, such as a copy number variant, likely represent the net effects of an individual's polygenic and environmental background on multiple traits representing various domains of brain function[47]. Thus, psychiatric, cognitive and motor phenotypes tend to co-occur in clinical populations because they share underlying etiological and pathogenic mechanisms, but the mix of outcomes in any individual case will reflect that individual's particular genetic complement and environmental history.

CONCLUSIONS AND IMPLICATIONS

Findings from genomic studies have implicated large, rare copy number variants in conferring risk to schizophrenia and shown that the same variants also confer risk to intellectual disability, autism spectrum disorders and ADHD. Similarly, there is emerging evidence that rare coding variants also confer risk of schizophrenia and for overlap between the genes impacted by damaging variants found in schizophrenia and those seen in autism spectrum disorders and intellectual disability.

The enrichment of large, rare copy number variants is highest in intellectual disability, then autism spectrum disorders, then schizophrenia, then bipolar disorder. There is also evidence that the enrichment of damaging rare coding variants is greatest in intellectual disability, then autism spectrum disorders and then schizophrenia, with insufficient data to date for ADHD and bipolar disorder.

The enrichment of rare mutations appears to be correlated with the degree of cognitive impairment both across and within diagnostic groups, but pathogenic copy number variants and rare coding variants are found in autism spectrum disorders and schizophrenia in the absence of gross cognitive impairment, and pathogenic copy number variants are present in individuals with subtle impairments of cognition but who do not have a psychiatric diagnosis.

There is also evidence for shared common allele genetic risk across schizophrenia and other neurodevelopmental disorders, and evidence that this overlaps with the genes and pathways implicated by rare variant studies. Indeed, the fact that, regardless of the specific diagnoses, rare *de novo* and damaging rare coding variants tend to implicate broadly similar processes (synaptic plasticity, chromatin modifiers and targets of fragile X mental retardation protein) suggests that individual mutations are likely to influence the same pathogenic mechanisms across disorders.

These findings not only support the view that schizophrenia is a disorder whose origins lie in disturbances of brain development, but also that it shares genetic risk and pathogenic mechanisms with the early onset neurodevelopmental disorders (intellectual disability, autism spectrum disorders and ADHD). They also support the view that these disorders lie on a gradient of severity, implying that they differ to some extent quantitatively as well as qualitatively.

There are a number of important implications of these findings for nosology, research and clinical practice. First, they suggest that we should widen the nosological concept of neurodevelopmental disorders to include the functional psychoses. Further work will be required to establish the extent to which genomic data support the inclusion of bipolar disorder and ADHD as well as other neurodevelopmental disorders, such as dyslexia and coordination disorder, not discussed in this paper. But there is compelling genomic evidence for the existence of a group of neurodevelopmental disorders that includes what are generally considered to be adult onset disorders and that is associated with pleiotropic effects on cognitive impairment. The pleiotropic nature of the relationship between psychopathology and cognition predicts that the severity of cognitive impairment in individuals with psychopathology who meet diagnostic criteria for one of these disorders will be variable and sometimes subtle and may possibly only be detected by comparison with parental cognitive function[12,75].

As far as research is concerned, the neurodevelopmental continuum underscores the need for new and flexible approaches to patient stratification[8,76]. First, it suggests that such approaches, rather than being categorical, will need to be multidimensional, accessing multiple different domains of brain function. Second, it indicates that etiological and mechanistic research should not be constrained by current diagnostic or age-related silos. In particular, there needs to be much greater communication and integration between the communities researching childhood neurodevelopmental disorders such as ADHD and autism spectrum disorders and those studying adult psychiatric disorders such as schizophrenia and bipolar disorder. Third, the pleiotropic effects of genetic risk factors have clear implications for mechanistic research using endophenotypes in human studies or animal models: researchers should be cautious when attempting to chart causal pathways that mediate the effects of genetic risk on clinical phenotypes[8,47].

Fourth, the range of outcomes of rare mutations such as copy number variants and some rare coding variants suggests that the brain is to some extent able to compensate for the disruptive effects of such mutations, and this, together with the identification of protective mutations[30,77], suggests that some of the biology may be tractable. A focus on what factors influence outcome in specific mutation carriers might be a fruitful area for future research[71]. Indeed, it is possible that a component of the common variant signal in schizophrenia detected by polygenic risk score and similar approaches relates to mechanisms that mitigate the consequences of neurodevelopmental disruption by damaging mutations or early environmental exposures.

Finally, the findings reviewed above have implications for understanding the potential role of psychosocial risk factors, a number of which have been implicated in schizophrenia[9]. One possibility is that the presence of pre-existing neurodevelopmental impairment increases susceptibility to these risk factors. Another is that there is a degree of etiological heterogeneity, and that both psychosocial and neurodevelopmental risk factors can result in similar syndromic outcomes. However, it is also possible that associations with psychosocial risk factors reflect confounding, pleiotropy or reverse causation rather than true causation, and we must await the application of study designs that allow these possibilities to be distinguished[9].

There are also implications of the neurodevelopmental continuum for clinical practice. There should be a high expectation of comorbidity, and greater emphasis on developmental history and on multi-domain assessment (psychopathological, cognitive, sensorimotor). Clinicians should increasingly take a developmental life-course approach ensuring that patients are effectively managed across the transition from childhood to adulthood, and developmental change over time should be expected and anticipated. The various agencies that currently assess and manage childhood neurodevelopmental and adult psychiatric disorders will need to build up shared language, classification and methods of assessment.

It will be challenging to treat underlying neurodevelopmental mechanisms, and therapeutic approaches, at least in the short and medium term, might need to focus upon symptomatic management of the particular domains (psychopathological, cognitive, sensorimotor) affected in an individual. For the medium and long term, recent genomic findings offer many opportunities for mechanistic research[78]. Moreover, there is evidence from genomics for tractable biology, and the high degree of pleiotropy suggests that therapeutic approaches might be successful across current diagnostic boundaries[47].

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Staging in bipolar disorder: from theoretical framework to clinical utility

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Illness staging is widely utilized in several medical disciplines to help predict course or prognosis, and optimize treatment. Staging models in psychiatry in general, and bipolar disorder in particular, depend on the premise that psychopathology moves along a predictable path: an at-risk or latency stage, a prodrome progressing to a first clinical threshold episode, and one or more recurrences with the potential to revert or progress to late or end-stage manifestations. The utility and validity of a staging model for bipolar disorder depend on its linking to clinical outcome, treatment response and neurobiological measures. These include progressive biochemical, neuroimaging and cognitive changes, and potentially stage-specific differences in response to pharmacological and psychosocial treatments. Mechanistically, staging models imply the presence of an active disease process that, if not remediated, can lead to neuroprogression, a more malignant disease course and functional deterioration. Biological elements thought to be operative in bipolar disorder include a genetic diathesis, physical and psychic trauma, epigenetic changes, altered neurogenesis and apoptosis, mitochondrial dysfunction, inflammation, and oxidative stress. Many available agents, such as lithium, have effects on these targets. Staging models also suggest the utility of stage-specific treatment approaches that may not only target symptom reduction, but also impede illness neuroprogression. These treatment approaches range from prevention for at-risk individuals, to early intervention strategies for prodromal and newly diagnosed individuals, complex combination therapy for rapidly recurrent illness, and palliative-type approaches for those at chronic, late stages of illness. There is hope that prompt initiation of potentially disease modifying therapies may preclude or attenuate the cognitive and structural changes seen in the later stages of bipolar disorder. The aims of this paper are to: a) explore the current level of evidence supporting the descriptive staging of the syndromal pattern of bipolar disorder; b) describe preliminary attempts at validation; c) make recommendations for the direction of further studies; and d) provide a distillation of the potential clinical implications of staging in bipolar disorder within a broader transdiagnostic framework.

Key words: Bipolar disorder, clinical staging, early intervention, neuroprogression, neuroprotection, cognitive functioning, biological markers, kindling, treatment outcome, lithium, transdiagnostic framework

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Clinical staging models are extensively used in medicine, especially in oncology and cardiology, where they are major determinants of prognosis and drivers of treatment choice. The utility of staging in these specialties is aided by clear biomarkers of the staging process. In cancer, for example, the "tumour, node, metastasis" (TNM) model of disease staging uses three easily operationalized and objective domains.

In contrast, psychiatry, lacking objective markers, has not been able to empirically define the critical components of stage definitions. The field has tentatively begun to use staging models as a template to model the sequence of vulnerability, at-risk states, prodrome, onset, progression, and end-stage chronicity, and to link these to outcome and choice of specific treatments.

The body of data on this topic in bipolar disorder and other mental illnesses is steadily increasing[1,2], allowing closer examination of the evidence supporting or refuting the theoretical underpinnings of the construct, and refining its applicability to targeted and individualized diagnostic, prognostic and therapeutic domains.

The first hint supporting clinical staging in psychiatry came from Kraepelin[3], whose detailed observations of the course of mental disorders over time suggested that this might be a useful validator of diagnostic assignment. However, his hard and largely tactical distinction between dementia praecox and manic depressive illness proved to be an oversimplification, and he did not define therapeutically useful stages or patterns of illness.

A century later, Fava and Kellner[4], focusing on mood and anxiety disorders, called staging the "neglected dimension in psychiatric classification", presaging current developments. Staging of mental disorders was formalized and operationalized by McGorry et al[5], who aimed to move beyond diagnostic silos to develop a widely used transdiagnostic model. Staging models have subsequently been adapted to bipolar disorder[6-9], depression[10,11], eating disorders[12], and anxiety disorders such as agoraphobia[13], where they share the same essential elements as the original models[14].

It needs to be emphasized that the early stages of most of these syndromes are non-specific and overlapping, favouring the application of transdiagnostic models of staging[15]. Models which focus on traditional diagnostic categories are largely used to describe the syndromal patterns emerging after a first full-threshold episode.

Whether transdiagnostic or disorder-specific staging models are more appropriate for mental illness has been debated. The relative concentration of specific diagnoses in some family histories and the differences in course and treatment outcomes across disorders support the latter approach, while the lack of specificity of genetic and biomarker findings, the extensive comorbidity between disorders, the similarity in effective treatments, and the symptomatic overlap between several disorders lend support to the former approach[16].

In broad terms, transdiagnostic staging models are probably optimal for the study of the at-risk and prodromal phases as a "trunk", while disorder-specific models can contribute to the understanding of the later phenomenon of syndromally expressed "branches". Individual psychiatric disorders, as currently defined, may not turn out to be discrete entities if and when their pathophysiology is identified, and are likely syndromal patterns only. Furthermore, the link between any syndromal phenotype and the underlying neurobiology remains tenuous[17].

MODELS

Clinical staging describes where an individual's presentation can be placed on a temporal spectrum of disorder progression. Staging models in psychiatry have generally adopted the numerical system that is used in medical staging models, being operationalized to begin with stage 0 (defined as an at-risk or latency stage), followed by stage 1 (defined as a prodrome), stage 2 as a first episode, and stage 3 of single or multiple recurrence, and ending with stage 4 of chronic disease[5].

This model captures the aggregate course and evolution of bipolar disorder (see Figure 1). However, some individuals may have a more severe and deteriorating presentation and course from the outset, while others may have an episodic illness with full inter-episode recovery. Linear stepwise progression through serial phases may not be applicable to the course of illness in all patients.

Moreover, developmental approaches examining the heterogeneity in evolution of bipolar disorder among youth at high familial risk have argued for different phases in the prodrome. Sleep disturbances, anxiety, psychotic symptoms, depression and impairments in cognition may be indicative of substages prior to the onset of classical or mixed/psychotic mania[18]. Similarly, a definition of stages based on functioning has been developed to attempt to clarify the latter end of the staging spectrum, based on inter-episodic recovery, comorbidity and ability to live independently[19].

These descriptions of clinical stages of bipolar disorder still need operationalization, specification of cut-off points, and consensus on terminology, and would greatly benefit from external validation through biomarkers.

This would ideally follow what has happened for cancer. First came the documentation of the progression from genetic and environmental vulnerability (including double hits) to precancerous histology to malignant lesions (small, localized to larger, more invasive) to metastases (local to distant, single to multiple). Then predictive validity was delineated by linking these descriptive stages of tumour progression to prognosis and outcome (1 and 5 years survival rates). Discriminant validity subsequently emerged from linking stages to the effectiveness or not of different treatments and to the correspondence

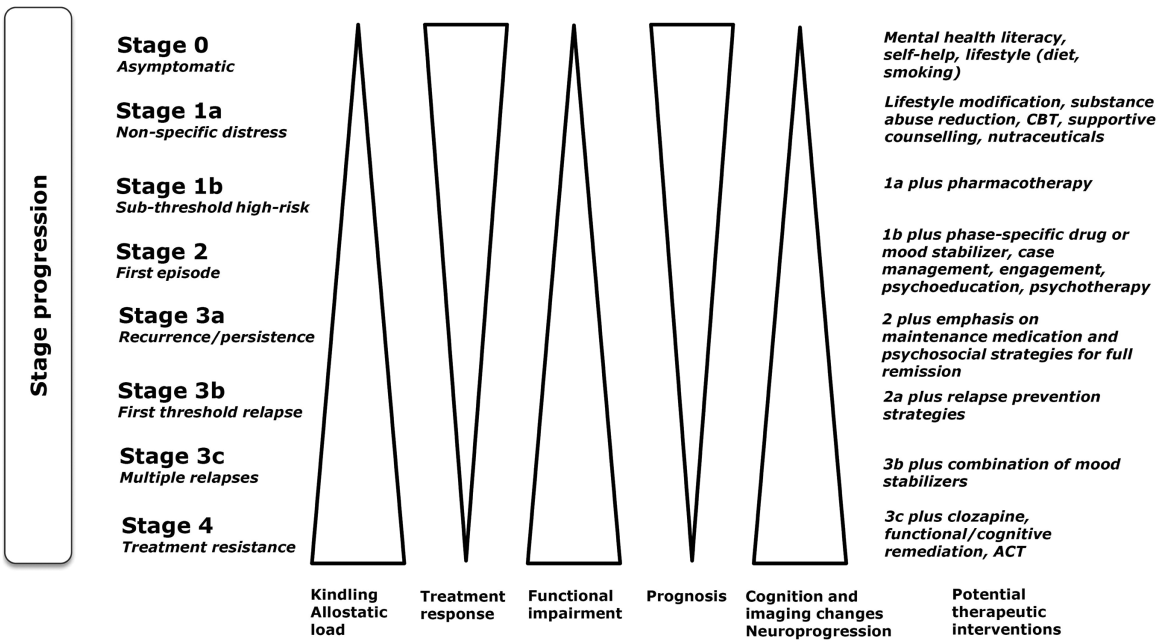

Figure 1 Staging in bipolar disorder. CBT – cognitive behaviour therapy, ACT – assertive community treatment

of numbers and sequences of somatic mutations (those driving cell replication and those reflecting loss of tumour suppressor factors) and other biological measures.

The attainment of many of the aforementioned steps in cancer is an aspiration for mental disorders[20]. This would permit relating descriptive stages to prognosis and ultimately to variables like survival (loss of years of life expectancy). The best validation would come from linking stages to neurobiological alterations and effectiveness (or not) of specific treatments. The task ahead is therefore to cluster clinically observable phenomena and label them as identifiable stages, and then proceed with demonstrating reliability, validity and clinical utility[21].

This model lends itself to further detailing and subdividing. For example, stage 0 could contain more refined characterization of risk based on genetic/familial loading; prenatal factors such as maternal infection or drug exposure; and perinatal factors such as infection, head trauma, neglect and psychosocial abuse. As vulnerability genes such as calcium voltage-gated channel subunit alpha1 C (CACNA1C) and others are better defined and validated, these could be incorporated into this stage.

TESTABLE HYPOTHESES

The model of staging begs the testable hypothesis that the natural history of the disorder progresses through an aggregate and stepwise temporal progression. If staging is to be clinically useful, it needs to demonstrate the same kinds of utility seen in medicine, particularly oncology and cardiology (i.e., to have clinical validity). It needs to be documented that treatments can be identified which have differential value across illness stages. Established examples in schizophrenia include the appropriate use of clozapine for the later stages of treatment, while atypical antipsychotics with a lower adverse event burden are used to treat acute symptoms in early and intermediate stages. Transdiagnostic approaches such as public health interventions, nutraceuticals, Internet-based self-help or indicated prevention could target asymptomatic or at-risk stages[22].

The staging model for bipolar disorder assumes that treatments chosen for earlier stages should have a more favourable risk-benefit ratio than those used for the later stages. Furthermore, treatments suited for clear diagnostic categories, such as antipsychotic and mood stabilizing medications, are less justifiable in the earliest stages of illness, where psychotic symptoms or mood swings are not overtly manifest, and their efficacy has not been systematically assessed[23]. Symptoms of psychological distress may be evident early in the illness course, and preliminary evidence supports intervention with psychotherapeutic strategies such as family-focused treatment for high-risk children with symptoms of depression, cyclothymia, and other specified and unspecified bipolar and related disorders[24]. In these circumstances, low-risk medicines and putative neuroprotective agents[25] may also be more appropriate in term of safety (see Figure 1), but ultimately demonstration of efficacy in these early stages is required[26]. More evidence is needed to determine if prognosis would be more favourable with earlier diagnosis and intervention, as predicted.

FROM NEUROPROGRESSION TO NEUROPROTECTION

The elements of the progressive underlying neuropathology in bipolar disorder appear to include epigenetics, telomere shortening, inflammation, oxidative and nitrosative stress and mitochondrial dysfunction, leading to decreased neurotrophins and consequent deficient neurogenesis and increases in cell shrinkage and apoptosis, ultimately compromising neuronal function and structure. The construct of neuroprogression has been proposed to incorporate the influence of the operative biological elements on the progressive course and outcome of the disorder[27,28]. The impact of neuroprogression may also go some way to explaining treatment non-responsiveness[29].

Social, psychological, environmental, behavioural, biological and genetic variables can be either risk or protective factors that interact in a complex and often unpredictable manner to mediate or moderate the process of disease progression. These factors vary from person to person within a disorder, and also may vary in terms of their impact on different stages. Some risk factors may operate across all stages and some may be stage-specific. For instance, physical or sexual abuse or early attachment disruption may increase risk for the onset phase of a disorder, substance abuse may be noxious across all stages, while adherence and engagement might positively impact by lowering the risk of progression to later stages and improving prognosis[30].

It is theoretically possible to modify an individual's trajectory of disease progression. Early intervention may have potential to alter the distribution of the stages in a given population over time[5,6]. A premise of staging is to define the earliest potential intervention window at any stage of disease evolution in order to prevent progression to the more advanced stages of a disorder and even engage the "reverse gear" towards more benign earlier stages. A person may move from a resistant stage 4 phenotype to a clinically improved and responsive stage 3 pattern. Strategies include primary prevention for those at highest risk, effective intervention in heterotypic and homotypic prodromes (secondary prevention), and attempts at limiting later stages of illness progression (tertiary prevention)[31] (see Figure 1).

The aspiration that appropriate therapy can both prevent neuroprogression and have neuroprotective effects is supported by observational studies indicating that lithium treatment might increase grey matter volume in hippocampus and cortex, increase the length of telomeres, prevent the accumulation of some medical comorbidities, and prevent the progression to

dementia[32-34]. While further evidence is needed, it is plausible that some agents (such as atypical antipsychotics) may avert episodes but may or may not secondarily prevent progression, while others such as lithium not only prevent episodes but might also impede neuroprogression[35].

Prevention of disease progression (i.e., stopping episodes) may differ mechanistically and prognostically from an impact on neuroprogression. As a recent example, lithium and quetiapine were compared in the first year following a first episode of psychotic mania, and lithium but not quetiapine was associated with both decreases in manic and depressive episodes and protection against white matter changes over that time period[36]. Observational data similarly suggest that lithium use may be associated with a greater protective effect on thalamic and grey matter volume than other mood stabilizers[37].

It is noteworthy that medications widely used for bipolar disorder – including lithium, valproate and some antipsychotics – appear to influence inflammation, oxidative biology, neurotrophins, neurogenesis and apoptosis[38]. However, a new generation of medications that may more specifically target these pathways are being investigated, including erythropoietin, minocycline, N-acetylcysteine and anti-inflammatory drugs[39]. Agents more specifically acting on epigenetic mechanisms may also become viable therapeutic options for bipolar disorder, as they have in oncology[40].

THEORETICAL PREMISES UNDERPINNING THE STAGING MODEL

Post et al[11] defined the constructs of sensitization and kindling to capture and describe the progression of bipolar disorder. That model incorporated an increase in primary pathological factors and a failure of endogenous compensatory mechanisms associated with illness progression. Kindled seizure episodes progress from early partial seizures to full blown seizures triggered by stimulation of the amygdala to seizures that occur spontaneously. Here, stage-specific anticonvulsant medications are clearly delineated, with some agents and not others working on the initial stages of seizure development, middle stages of triggered seizures, or late stage spontaneous seizures.

The construct of allostatic load, pioneered by McEwen and Stellar[41], was adapted to bipolar disorder by Kapczinski et al[42]. Allostatic load is the accumulated attempts to re-establish homeostasis after perturbations caused by, for example, stressors and abused substances. The compensatory adaptations required to achieve the new balance are generated at a cost to the organism. More stressors, mood episodes, and bouts of substance use provoke further adaptations, increasing allostatic load. This can generate a potential vicious cycle which can further impact brain circuits required for mood regulation and cognition and amplify vulnerability to recurrent episodes of illness. As an example, cortisol dysregulation could play a role in both the primary pathology and allostatic adaptations, leading to illness progression and cognitive dysfunction[43]. Gut dysbiosis may play a role in these inflammatory processes[44], although evidence for bipolar disorder remains limited[45].

WHAT IS THE EVIDENCE SUPPORTING STAGING?

The evidence supporting the descriptive components of staging in bipolar disorder is initially derived from observational studies of the course and natural history of the illness. Kraepelin was the first to observe that, with each successive episode, periods of euthymia in people with bipolar disorder become shorter[3]. His seminal observations have been repeatedly verified. More recent data derived from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study support the utility of staging, as the number of episodes was positively associated with more severe mania and depression, and poorer functioning and quality of life[46].

Considerable evidence supports the view in psychosis that: a) treatment earlier in the full-blown illness (i.e., after a shorter duration of untreated psychosis) is more effective; b) continuous treatment may be more effective than intermittent treatment; and c) response to an antipsychotic medicine decreases as the number of medication trials increases[47].

Similar evidence exists for lithium in bipolar disorder, as this medication is generally more effective if used earlier in the illness course, and response is poorer in those with multiple prior episodes. A number of observational studies have suggested that the efficacy of lithium declines with successive episodes[48-50]. A similar pattern appears to occur with atypical antipsychotics in the treatment of bipolar disorder, with data for both olanzapine[51] and cariprazine[52]. Lamotrigine is less effective as a function of the number of prior depressive episodes, and so is treatment in general[53].

A cross-sectional examination of differences in medication prescription patterns found that monotherapy was common in stage 1, two drug combinations were common in stage 2, while the later stages were characterized by polypharmacy, with social and occupational functioning inversely correlated with number of medications[54].

The pattern seen in pharmacological studies is also seen in studies of psychological treatments for bipolar disorder. In one of the largest trials of cognitive behaviour therapy (CBT) for this disorder to date, while negative on the primary outcome measure, the therapy was found in post-hoc analyses to be more effective in people who had the fewest prior episodes, but appeared to aggravate outcomes of those who had more than 30 episodes[55]. Similarly, data from psychoeducation studies showed that participants who had the fewest prior episodes had the greatest benefit from the intervention[27,56].

Neuroimaging evidence also supports the staging construct. The available data suggest, although with some inconsistencies, that brain structure is relatively preserved during the early stages of bipolar disorder[57,58]. It appears that progressive

structural changes develop as the disorder evolves[59]. Among a cohort of individuals with a first episode of mania, ventricular size was comparable to controls, while individuals with recurrent illness had ventricular enlargement[60]. Over time, there is also progressive loss of grey matter[61,62] in those who have a recurrence compared with those who remain episode free[58].

Some studies show smaller amygdala and insular volumes among ultra-high risk individuals prior to a threshold first episode of mania, suggesting that these potentially represent vulnerability markers[63]. Some of these differences may be neurodevelopmentally mediated and interact with neuroprogression[64].

A decline in cognition is apparent in bipolar disorder. Cognitive dysfunction is also a major driver of the functional disability seen in the disorder[65] and may correlate to some extent with the structural changes noted above. There is strong evidence that cognitive changes are associated with the number of prior episodes of illness[66,67]. That the number of episodes determines the magnitude of cognitive impairment was confirmed in a prospective cohort study, which showed that those who had a recurrence of a mood episode within a year after a first manic episode continued to show cognitive impairment, while those who remained episode free had significant improvements in cognition, suggesting that early intervention has the potential to reverse cognitive deficits[68].

Further, in a study that compared cognitive functioning among people who had had a first, second and third episode, participants who had a first or second episode showed relatively preserved cognitive functioning compared to controls, but subjects with three or more episodes performed more poorly compared to both controls and early-episode bipolar patients[59]. Another study found that cognition was significantly worse than healthy control groups only for persons with stage 3 (recurrent) or 4 (chronic, late illness) bipolar disorder, while it was not in those in earlier illness stages[69].

A combination of cognitive measures such as verbal intelligence and cognitive control, along with episode density and level of residual depressive symptoms, were the best predictors of classification of persons with bipolar disorder into those with good and poor function[70]. Similarly, a cluster analytical study of a historical cohort identified two subgroups of persons with bipolar disorder categorized as early and late stages based on differences in their functioning, age of onset, number of episodes and time from the onset of their first episode[71].

Overall, the use of such a "reduced" or simplified staging such as "good or poor" outcome or "early or late" stages in bipolar disorder is likely to most easily show relationships with neurobiological markers. However, to be truly useful, more refined definitions of sub-stages may be required to define relationships to neurobiological markers and association with clinical response.

Some biochemical alterations are putative markers of an underlying disease process. For example, measures of inflammation, in particularly cytokines, are among the most robustly established correlates of both depression and mania[72]. The first study of biomarkers and staging found that pro-inflammatory cytokines, notably interleukin 6 (IL-6) and tumour necrosis factor alpha (TNFα), were raised in both early and late stage participants, but the increase of TNFα was more accentuated in the late stage, while that of IL-6 was more marked in the early stage. Anti-inflammatory cytokines such as interleukin 10 (IL-10) were increased in the early stage, with no differences from controls in the late stage. Brain-derived neurotrophic factor (BDNF) levels were normal in the early stage but decreased in the late stage participants[73]. There are further data showing that BDNF and TNFα could be useful peripheral blood biomarkers aiding in the discrimination of the early from the late stage of bipolar disorder with an accuracy of 0.95 and 0.96, respectively[74]. The fact that patients at a later stage have lower levels of IL-6 possibly indicates underlying differences in inflammation or allostatic load[71].

Stage dependent changes in redox markers have been studied, particularly the glutathione pathway, where the activity of glutathione reductase and glutathione transferase appeared increased in late stage participants[75]. A recent study that examined the differences between those at early and later illness stages showed that matrix metallopeptidase 9 and soluble intracellular adhesion molecule (sICAM) levels were significantly different across stages, even when patients were euthymic[76]. While these biomarkers were associated with measures of functioning, cognition and subthreshold symptoms, the gross separation of early and later stages offered a pragmatic first-pass system to categorize participants into meaningful subgroups for biomarker analyses.

Neurotrophins may similarly display stage-related changes, with normal levels found in the early stages of the disorder, and decreases later in the illness course[73,77].

It is unclear whether these stage-related changes in biomarkers – including neurotrophins, oxidative stress and inflammatory measures – reflect the primary progression of the disorder or the failure of adaptive homeostatic mechanisms.

CAVEATS AND LIMITATIONS

The biochemical, cognitive and structural markers highlighted in the previous section do not have replicated sensitivity and specificity, which limits their clinical utility. The operationalization of staging, therefore, remains a challenge.

The staging model is at this point heuristic, and remains an exploratory framework. In contrast to staging in medical illnesses, where anatomic extent and impact of the disease determine stage, staging models in psychiatry remain largely based on a course-based definition of illness, using number of episodes and relapse criteria in defining stages[8]. A clear limitation of a course-based approach is that some individuals can have a benign course of illness with excellent inter-episode functioning despite multiple episodes, while others have a

seemingly malignant course from the outset[78]. Any staging model needs to account for the between-individual as well as the within-individual variability over time in people with bipolar disorder. Staging, therefore, is an aggregate construct.

The difficulties in defining boundaries between hypomania and mania, and between mood episodes in general, have been described as representing a challenge to the staging model[79,80], but could potentially be overcome with precise definitions and criteria. Furthermore, the question whether persons with hypomania and depression of varying severity fit into stages 1b or 2 needs further clarification.

Research exploring the staging model has been so far largely cross-sectional, while longitudinal prospective cohort studies are necessary. The moderating effects of personality and temperament, environmental influences such as societal networks and supports, and occupational and environmental resources, have not been adequately explored.

Furthermore, comorbid physical and psychiatric diseases are not currently incorporated in staging models, although they are drivers of outcome and an almost universal feature of most mental disorders. More detailed sub-staging of illness evolution could include the presence or absence of prominent comorbidities such as anxiety and substance abuse, psychosis and other phenotypes. Not only will this be appropriate to refine the relationship to neurobiological markers, but the descriptors of effective therapeutic strategies in those with and without these comorbidities remains to be better defined and is clearly an unmet need for the field.

IMPLICATIONS AND DIRECTIONS

There are a number of implications of the staging model. The presence of a demonstrable process of disease progression moving along a definable temporal trajectory suggests the presence of targets that could be amenable to intervention and a focus for health services and providers. The progressive evolution of clinical phenotypes implies that the best opportunity for effective treatment may be the earliest. The staging model therefore logically segues to that of early intervention and hence a transdiagnostic approach.

Intervention is theoretically possible at a public health level focusing on the general population through strategies operating on identified risks, as with smoking for heart disease and cancer prevention. For bipolar disorder, lifestyle, diet, exercise and well-being interventions, including meditation and mindfulness, could be employed at a public health level, taking into consideration that these would be of value across emerging clinical phenotypes and other non-communicable medical disorders[81]. Indicated prevention targeted to people identified as being at high risk is feasible, as is targeting the "at-risk" or ultra-high risk stage[82,83].

Some heterotypic prodromes are by definition non-specific, with inattention symptoms, substance use, mood lability, anxiety, depression, sleep symptoms and non-specific behavioural change documented[84-86], and these may require different interventions. Once a homotypic prodrome or syndrome occurs, with manic-like symptoms, especially when accompanied by added risk factors such as family history loading and psychosocial adversity in childhood, one is at extremely high risk for evolution to full-blown illness and other specified and unspecified bipolar and related disorders[87-89]. The morbidity and dysfunction accompanying other specified and unspecified bipolar and related disorders is considerable, and clearly deserves concerted therapeutic efforts.

An essential first step in preventing the progression of the disorder, therefore, is accurate and timely diagnosis. The diagnosis of bipolar disorder is complex, and the disorder is often initially misdiagnosed, since the diagnosis is predicated on the presence of mania, yet the index presentation is more commonly depression. Mania, and even more so hypomania, can be missed, as it is often not associated with subjective distress and easily misinterpreted or misattributed, for example, to substance abuse. Full-blown mania can present with psychosis and be difficult to distinguish from schizophrenia. The affective storm and extreme mood lability of borderline personality disorder is a frequent diagnostic confounder[90]. Another set of confounders accompany childhood onset bipolar disorder, a diagnosis which appears more common in the US than in many other countries, where the disorder is rarely seen before late adolescence or early adulthood[91]. The delay to first treatment is inversely associated with an earlier age of onset of bipolar disorder, and both early onset and treatment delay are independent predictors of a poor outcome in adult-hood.

There are very few clinical trials that use staging to stratify recruits. Conus et al[92] compared chlorpromazine and olanzapine in a first-episode mania cohort. They found that there was a shorter time to stabilization with the atypical agent, an interesting finding given that the extant literature generally shows atypical and typical agents to have broadly similar efficacy in mania[92]. More recently, a first-episode mania cohort stabilized on lithium plus quetiapine was randomized to one-year continuation with either agent alone[93]. Unlike head-to-head studies in non-stage stratified cohorts, where no major differences between these agents were seen[93], lithium was superior to quetiapine on most clinical measures. It remains uncertain whether this superiority of lithium over quetiapine reflects the effects of staging (i.e., treating early after the first episode), primary efficacy differences, or methodological factors. A few other studies have targeted the later stages of the disorder. Murray et al[94], for example, have developed online acceptance and commitment approaches to people with chronic stages of the disorder.

Early intervention promises to prevent or minimize the secondary consequences of recurrent episodes[95]. Kessing et al[96] documented that randomization to two years of comprehensive, expert, special clinic treatment after a first manic hospitalization not only led to fewer relapses than treatment as usual for the first two years, but its effect persisted and was

magnified over the next four years (even though all patients received treatment as usual during those years). This is important evidence that early high-quality intervention can change the trajectory and course of illness for the better in the intermediate term, if not indefinitely. Further, early intervention at first episode has been shown to reverse cognitive deficits and preserve grey matter volumes, especially in those that remain episode free[58,68]. Similar benefits of early intervention programs are documented in first-episode psychosis[97].

With multiple recurrences, relationship, employment and financial difficulties erode self-esteem, corrode supports and coping strategies, and lead to guilt and loss. These are powerful stressors that can further perpetuate and exacerbate the illness[55]. As the disorder typically begins in adolescence or early adulthood, it interrupts critical emotional, educational and psychosocial developmental goals and milestones, again acting as a secondary stressor. The earlier the illness begins, the poorer the outcomes in adulthood are[91].

Early intervention strategies should aim to minimize disruption to normal developmental trajectories. It is likely that multifaceted strategies will be required, ones that integrate effective psychopharmacology with stage-specific and evidence-based psychosocial interventions. New research is beginning to emphasize the value of cognitive remediation and vocational recovery for late stage illness[98]. Given the impact of the disorder on families, and the secondary consequences of family dysfunction, assisting with family and caregiver support is invaluable[99-101].

Staging models can also encourage help-seeking and improve access. A critical avenue is via service reform, especially the creation of early intervention services[102]. They can also provide further impetus to study the efficacy of potential primary and secondary preventive strategies where evidence is so far scant[103]. Education campaigns may help ill persons or those at risk to seek help in earlier stages, and service changes that welcome persons at earlier illness stages may lead more timely delivery of effective interventions.

There is a clear need to study which treatments actually work for the early stages. Delivering care for more persons at an earlier stage may lead to a better resolution for those who would otherwise be "pre-destined" to have an adverse illness course, and an amelioration of the course for those who would go on to develop later stages.

CONCLUSIONS

The staging model is supported by observations that, with some exceptions, the clinical course of untreated or poorly treated bipolar disorder evolves in a complex but progressive fashion. Poorer response to treatment (principally lithium) occurs in the later stages of illness, and preliminary biomarker data (primarily neuroimaging) supports stage-specific brain changes.

A fundamental proposition of the staging model is that early intervention is more effective and needs to be less complex than later intervention. Early intervention implies that optimal use of biological and psychosocial interventions in at-risk, prodromal, and first-episode phases of bipolar disorder could mitigate some of the clinical and neurobiological consequences of the illness. These include markers of neuroprogression such as brain volume loss and cognitive and physical impairment.

It is hoped that some effective therapies for preventing episodes might also be neuroprotective and reduce the physical burden and reduced life expectancy that accompanies bipolar disorder. Defining and validating the staging of bipolar disorder is part of ongoing research efforts to improve management of this all too often destructive illness.

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The third wave of cognitive behavioral therapy and the rise of process-based care

The term cognitive behavioral therapy (CBT) identifies a family of interventions that are widely recognized as the set of psychological treatments with the most extensive empirical support[1]. CBT is not monolithic, however, and it has been through several distinct eras, generations, or waves. The first generation of this tradition was behavior therapy: the application of learning principles to well-evaluated methods designed to change overt behavior. By the late 1970s, behavior therapy had moved into the era of classic CBT: a new generation of methods and concepts focused on the role of maladaptive thinking patterns in emotion and behavior, and the use of methods to detect and change those patterns.

The arrival of a "third wave" of CBT was declared 13 years ago[2]. The claim was that a change was occurring in orienting assumptions within CBT, and that a set of new behavioral and cognitive approaches were emerging based on contextual concepts focused more on the persons' relationship to thought and emotion than on their content. Third wave methods emphasized such issues as mindfulness, emotions, acceptance, the relationship, values, goals, and meta-cognition. New models and intervention approaches included acceptance and commitment therapy, dialectical behavior therapy, mindfulness-based cognitive therapy, functional analytic psychotherapy, meta-cognitive therapy, and several others.

The idea that a "third wave" of CBT had arrived led to significant controversy[3]. The metaphor of a "wave" suggested to some that previous generations of work would be washed away, but that was not the intent and that was not the result. Waves hitting a shore assimilate and include previous waves – but they leave behind a changed shore. It seems to us that we are now in a position to begin to evaluate what will be left behind in a more permanent way from third wave CBT.

There is no doubt that several concepts and methods that have been central to third wave interventions (mindfulness methods; acceptance-based procedures; decentering; cognitive defusion; values; psychological flexibility processes) are now permanently part of the CBT tradition and indeed of evidence-based therapy more generally, in large part because evidence suggests that they are helpful[4]. These newer concepts and methods now largely co-exist side by side with previously established ones, with the dialectic between them serving as a useful spur to theoretical and technological investigation. In some cases, we now know that traditional CBT methods work in part by changing processes that became central after the arrival of third wave methods[5]. Third wave methods have been added to packages that include traditional behavioral and cognitive methods, resulting in useful approaches[6]. Research has begun to identify moderators indicating when older and newer methods work best with different populations[7], suggesting that evidence-based practitioners can serve their clients by knowing methods from all of the CBT generations.

While new concepts and methods are important, in our opinion, there is a more profound set of changes that has been introduced by the third wave. A subtle but important change is that there is now greater recognition of the central importance of philosophical assumptions to methods of intervention and their analysis. Science requires pre-analytic assumptions about the nature of data, truth, and the questions of importance, and some of the differences between the waves and generations of CBT work were philosophical, not empirical. Recognizing this, the Inter-Organizational Task Force on Cognitive and Behavioral Psychology Doctoral Education[8] recently concluded that all CBT training should place more emphasis on philosophy of science training, in the hope of increasing the coherence and progressivity of research programs.

An examination of assumptions leads naturally to a concern for theories, models, and processes. The third wave has been far less focused on protocols for syndromes, and more focused on evidence-based processes linked to evidence-based procedures[8,9]. Increased emphasis on processes of change and their biobehavioral impact has meanwhile been strengthened by Research Domain Criteria[10] and transdiagnostic models, among other trends. A notable result is that there is now much more focus on moderators and mediators of change, and the construction of intervention models that emphasize the role of changeable transdiagnostic processes (i.e., functionally important pathways of change that cut across various diagnostic categories).

In part because of its greater process focus, modern CBT and evidence-based therapy is more open to the investigation of a wider range of approaches from humanistic, existential, analytic, and spiritual traditions. This promises over time to reduce the dominance within intervention science of walled off schools of thought, or trademarked intervention protocols, and to bring different wings of the field together in an evidence-based search for coherent and powerful sets of change processes.

As a purely syndromal focus weakens and a process focus strengthens, human psychological prosperity and the thriving of whole persons, not merely psychopathology, is also becoming more central. Behavioral and mental health is ultimately about *health*, not solely the absence of disorders.

This set of changes is accelerating a transition in evidence-based care toward a process-based field that seeks to integrate the full range of psychosocial and contextual biological processes. Such a field is so broad that it stretches the very term CBT almost to a breaking point and we would not be surprised if that term soon wanes in importance.

Researchers and practitioners alike seem ready for a turn toward *process-based therapy (PBT)*, in which processes, procedures and their linkage are evidence-based, and are used to alleviate the problems and promote the prosperity of people. Similar to the trend toward personalized and precision medicine, focusing on changeable processes that can make a difference in

the behavioral and mental health of individuals provides a way for evidence-based care and person-centered care to merge under a single umbrella of process-based care. Orienting the field in that direction may ultimately be the most important "changed shore" produced by the third wave of CBT.

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The use of virtual reality in psychosis research and treatment

Recent years have witnessed a renewed interest and an increase in the popularity of virtual reality, the aim of which is to generate a virtual world that feels immersive and realistic. The user wears a head mounted display, and computer generated images and sounds are synchronized with his/her movements.

The potential of virtual reality for mental health research, assessment and treatment is that it enables researchers and clinicians to bring real-time life experiences into a lab environment. In standard practice, i.e. not in a virtual reality environment, the assessment of clinically relevant phenomena – such as neurocognitive processes, emotional reactions, physiological activation or behavioural responses – involves standardized questionnaires, semi-structured interviews about symptoms, doing computer tasks, watching videos or images, or role playing a situation while the physiological response is measured. Although the reliability and validity of these methods have been tested extensively, they lack ecological validity and do not represent the complexity of real life experiences[1].

The innovative potential of virtual reality is that it allows to measure real-time cognitive, emotional, physiological and behavioural responses to a variety of "real-life" situations, while enabling experimental control.

Till recently, the high cost of virtual reality equipment and software as well as cyber-sickness, a side effect associated with the older head mounted displays, have represented a major barrier to the implementation of virtual reality in standard practice. As head mounted displays have become popular devices for entertainment and gaming, they are increasingly affordable, so that implementation of virtual reality in daily clinical practice has come within reach.

Enthusiasm is growing among clinicians and researchers around the world about the potential that virtual reality offers to improve the assessment and treatment of mental and physical health problems. Fortunately, this technique has been around for over half a century and has been used in psychology research for well over 25 years[2]. A significant body of research has also explored its use for the assessment and treatment of different mental health problems, ranging from phobias, to eating disorders, autism and post-traumatic stress disorder[3].

A substantial number of studies have been conducted to establish the safety of using virtual reality with people experiencing psychosis and to elucidate the psychological mechanisms underlining the onset and maintenance of psychotic symptoms[4]. In this type of studies, participants enter a virtual environment, like public transport or a café, populated by avatars who show behaviours which can be interpreted as ambiguous, like for example looking at the participant and looking away. The occurrence of paranoid ideation or hallucinations triggered during the virtual reality experience is then assessed.

The use of virtual reality for the clinical assessment and treatment of psychosis is still in its infancy, but the first clinical trials have been published or are ongoing. In these studies participants either practice new social skills[5], or are encouraged to drop their safety behaviours and explore new ways of approaching social situations[6,7] or challenge the omnipotence of the voices they hear[8]. The initial results indicate that virtual reality assisted therapy can be a powerful tool to help people break the cycle of avoidance involved in the maintenance of symptoms and develop new skills and strategies to cope with them. They also show that improvements are maintained at follow-up.

Although the coming years are exciting times for the development and implementation of virtual reality for psychosis, our enthusiasm should not prevent us from considering safety and ethical concerns associated with this technique. Moreover, it is essential to emphasize that all research to date has evaluated the use of virtual reality as an adjunct to standard procedures with a therapist guide and not as a stand-alone intervention which patients can download and follow on their own.

Rigorous research is needed to confirm the initial positive findings regarding the use of virtual reality assisted assessment and therapy. To date most research in psychosis has focused on paranoia and hallucinations, and there is an urgent need to explore the use of virtual reality for negative symptoms. Future studies should integrate virtual reality with physiological measures (e.g., galvanic skin response, cortisol levels, heart rate) to better understand the mechanisms that trigger and maintain psychotic symptoms. Research endeavours should also inves-

tigate whether combining virtual reality assisted therapy with wearables and phone apps could help overcoming the barrier between treatment room and daily life.

A new exciting area of research is exploring the use of virtual reality in the training of army medical personnel to increase resilience when deployed to war zones and prevent the onset of mental health problems[9]. Moving forward this approach will be interesting to investigate the use of virtual reality in the training of mental health staff to improve their skills in recognizing and treating psychosis.

Virtual reality could also play a crucial role in researching resilience factors to stressful events in relation to different mental disorders and could inform the development and implementation of prevention strategies. A multi-disciplinary understanding of the mechanisms involved in the onset and maintenance of psychosis that draws connections between psychology, psychiatry, neuroscience, education, computer science and gaming technology will inform core research questions, such as the following: How does emerging psychosis affect behaviour in social situations? How can social environments be effective in building resilience and improving well-being of young people at ultra-high risk for psychosis? How can we use virtual reality in teaching settings to educate young people about early signs of mental health problems? To achieve these ambitious goals, we need to break down the invisible barriers between academia, health providers and new technology industry. We also need to embrace new flexible research designs to evaluate the effectiveness of these continuously evolving technologies[10].

To conclude, a comment about augmented reality. While virtual reality head mounted displays immerse the user in an artificial world, augmented reality displays superimpose virtual images to the real world so that both are visible at the same time. Augmented reality is in development and has enormous potential for training and education as well as for health applications in the next two decades.

For a video example of the use of virtual reality with psychosis, please watch a documentary at https://www.youtube.com/watch?v=DeLBb7BYJ9E.

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Mental health Internet support groups: just a lot of talk or a valuable intervention?

Over the past 15 years there has been a rapid growth in research demonstrating the effectiveness of online cognitive behavioural interventions for the treatment of common mental disorders[1]. There has been substantially less professional and research interest in Internet support groups (ISGs) that provide peer-to-peer support to individuals with a mental illness. This is surprising given the widespread availability and popularity of ISGs[2] and the recommendation in at least one leading clinical practice guideline that individuals with depression be advised of self help and support groups[3].

ISGs provide an accessible form of support regardless of geographical location or time of the day. They enable anonymous participation and may facilitate engagement of individuals with symptoms (such as social anxiety) which hinder face-to-face interaction. Online groups differ in whether or not they are overseen by mental health professionals or moderated to ensure members adhere to the rules of the group. Some groups are synchronous, enabling real-time conversations between users, although most are asynchronous, involving sequential posts and delayed responses.

Support groups, including ISGs, are typically seen as a device for facilitating recovery among people with mental illness. In this context recovery is characterized not as the elimination of symptoms but rather as living a hopeful, contributing and satisfying life[4]. Nevertheless, there is some high quality evidence of the effectiveness of ISGs in reducing depressive symptoms, with a large randomized controlled trial showing a greater reduction of depressive symptoms in the medium and long term following an ISG intervention than an attention control condition[5]. Such evidence is consistent with survey research reporting user-perceived reductions of depressive symptoms with depression ISG use[6]. Further, consistent with hypotheses that ISGs may contribute to recovery, the above ISG trial found a greater short-term increase in perceived empowerment among the ISG than the control group[7].

Other reported benefits of depression ISGs, emerging from user self-reports and qualitative analysis of user posts, include improved daily functioning, reduced isolation, and increased professional help seeking and knowledge of medications[6]. Qualitative evidence suggests that users value the emotional

support, information, advice and companionship provided by depression ISGs, and appreciate the opportunity to express their feelings in a non-judgmental, emotionally safe environment without burdening their family and friends[8]. Users particularly value the opportunity for "shared understanding", which they perceive as "validating, reducing the sense of isolation and enhancing a sense of belonging"[8]. The extent to which one or more of these effects underpin improved health and other outcomes is unclear.

Overall, the above evidence suggests that ISGs might prove a useful tool in the management of depression. However, ISGs are not universally valued by consumers and, although adverse effects are less commonly reported than benefits in the extant literature, mental health ISGs have the potential for such effects. For example, a minority of ISG users in the above-mentioned trial of a depression ISG reported feeling distressed and anxious that they were unable to help others more[9]. Future research is required to determine who is at most risk of this unfavourable outcome and whether there are effective interventions either on the ISG itself or delivered *a priori* to mitigate this distress.

There have also been in-principle concerns that prolonged exposure to negative emotional content might exacerbate a user's depression. There is no evidence at a group level of such contagion in the experimental trials undertaken thus far. However, given the potential risks, a case can be made for precluding discussion about suicidal behaviour to eliminate the possibility of suicide contagion.

Although ISGs typically aim to provide a supportive environment, not all boards are closely moderated to prevent negative or combative posts. Conversely, moderation and the rules themselves may anger or distress some users, who may question the rationale for removing a post or for instituting a particular rule[9]. There is also potential for participants in an ISG to inadvertently disclose identifying information across multiple posts. Whereas the information on a post may not be identifying when taken in isolation, the pattern emerging from multiple posts may provide indicators of the user's identity unless closely monitored by moderators.

What then are the implications of these findings and concerns for psychiatrists and other mental health practitioners? At a minimum it is important to recognize that some clients may already be using these groups. The practitioner can take steps to identify if this is the case and, if so, to elicit information about the type of ISG used. Does it have a moderator, does it have rules to protect the safety of participants, does the ISG allow discussion of triggering material such as suicidal ideation and behaviours? Furthermore, the practitioner can explore the impact of the ISG on the individual and provide appropriate support and guidance if indicated.

But should practitioners proactively refer individuals under their care to a depression ISG or instead actively discourage participation? As with any health management decision, the answer requires a consideration of the relative costs and benefits of a strategy and the circumstances and preferences of the particular client. Rarely is an intervention without any potential risk. The current evidence does not justify the use of ISGs as a primary treatment. However, a case could be made for the use of depression ISGs as an adjunct to usual care for selected clients, provided that suitable protections, safety nets and monitoring are instituted.

What are the next steps? Further research is required to explore the effectiveness and any potential adverse consequences of ISGs, not only for depression but also for other mental health conditions, and to identify the predictors of positive and negative outcomes if and where they occur. Research is also required to further explore the potential for the development of automated classifiers which detect and flag "at risk" posts[10] to assist ISG providers in ensuring the safety of users.

Moreover, educational resources are required for practitioners and users. Training in the use of e-mental health resources, including ISGs, is already available online to Australian practitioners as part of a government-funded initiative to implement e-mental health in practice. Similar initiatives are required elsewhere.

Finally, there is an urgent need to establish a sustainable, independent international quality assurance body to publish accessible reviews of individual ISGs, their characteristics and any evidence associated with them, for the benefit of both practitioners and potential users. The Internet provides users with access to global communities of consumers. Global initiatives are required to optimize the potential of the resulting resources.

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Mental health interventions for people involved in disasters: what not to do

Over recent decades our knowledge about the psychological impact of disasters has increased exponentially. Hand in hand with this increase in understanding has been a dramatic growth in claims of effective intervention techniques and approaches which purport to mitigate the effects of exposure to traumatic events upon mental health.

Furthermore, modern media reporting has made the general public all too aware of the frequency of disasters. Indeed, it is a rare day when we do not hear about a disaster, man-made or natural, somewhere in the world. As such the public frequently expect the authorities or another responsible organization to "do something" to alleviate the distress, and the less frequent cases of mental ill health, which disasters inevitably cause. So what should be done?

As a general principle, we repeat what sadly continues to require frequent repetition. Just as we find it difficult to accept that the idea of a panic prone public is just a myth[1], we also find it difficult to accept that, in general, people are rather more resilient than people like us – experts – think they are. Be it psychiatrists, politicians or planners, there is a long history of overestimating vulnerability and underestimating resilience stretching back many generations[2].

Towards the end of the last century, it became a commonly held belief that people who had been exposed to disasters or other traumatic events should be provided with psychological debriefing or immediate "trauma counseling". Critical incident stress debriefing, which was the first of these techniques to be developed in the late 1980s in the US, was a seven stage structured therapeutic intervention originally designed to be used with emergency responders. However, this technique was frequently used with those directly exposed to traumatic events as well. The original intent of this intervention, and indeed other forms of psychological debriefing, was to prevent the onset of post-traumatic stress disorder (PTSD).

However laudable the objective, it became clear that debriefing was a flawed process[3]. Indeed, available evidence seems to strongly suggest that individuals provided with psychological debriefing approaches actually have poorer long-term mental health than those who are not debriefed at all. Such is the evidence against the use of debriefing that, outside of overly enthusiastic and non-evidence based guideline documents, it is now accepted that such techniques should not be routinely used. Instead, as the UK National Institute for Health and Care Excellence recommend in its PTSD management guidelines[4], watchful waiting for the first month after exposure to a traumatic event is current best practice.

Another approach which is often used by organizations which routinely deploy staff to high threat environments (e.g., the military, emergency services) is to screen them after they return from such duties. Such screening aims to identify the presence of the early symptoms and signs of post-traumatic mental health difficulties in order to advise, or even mandate, that individuals who exhibit these signs seek professional help.

Screening programs such as these are routinely used by the US, Canadian and Australian military with the intent of protecting the mental health of troops returning from operational deployments. Such screening programs are not easy or cheap to administer and there is some evidence from other health screening that they may cause considerable distress if people are incorrectly labelled as having a health problem when in fact they do not[5].

In spite of their widespread use, until recently there was a distinct lack of evidence of their effectiveness. The first randomized controlled trial of post-deployment screening, carried out in the UK military, examined the potential benefits of screening in around 10,000 troops returning back from intense operations in Afghanistan[6]. The results of the trial were that, some 15 months or so after returning from deployment, there was no apparent beneficial impact of screening in terms of either mental health status or help seeking. Whilst no evidence of harm was found in this study, its results call into question the usefulness of establishing such screening programs within organizations where staff members are likely to fear being stigmatized or having limitations placed on their career if they answer questions honestly. Given that many people recover spontaneously, and others do not become unwell for what might be a considerable period of time, the benefits of screening are always going to be much less than in disorders with a well-established trajectory, such as cervical cancer.

Whilst population screening and that within organizational settings has not been found to be effective, selected screening programs for those at high risk has shown promise. In the aftermath of the London bombing of 2005, a "screen and treat program" was set up for those directly affected in the trains and bus that were attacked. This is a very different situation from, for example, well-trained professionals with established social ties returning from deployment where the expected prevalence of disorder is low. Evaluation of this program suggested that it was able to attract many people who had not otherwise sought care, and many of those who were found to need treatment recovered with the care they received[7].

Although the results of screening programs are mixed and the use of debriefing is to be avoided, recent decades have provided some positive findings in respect of improving mental health after disasters. There is good evidence that social support both within communities and organizations can be highly protective of mental health. For instance, within the military, camaraderie has been shown to be protective of troop's mental health both whilst deployed and when in safer environments[8].

The social bonds between people have also been found to be protective within community settings[9] after disasters. More recently, peer support programs have been trialed within organizations in an attempt to ensure that consistent social support is available to trauma-exposed individuals. The most widely researched of these is the Trauma Risk Management program which started in the UK Royal Marines Commandos and has since been adopted by the whole UK military, many UK emergency services and a number of other trauma exposed organizations[10].

Trauma Risk Management has been the subject of a number of research studies which show that it helps to mobilize social support and improve post-traumatic help seeking as well potentially having a positive impact on sickness absence post-disaster in emergency service personnel[10]. Whilst certainly not a panacea for dealing with any traumatic incident, there appears to be good evidence that peer support systems such as this program may be of benefit within trauma-exposed organizations.

In summary, over recent decades, science has helped confirm that it is better to rely on supporting the bonds between people within communities and trauma-exposed organizations to mitigate the psychological impact of disasters than it is to fly in "experts" who neither properly understand those involved or the situation which people have been exposed to.

In the end, we can do well to remember what was learned by previous generations about the immediate versus longer term responses to trauma. The best immediate mental health measures turn out to be practical, whilst our more skilled psychological interventions only really come into their own later on[2].

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Improving outcomes of first-episode psychosis: an overview

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Outcomes of psychotic disorders are associated with high personal, familiar, societal and clinical burden. There is thus an urgent clinical and societal need for improving those outcomes. Recent advances in research knowledge have opened new opportunities for ameliorating outcomes of psychosis during its early clinical stages. This paper critically reviews these opportunities, summarizing the state-of-the-art knowledge and focusing on recent discoveries and future avenues for first episode research and clinical interventions. Candidate targets for primary universal prevention of psychosis at the population level are discussed. Potentials offered by primary selective prevention in asymptomatic subgroups (stage 0) are presented. Achievements of primary selected prevention in individuals at clinical high risk for psychosis (stage 1) are summarized, along with challenges and limitations of its implementation in clinical practice. Early intervention and secondary prevention strategies at the time of a first episode of psychosis (stage 2) are critically discussed, with a particular focus on minimizing the duration of untreated psychosis, improving treatment response, increasing patients' satisfaction with treatment, reducing illicit substance abuse and preventing relapses. Early intervention and tertiary prevention strategies at the time of an incomplete recovery (stage 3) are further discussed, in particular with respect to addressing treatment resistance, improving well-being and social skills with reduction of burden on the family, treatment of comorbid substance use, and prevention of multiple relapses and disease progression. In conclusion, to improve outcomes of a complex, heterogeneous syndrome such as psychosis, it is necessary to globally adopt complex models integrating a clinical staging framework and coordinated specialty care programmes that offer pre-emptive interventions to high-risk groups identified across the early stages of the disorder. Only a systematic implementation of these models of care in the national health care systems will render these strategies accessible to the 23 million people worldwide suffering from the most severe psychiatric disorders.

Key words: Psychosis, schizophrenia, psychosis risk, clinical high risk, first episode psychosis, universal prevention, selective prevention, indicated prevention, outcomes, clinical staging

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Psychotic disorders such as schizophrenia are common, with 23.6 million prevalent cases worldwide in 2013[1]. One in two people living with schizophrenia does not receive care for the condition[2]. The recovery rates (one in seven[3]) and associated disability (11th cause of disability worldwide in 2013[1]) following a first episode of psychosis have not improved over the past seventy years under routine clinical care[1,3]. Although existing psychopharmacological treatments alone can reduce some symptoms, they have little impact on the outcome of the illness[4].

The annual national costs for the schizophrenia population ranged from US$94 million to US$102 billion worldwide, up to 1.65% of the gross domestic product[5]. Furthermore, risk of all-cause mortality for psychotic disorders is twice (risk ratio 2.54) that of the general population[6]. There is thus an urgent clinical and societal need for improving outcomes of psychosis.

Recent advances in research knowledge have opened new opportunities for ameliorating outcomes of psychosis during the critical periods surrounding the first episode of the illness (about 2 years before[7] and 3 years after[8] the onset). In this paper, we critically review these opportunities, summarizing the state-of-the-art knowledge and focusing on recent discoveries and future avenues for first episode research and clinical interventions.

As a conceptual framework we will adopt a revised version of the clinical staging model[9] (Table 1). We will mostly focus on non-affective psychoses, although some issues can also be applied to the other types of psychoses.

PRIMARY PREVENTION

Mental health promotion aims to promote positive mental health by increasing psychological well-being, competence and resilience, and by creating supporting living conditions and environments. It is not addressed in the present paper.

Primary prevention aims to reduce the incidence of symptoms and ultimately of mental disorders[10]. The three categories of primary prevention identified by the World Health Organization (WHO)[11] are: *universal prevention*, targeting the general public or a whole population group that has not been identified on the basis of individual risk; *selective prevention*, targeting individuals or subgroups of the population whose risk of developing a mental disorder is significantly higher than the rest of the population; and *indicated prevention*, targeting high-risk individuals who are identified as having minimal but detectable signs or symptoms foreshadowing mental disorders.

Universal prevention of psychosis

Universal primary prevention must take the form of a safe population-wide intervention that promotes normal development. Research in this area is still in its infancy, because no established pathophysiological mechanisms to be targeted have been validated[12].

A recent pioneering, randomized placebo-controlled clinical trial of dietary phosphatidylcholine supplementation was

Table 1 Revised clinical staging model for psychotic disorders and interventions for improving the outcomes of first-episode psychosis (FEP)

Clinical stage	Definition	Definition in clinical staging model	Intervention
0	Asymptomatic genetic risk	Premorbid	*Selective primary prevention*
			Improved mental health literacy
			Family psychoeducation
1a	Negative and cognitive symptoms	CHR-P	*Indicated primary prevention*
			Formal mental health literacy
			Family psychoeducation
			Active reduction of substance misuse
1b	Attenuated psychotic symptoms	CHR-P	*Indicated primary prevention*
			Family and individual psychoeducation
			Active reduction of substance misuse
			Vocational support
			Psychological therapies
1c	Short-lived remitting psychotic episodes	CHR-P	*Indicated primary prevention*
			As for 1b
			Close-in monitoring
2	Full-threshold FEP	Early full recovery	*Early intervention and secondary prevention*
			Family and individual psychoeducation
			Psychological therapies
			Active reduction of substance misuse
			Atypical antipsychotics and other medications
			Vocational rehabilitation
3a	Single relapse of psychotic disorder	Late/incomplete recovery	*Early intervention and tertiary prevention*
			As for 2, but with emphasis on relapse prevention and early warning signs
3b	Multiple relapses	Late/incomplete recovery	*Early intervention and tertiary prevention*
			As for 2, but with emphasis on long-term stabilization
3c	Incomplete recovery from first episode	Late/incomplete recovery	*Early intervention and tertiary prevention*
			As for 3a; clozapine in case of treatment resistance
4	Severe, persistent or unremitting illness	Chronicity	*Maintenance intervention*
			As for 3a-c, but with emphasis on social participation despite ongoing disability

CHR-P – clinical high risk for psychosis

conducted in a small sample of healthy pregnant women, starting in the second trimester and continuing through the third postnatal month[13]. The intervention aimed at correcting delays in cerebral inhibition that may develop perinatally, as indexed by electrophysiological biomarkers. The intervention was free of significant side effects and showed proof of concept efficacy.

Although larger studies need to be conducted to validate these initial findings, future research in this field is warranted over the next decade. Promising research candidates for the universal prevention of psychosis and the supporting evidence, which awaits future replication, are listed in Table 2.

Table 2 Candidate universal interventions for primary prevention of psychosis

Intervention	Supporting evidence	Target
Perinatal phosphatidylcholine	Randomized controlled trial[13]	Electrophysiological biomarkers of neonatal development
School-based interventions	Randomized controlled trials[14,15]	Bullying, victimization, pro-bullying attitudes, pro-victim attitudes, empathy toward victims
Fetal and neonatal N-acetylcysteine	Randomized controlled trial[16]	Biomarkers of neuroinflammation and neuroprotection
N-3 polyunsaturated fatty acids	Review[17]	Biomarkers of neuroinflammation
Vitamins A, D, B-group, folic acid	Original study, meta-analysis[18,19]	Biomarkers of neuroinflammation
Sulphoraphane	Review[20]	Biomarkers of oxydative stress
Prebiotics	Review[21]	Microbiota dysbiosis
School-based interventions	Randomized controlled trial, review[22,23]	Substance abuse
Exercise training	Original studies[24-27]	Brain plasticity, structure, connectivity, cognitive functioning

Asymptomatic genetic risk (stage 0)

The staging perspective (Table 1) provides a framework for research and conceptualization of earlier premorbid interventions to alter the developmental pathway to first-episode psychosis. Selective interventions in this stage could target parental, perinatal, social or later environmental risk factors before symptoms and help-seeking behaviour manifest[28], such as those listed in Table 3.

Although this is an exciting area for future research, currently there are no robust and effective preventive strategies to reduce the risk of psychosis in asymptomatic individuals exposed to these environmental risk factors[51]. For now, the primary viable strategy is to use the family high-risk approach (selecting offspring of individuals with schizophrenia), even though this approach will only yield roughly 10% of the individuals from these families who will develop psychosis[51].

Improving mental health literacy in these at-risk populations may represent an effective pragmatic strategy to help prevent or facilitate earlier intervention in psychosis (Table 1).

Clinical high risk for psychosis (CHR-P, stage 1a-c)

State of the art

The introduction of specific semi-structured interviews[52-54], about two decades ago[55], for the ascertainment of signs and symptoms suggestive of psychosis risk states has allowed the identification of individuals at clinical high risk for the development of psychosis (CHR-P) before full symptoms manifest[56]. These individuals are functionally impaired in comparison with matched controls at baseline[57] and have an up to 20% 2-year risk (95% CI: 17%-25%) of developing psychosis[58].

Their risk peaks in the first two years[59] and is specific for the development of psychotic disorders but not for emerging non-psychotic disorders[60,61]. However, less than half of those who will *not* develop psychosis will eventually remit (35% of the baseline cohort)[62], since persistent comorbidities (that were already present at baseline[63-65]) and functional impairment are frequently observed at follow-up[64].

Indicated interventions through specialist CHR-P provision have been recognized as an important component of clinical services for early psychosis intervention[66-68] – see, for instance, the guidelines of the UK National Institute for Health and Care Excellence (NICE)[69], and the Access and Waiting Time (AWT) standards of the UK National Health Service[67].

Conceptually, although most of CHR-P individuals (73%) would present with some comorbid DSM-IV diagnosis at baseline[63,70], the intervention is still considered preventive[71] (indicated) since these individuals are selected on the basis of having early signs or symptoms of psychosis risk.

Indicated interventions in CHR-P people may improve the outcome of first-episode psychosis through the following mechanisms: a) delayed or prevented onset of a first episode; b) better engagement with services and reduced comorbidity; c) reduced duration of untreated psychosis (DUP); and d) improved early detection and amelioration of the severity of first-episode cases (secondary prevention).

Meta-analysis of randomized controlled trials in CHR-P individuals suggests that short-term (6-12 months) psychological interventions can halve the risk of illness onset at 12 months[72]. However, the preventive effect is not sustained over a longer period of time (24 months and longer); so, these findings should be interpreted cautiously and may indicate a delayed rather than prevented psychosis onset. No trials have investigated whether long-term provision of focused interventions may result in sustained benefits. Furthermore, the three largest studies of preventive interventions in individuals at ultra-high risk for psychosis have turned out to be negative, possibly because of low power[73-75]. At the moment, there are no approved interventions that have been shown to reliably alter the long-term course of the disorder[12].

CHR-P services are effective in improving trust and engagement[76], with high satisfaction of users. Furthermore, since

Table 3 Some environmental risk factors for psychosis supported by meta-analytical level of evidence in the current literature

Type of environmental risk factor	Meta-analytical association with psychosis	Association measure type: mean (95% CI)
Parental risk factors	Parental psychosis[29]	RR: 7.87 (4.14-14.94)
	Parental affective disorder[29]	RR: 6.42 (2.20-18.78)
	Old paternal age[30]	RR: 2.22 (1.46-3.37)[a]
Perinatal risk factors	Complications of pregnancy[31-33]	OR: 2.44 (1.13-5.26)[b]
	Abnormal foetal growth and development[31,32]	OR: 3.89 (1.40-10.84)[c]
	Complications of delivery[31,32]	OR: 2.21 (1.38-3.54)[d]
	Gestational influenza[33]	RR: 1.56 (1.05-2.32)
	Season of birth[34]	OR: 1.07 (1.05, 1.08)
Social risk factors	Ethnic minority[35-37]	RR: 4.7 (3.3-6.8)[e]
	First and second generation immigrant status[38]	IRR: 2.3 (2.0-2.7)[f]
	Urbanicity[39]	OR: 2.37 (2.01-2.81)
Later risk factors	Infections[40-42]	OR: 2.70 (1.34-4.42)[g]
	Traumatic brain injury[43]	OR: 1.65 (1.17-2.32)
	Vitamin D deficiency[44]	OR: 2.16 (1.32-3.56)
	Daily tobacco use[45]	OR: 2.18 (1.23-3.85)
	Cannabis heavy abuse[46]	OR: 3.90 (2.84-5.34)
	Childhood trauma and adversity[47]	OR: 2.75 (2.17-3.47)
	Adult life events[48]	OR: 3.19 (2.15-4.75)
	Premorbid IQ[49,50]	OR: 4.78 (3.19-7.13)[h]

RR – risk ratio, OR – odds ratio, IRR – incidence rate ratio
[a]age >55, [b]gestational age <37 weeks, [c]birth weight <2000g, [d]incubator or resuscitator, [e]Black African vs. White British, [f]first generation migrants, [g]Toxoplasma gondii, [h]IQ<70. Some of these risk factors may also include a genetic component.

most CHR-P people present with comorbid disorders that are not severe enough to be accepted and treated by generic mental health services, CHR-P services may also improve these problems as well as provide vocational support and reduce family stress.

Patients who engage with CHR-P services and who will later develop the disorder show a substantial reduction of their DUP (11 days on average) compared to patients who do not present to clinical services until the first episode (approximately 1 year on average)[77]. Compared to patients accessing first episode services, patients who presented in the CHR-P stage are also less likely to require admission following the onset of psychosis (46% vs. 68%) and less likely to require a compulsory admission in the short term (30% vs. 62%)[77].

Finally, the presence of CHR-P services may have extended benefits for the identification of first-episode cases and for secondary prevention. In fact, about one-third of patients referred to CHR-P services have already developed a first episode of psychosis at the time of initial contact[78]. First-episode patients presented to CHR-P service spent fewer days in hospital (less than 17), had a shorter referral to diagnosis time (–74.5 days), a lower frequency of admission (incidence rate ratio = 0.49), and a lower likelihood of compulsory admission (odds ratio = 0.52) compared to patients who were first diagnosed by first-episode services[78]. However, these findings may be confounded by a selection bias, which is discussed below here.

Challenges and future advancements

Even assuming that an effective preventive treatment altering the course of the illness may be discovered in the next generation of interventional studies, the overall impact of treating CHR-P individuals on the outcomes of first-episode psychosis is still undetermined. This is mostly due to the fact that the potential benefits of the primary prevention during the CHR-P stage are practically limited by the difficulty to identify and treat all the individuals who are at risk of developing the disorder.

How should CHR-P individuals be recruited from secondary mental health services?

Current guidelines recommend that the CHR-P assessment should be primarily offered to individuals who are "already distressed by mental problems and seeking help for them"[79]. These individuals represent an exceptional window of opportunity for preventive interventions as they are already in contact with secondary mental health services. Unfortunately, only 5.19% of the total cases of emerging first-episode psychosis among patients

accessing secondary mental health services are detected and under the care of CHR-P services that had been well established (several years before) in the local national health system[80].

This result is highly disturbing, as it indicates that the overall real-world impact of CHR-P detection and treatment for improving the outcomes of first-episode psychosis is minimal, missing 95% of individuals who will eventually develop psychosis. Thus, it seems crucial to optimize the proportion of individuals at risk of developing psychosis who are referred to CHR-P services. Individualized risk estimation e-tools that are based on easily collectable variables have recently been developed and externally validated (www.psychosis-risk.net)[80]. Since the vast majority (91%) of patients referred to first-episode services had a first point of contact within secondary mental health care[81], the use of these tools can substantially extend the benefits of preventive interventions to most at-risk individuals and eventually result in a massive impact for the improvement of first-episode psychosis outcomes.

How should CHR-P individuals be recruited outside clinical samples?

The use of the CHR-P approach outside clinical samples or for screening purposes is not recommended, because its low ability to rule in psychosis[52] produces a substantial dilution of risk enrichment[82], leading to underpowered clinical trials[75] and questionable clinical relevance for preventive interventions[52,83-85]. For example, using CHR-P assessment in the general non-help-seeking adolescent population is associated with a 2.5-year risk of psychosis onset of 2% only[86].

At the same time, it seems important to continue exploring the usefulness of an extended use of CHR-P assessment to populations not accessing mental health services in order to improve detection of at-risk cases. Possible solutions may include the use of meta-analytical Fagan's nomogram[52] or stratification models[84] that have recently been made available to estimate the overall risk enrichment of samples undergoing CHR-P assessment.

A complementary approach may be based on the use of sequential testing methods[87]. The sequential use of screening instruments and CHR-P assessment in non-help-seeking adolescents from the general population may identify individuals who are at potential risk of developing psychosis in the following years[88]. Sequential testing is in line with the clinical staging model and can be further enhanced by front-line primary care youth mental health models developed to facilitate the access of young people from the school and community (see https://www.headspace.org.au).

Innovative strategies to identify non-help-seeking individuals at risk of psychosis can also involve the use of e-health technologies, for example based on semantic analysis of social media postings.

Can we provide stratified treatments to the CHR-P subgroups?

Future advances could also develop stratified preventive treatments targeting the different CHR-P clinical stages (a, b or c), that may have different characteristics with respect to underlying disease processes and prognosis[89]. On the basis of the increasing risk (clinical stage 1a: 3% at 2 years[58]; clinical stage 1b: 19% at 2 years[58]; clinical stage 1c: 39% at 2 years[58] and 51% at more than 3 years[90]), and symptoms severity[91] (individuals in the clinical stage 1c would formally meet the ICD criteria for a brief psychotic disorder[92]), preventive interventions for the clinical stage 1a can be supplemented by specific psychological therapies and individual psychoeducation for the clinical stage 1b.

These treatments may be further supported by a more intensive or close-in monitoring for the clinical stage 1c, which is characterized by short-lived and self-remitting psychotic episodes lasting few weeks only (e.g., less than 4 weeks)[90]. In line with the clinical staging model, the stage 1c is less severe compared to patients experiencing a first episode of schizophrenia (clinical stage 2), who do not spontaneously remit from their symptoms without antipsychotic treatment and who show substantial higher risk of relapses[90].

EARLY INTERVENTION AND SECONDARY/TERTIARY PREVENTION

Full threshold first-episode psychosis with early recovery (stage 2)

State of the art

The stage 2 encompasses the acute phase or crisis, that is characterized by florid psychotic symptoms (sustained symptoms lasting four weeks or more as suggested by the NICE Quality Standard 102[93]), followed by an early recovery phase or post-acute phase observed in the first 6-12 months following the acute episode.

Recovery is usually operationalized as concurrent clinical remission – less than mild symptoms at the Positive and Negative Syndrome Scale (PANSS) ($\leq$3), the Scale for the Assessment of Positive Symptoms (SAPS)/Scale for the Assessment of Negative Symptoms (SANS) (<3), or the Brief Psychiatric Rating Scale (BPRS) ($\leq$3), sustained for at least 6 months[94] – and functional remission (proper social functioning in the main domains of everyday life)[95]. Early interventions and secondary preventive interventions during stage 2 may improve the outcome of first-episode psychosis through the following mechanisms: a) DUP reduction; b) improvement of treatment response; c) improved well-being, functioning and social skills with reduction of burden on the family; d) treatment of comorbid substance use; e) secondary prevention of disease progression.

A long DUP is associated with poor general symptomatic outcome, more severe positive and negative symptoms, lesser likelihood of remission, and poor social functioning and global outcome, but not employment, quality of life or hospital treatment[96]. The meta-analytical correlations are small in magnitude

(r = 0.13-0.18), yet robust[96]. Since the majority of DUP is accounted for by delays in accessing early intervention services and help seeking[97], at least in the UK, it is a modifiable factor even during the clinical stage 2. Community psychosis awareness campaigns, including publicity and community engagement integrated with a specific youth mental health direct care pathway, can halve the DUP compared to detection as usual (mean 104 vs. 285 days)[97].

Beyond the impact on DUP, intervention in the clinical stage 2 can be associated with substantial improvements in treatment response. A systematic research of the literature summarizing the results of randomized controlled trials of integrated multicomponent early intervention services for patients experiencing a first episode of psychosis is presented in Table 4. The multicomponent interventions were mostly based on the comprehensive use of antipsychotics[98-100,102,105-108], individual psychological treatments[98-100,105-108], family[98-100,102,105-107] and vocational[98,99,102,105,107] support. Small trials showed minimal beneficial effects or no effects at all on clinical outcomes[99,100,110]. Larger trials showed a significant short-term (i.e., up to 24 months) improvement of treatment response under specialized integrated early interventions compared to standard community care. The improved response to the comprehensive treatments was characterized by lower disengagement from care[98,102,105]; reduction of positive[100,102,107], negative[100,102] and total[105-107] psychotic symptoms; reduced hospitalization[98,107], lower dosages of antipsychotic medications[102], and improved functioning[106].

Specialized interventions during the clinical stage 2 are associated with higher patients' satisfaction with treatment[102] and improved personal well-being[105,106], characterized by better sense of purpose, motivation, curiosity and emotional engagement[105]. These improvements translated into better quality of life[105] and greater involvement in school and work[105,107], with an overall reduced burden to the family[102]. Family interventions for first-episode psychosis are an integral component of treatment, but they can have beneficial effects even as standalone treatment, with greater 12-month improvements in family burden and caregiving experience, reductions in severity of psychotic symptoms and duration of re-hospitalizations[111].

The detrimental impact of illicit substance abuse on the long-term outcome of psychosis is well known, with a dose-dependent association[112]. Available trials confirm that it is possible to reduce substance abuse in first-episode psychosis through specialized integrated early intervention services[102]. Randomized controlled trials are directly investigating the effectiveness of a behavioural intervention for reducing cannabis use among young people receiving treatment from early intervention services[113,114].

Finally, interventions in this phase are crucial for the secondary prevention of illness progression to clinical stage 3, in particular to prevent relapse into a second episode of psychosis (3a). This is significant, because relapse interferes with the social and vocational development of individuals suffering from a first episode of psychosis, which has an impact on long-term outcomes[115].

Challenges and future advancements

Although specialized first episode services that provide a comprehensive care can significantly improve outcomes of first-episode psychosis, and their implementation is overall recommended[116], there are some significant challenges.

Are specialized integrated early intervention services effective in preventing relapses?

Despite the benefits yielded by specialized integrated early intervention services, many patients still have an increased risk of relapsing into a second episode of psychosis following an initial recovery (clinical stage 3a). Criteria for relapse vary across studies, but readmission to a psychiatric hospital is the most common definition of psychotic relapse in the existing literature[117].

Since randomized controlled trials provide the gold standard methodology for evaluating interventions for relapse prevention, we have updated an earlier meta-analysis that included only three trials investigating the risk of relapse/admission to psychiatric hospital under specialized early intervention services, compared to standard care[118]. We now include 12 trials stratified for different time points, as indicated in Table 4.

We found that mean relapse rates under treatment as usual were 14% (95% CI: 10%-20%) at 9 months, 49% (95% CI: 29%-69%) at 24 months, and 76% (95% CI: 53%-90%) at more than 10 years, while under the specialized integrated early intervention services they were 17% (95% CI: 13%-21%) at 9 months, 38% (95% CI: 14%-66%) at 24 months and 54% (95% CI: 36%-70%) at more than 10 years.

Figure 1 shows that there was no meta-analytical evidence that specialized integrated early intervention services can substantially improve the odds ratio for having a relapse compared to standard care, at any time points. These negative findings are in line with naturalistic studies, showing that about 50% of cases of first-episode non-affective psychosis relapse at least once (clinical stage 3a), while 34% have multiple relapses (clinical stage 3b). Adherence (odds ratio 2.9) and schizophrenia diagnosis (odds ratio 2.2) were the most robust predictors of the first relapse[119].

These findings are also in line with the lack of stringent evidence for a robust effect of antipsychotics on relapse prevention in the long term and with meta-analyses indicating that the overall rate of long-term recovery following a first episode of psychosis has not improved much worldwide over the past decades[3]. There is still much to be done to develop effective integrated treatments for tertiary relapse prevention in early psychosis.

Should we use long-acting injectable antipsychotics earlier?

International treatment guidelines for first-episode psychosis recommend antipsychotic medication maintenance for at least 1-2 years to prevent relapse[120]. The

Table 4 Randomized controlled trials of the effectiveness of specialized integrated early intervention services for first-episode psychosis

Study	Intervention	Control	Treatment group (N)	Control group (N)	Follow-up (months)	Outcome
Craig et al[98]	Specialized integrated early intervention (antipsychotics, cognitive behaviour therapy, family counselling, vocational help)	Treatment as usual in community care	71	73	18	No difference in relapse, reduced psychiatric hospitalization and disengagement
Kuipers et al[99]	Specialized integrated early intervention (atypical antipsychotics, cognitive behaviour therapy, family intervention, vocational help)	Treatment as usual in community care	32	27	12	No significant benefits including psychiatric hospitalization
Grawe et al[100] Sigrúnarson et al[101]	Specialized integrated early intervention (family psychoeducation and therapy, home crisis management, cognitive behaviour therapy, antipsychotics)	Treatment as usual in community care	30	20	24 168	At 24 months, reduced negative and positive symptoms; no benefits on psychiatric hospitalization or recurrences. No substantial long-term effects.
Petersen et al[102] Bertelsen et al[103] Secher et al[104]	Specialized integrated early intervention (family psychoeducation, social skills training, antipsychotics)	Treatment as usual in community care	275	272	12, 24 60 120	At 12 months, reduced hospitalization. At 24 months, improvement on positive and negative symptoms, substance abuse, treatment adherence; lower dosage of antipsychotic medication, higher satisfaction with treatment, reduced burden to the family; no effect on psychiatric hospitalization. At 60 months, many positive effects disappeared; more patients living independently. At 120 months, most positive effects had diminished or vanished.
Kane et al[105]	Specialized integrated early intervention (family psychoeducation, resilience-focused individual therapy, supported employment and education, antipsychotics)	Treatment as usual in community care	223	131	24	Reduced disengagement, greater improvement in quality of life, well-being and total psychopathology, greater involvement in work and school, no effect on psychiatric hospitalization
Ruggeri et al[106]	Specialized integrated early intervention (cognitive behaviour therapy, family intervention, case management, antipsychotics)	Treatment as usual in community care	272	172	9	Reduced total symptom severity, improved functioning and emotional well-being; no effect on psychiatric hospitalization or disengagement
Srihari et al[107]	Specialized integrated early intervention (antipsychotics, family education, cognitive behaviour therapy, vocational support)	Treatment as usual in community care	60	57	24	Reduced psychiatric hospitalization, positive and total psychotic symptoms, improved vocational engagement, no effect on functioning
Chang et al[108] Chang et al[109]	3-year specialized integrated early intervention (psychosocial interventions, cognitive behaviour therapy, antipsychotics)	2-year specialized integrated early intervention and 1-year step-down care	82	78	12	Better functioning, reduced negative and depressive symptoms and disengagement, no effect on psychiatric hospitalization
Ando et al[110]	Specialized integrated early intervention	Treatment as usual in community care	34	34	9	No effects on disengagement, functional remission, psychiatric hospitalization, self-harm, suicide attempt, social relationship

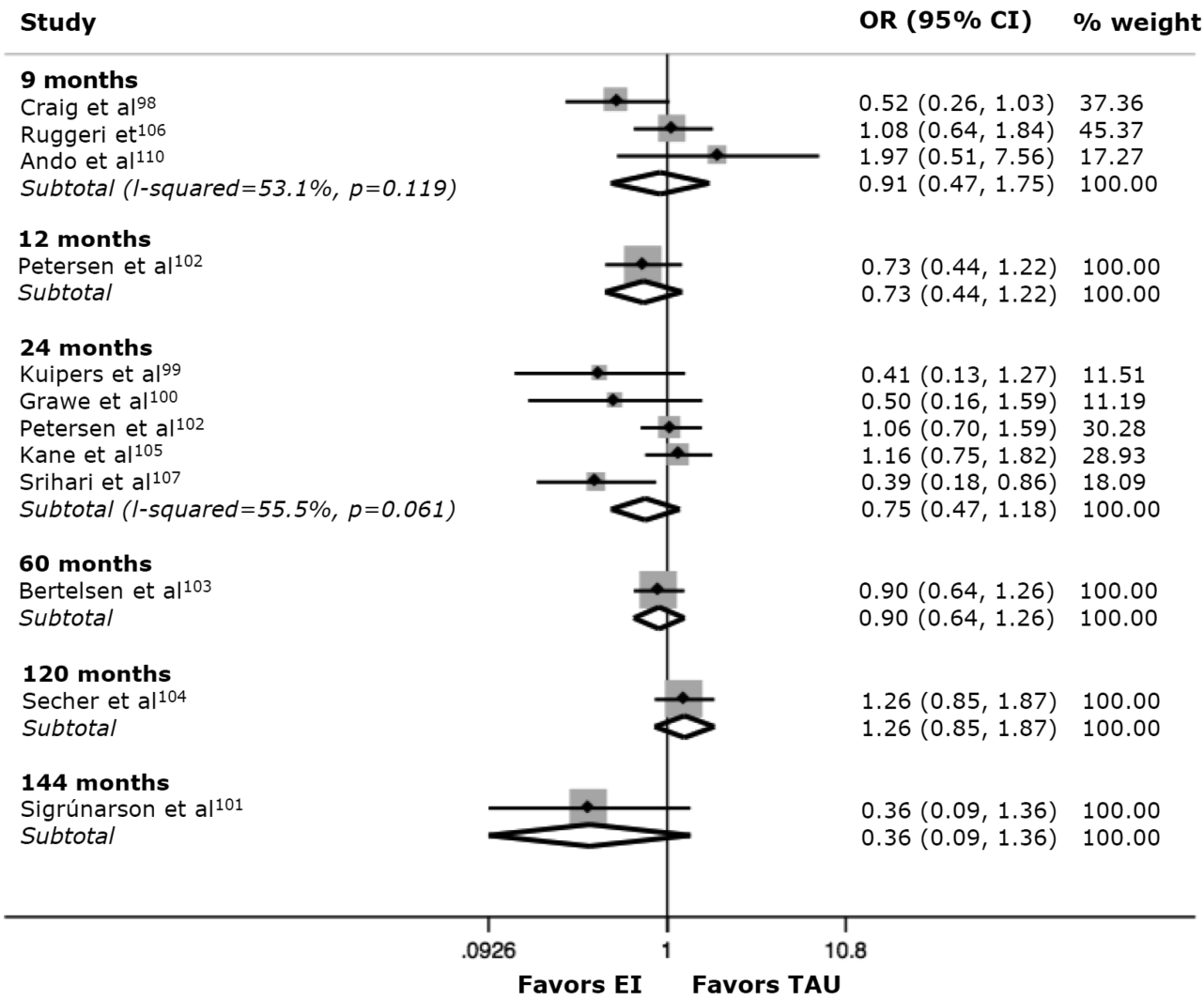

Figure 1 Meta-analytical odds for relapses (hospital readmission) with specialized integrated early intervention services (EI) compared to standard care (TAU) in the community. Odds ratios smaller than 1 indicate an association of reduced relapses with EI, while odds ratios greater than 1 indicate an association of reduced relapses with TAU. Weights are from random effects analysis.

most robust meta-analysis of randomized controlled trials of antipsychotics in first-episode patients showed 26% risk of relapse in the treatment group at 1 year, compared to 61% in the placebo group at 1 year (risk ratio = 0.47)[121].

Since antipsychotics are effective in the short term to prevent relapse, and non-adherence is a modifiable risk factor, it seems justifiable to introduce the use of long-acting injectable antipsychotics (LAIs) earlier in the treatment of psychosis, during the clinical stage 2[122]. LAIs are superior to placebo not only for the prevention of relapse but also for the reduction of symptoms in acutely ill patients with established psychosis[122].

However, seven independent meta-analyses of available randomized controlled trials, including one conducted in recent-onset psychosis (including only three trials enrolling patients with a diagnosis of psychosis within 1-5 years)[123], found no evidence that LAIs are associated with better efficacy on relapse prevention, compared to oral antipsychotics[124-129].

It is possible that randomized controlled trials enrol patient samples that are not representative of real-world clinical practice. In fact, meta-analyses of studies comparing LAIs vs. oral antipsychotics in the same patients, that better reflect real-world efficacy, found strong evidence for LAIs superiority on preventing hospital admission (risk ratio = 0.43)[130]. Furthermore, since the available trials have been mostly conducted in chronic patients or in patients with some years of active psychosis, the actual efficacy of LAIs in patients with a first episode of psychosis (clinical stage 2) is undetermined. In general, LAIs are similar to one another in terms of relapse prevention[122].

Using LAIs in first-episode patients with clear risk factors for relapse – such as a diagnosis of schizophrenia, non-adherence to oral antipsychotics, comorbid substance misuse and poor insight – may thus substantially improve outcomes of first-episode psychosis.

For how long should early intervention services be offered?

Beyond relapse prevention, most trials indicate that the benefits provided by early intervention services are attenuated over the long term[101,103,104], at more than 2-year follow-up, although these findings may be due to insufficient power. It is likely that the positive effects of intensive early treatment are sustained only if patients continue to receive specialized services (though at what intensity/frequency remains a question).

A recent trial compared a 3-year provision of specialized services versus a 2-year provision of the same. The extended year was associated with significant benefits on negative and positive symptoms, as well as on functioning[108]. This also aligns with the clinical staging model, wherein symptom resolution and clinical stabilization take place at an earlier stage followed by gradual functional improvement, which occurs later and requires substantially longer to achieve.

Discharging first-episode patients back to primary care or poor morale generic mental health services that focus heavily on patients with persistent illness, after 1-2 years of specialized early intervention care, is likely to result in the erosion of the initial advantages and gains and is thus unlikely to change their long-term recovery outcomes.

Longer-term early intervention services spanning the entire critical period of 5 years[8] are under development[131]. A subset of cases will almost certainly need longer-term expert care. In the context of competing demands and budgetary constraints, it is important to note that the costs for comprehensive specialized integrated care are exceeded by its benefits, relative to standard community care[132-134].

Schizophrenia spectrum vs. affective spectrum first-episode psychosis: does it make any difference?

Formulating a specific ICD or DSM diagnosis of psychosis at the time of the first contact with the first-episode services is challenging, because the clinical features are relatively non-specific. However, the NICE recommendation 1.3.4.3 for first-episode psychosis clearly indicates that if the patient's presentation suggests an affective rather than schizophrenia spectrum psychosis, different clinical guidelines (e.g., those for bipolar disorder or for depression) should be followed at least for psychopharmacological treatments[120].

A meta-analysis conducted in 14,484 first-episode patients, with an average follow-up of 4.5 years, found a high prospective diagnostic stability for schizophrenia spectrum psychoses (0.93; 95% CI: 0.89-0.97) and for affective spectrum psychoses (0.84; 95% CI: 0.79-0.89), which is comparable to other clinical diagnoses in medicine[135]. In line with the clinical staging model, the retrospective diagnostic stability was low for both spectra (0.60), indicating that many first-episode patients who receive a non-specific diagnosis of psychosis (e.g., psychosis not otherwise specified) will eventually develop schizophrenia or affective psychoses[135]. Therefore, having a baseline diagnosis of schizophrenia spectrum or affective spectrum psychotic disorder may still have significant clinical impacts[136].

Schizophrenia features are strong predictors of poor long-term outcomes (e.g., at 3 years[137] and 10 years[138-140]) in first-episode patients, with odds ratio ranging from 5.70 to 8.86[140]. An initial diagnosis of schizophrenia has been associated with higher risk of relapse at 3 years (odds ratio 2.7)[119]. The worse prognostic outcome of an initial schizophrenia diagnosis has been confirmed even in modern specialized integrated early intervention services that were offering state-of-the-art treatments to improve outcome for first-episode psychosis[119,140,141]. However, when communicating with patients, it may be preferable to use the broader term psychosis rather than schizophrenia, to fully reflect the possibility of plastic and heterogeneous outcomes.

For how long should we treat remitted patients with antipsychotics?

Because evidence is robust for the effectiveness of antipsychotic medication in reducing the short-term risk of relapse, it would seem reasonable to recommend medication maintenance for all first-episode individuals. However, the long-term efficacy of antipsychotics for relapse prevention is less established. Furthermore, since treatment disengagement is common early in the illness and is largely patient-driven[142], more effective alternatives could be considered[143]. Finally, there is increasing concern that cardiometabolic risk factors and abnormalities are present early in the illness, and related to the underlying mental disorder, unhealthy lifestyle and antipsychotic medications[144], as well as subtle extrapyramidal symptoms[145].

As a consequence of these considerations, the long-term use of antipsychotic medications has been recently questioned[146] and discontinuation of antipsychotic medication after 1-2 years is partially recommended by some clinical guidelines[147]. Two recent trials have investigated this issue, comparing treatment maintenance versus reduction/discontinuation strategies. In the short term (within the first 3 years), the risk of relapse was twice in the reduction/discontinuation group compared to the maintenance group[145,148]. However, in the longer term (at 7 years), the risk of relapse was comparable (62% in the reduction/discontinuation group vs. 69% in the maintenance group)[145].

Despite some important methodological limitations[136], it was additionally found that recovery and functional remission rates in the reduction/discontinuation group were twice those seen in the non-dose reduction/discontinuation group[145]. Importantly, the patients included in these trials had all experienced a clinical or functional remission that was sustained for six[145] or 18[148] months (i.e., clinical stage 2). Discontinuing antipsychotic treatment before remission is achieved (e.g., for the clinical stage 3) is associated with higher time to remission and later risk of relapse[149,150].

Overall, these findings indicate that the effect of antipsychotics is mostly symptomatic and unlikely to change the underlying course of the disorder, raising suspicion that these drugs may delay but

not actually prevent relapses[12]. In fact, longer treatment periods with antipsychotics before withdrawal are not associated with reduced risk of relapse[143], with a rapid return of symptoms in the relapse episode to severity levels similar to those in the first psychotic episode[143].

On the basis of the existing conflicting evidence, treatment reduction may be a stage 2 specific option only for the subset of patients who had achieved a clinical remission[94] and are not at high risk of relapse. The challenge would be to identify these low-risk individuals prior to considering treatment reduction[151]. Future research is thus needed to develop reliable stratification models for these patients according to the most robust risk factors for relapse: longer duration of untreated psychosis, male gender, poor baseline functioning and educational status, and a diagnosis of schizophrenia[152,153].

A recent meta-analysis indicated that the risk of relapse in patients diagnosed with schizophrenia who have achieved a clinical remission and then discontinued antipsychotic medications was 78% at 24 months and 84% at more than 36 months[90]. Accordingly, it has been suggested to exclude from treatment discontinuation/reduction strategies first-episode patients who have been diagnosed with schizophrenia at baseline[152].

However, future replication trials are required before treatment discontinuation/reduction can be safely implemented in clinical practice. A viable solution could be to use psychological treatments rather than placebo in both arms of a future discontinuation/reduction vs. maintenance trial, which may be an acceptable and effective alternative for patients who have chosen not to take antipsychotic drugs[154].

Incomplete recovery from first episode of psychosis (stage 3)

State of the art

The critical period after the onset of psychosis extends to the clinical stage 3. There are three forms of incomplete recovery: a) recovery is initially achieved but then followed by a relapse (clinical stage 3a); b) initial recovery is followed by multiple relapses (clinical stage 3b); c) premorbid functional or symptoms levels are never fully reached (clinical stage 3c).

Early interventions and tertiary preventive interventions during stage 3 may improve the outcome of first-episode psychosis through the following mechanisms: a) addressing treatment resistance; b) improving well-being and social skills with reduction of burden on the family; c) treatment of comorbid substance use; d) prevention of multiple relapses and disease progression.

The failure to respond to two different antipsychotics, at therapeutic doses and for a sufficient duration[155], means that a person meets the criteria for treatment resistance, and may thus be in the clinical phase 3c. Approximately 30% of patients with first-episode psychosis manifest a minimal response to antipsychotics[156]. Recognizing treatment resistance earlier and treating these cases with clozapine[157] at this stage could produce larger benefits in several domains of outcomes, because of the greater retention of patients' personal and social agency[114,158,159].

Early interventions that can improve the well-being, functioning and social skills with reduction of burden on the family as well as treating comorbid substance use are similar to those described for the clinical stage 2.

Although it has been suggested that acute psychotic exacerbations represent active periods of a morbid process that leads to disease progression (the "neurotoxic hypothesis of psychosis"), to date there is limited empirical evidence to support illness progression after each relapse[143]. The mechanisms of toxicity have not been described[160] and supporting evidence is conflicting[161]. On the one hand, based on limited data, times to remission are significantly longer for the second and third episodes[162]; treatment discontinuation[163] and the effective dose[164] are higher during the subsequent episodes compared to the first one (suggesting reduced effectiveness of antipsychotics when reintroduced after illness recurrence); and relapse duration (but not frequency) is associated with gray matter alterations[165]. On the other hand, patients' symptoms return to baseline with resumption of antipsychotic medication after the relapse[148], and the pattern of treatment response across single episode and multiple episodes patients is not different and highly variable[163,166]. For example, emergent treatment failure after relapse is evident in 16% of the first-episode and 14% of the multi-episode samples respectively[163,166], replicating an earlier finding that 1 in 6 patients failed to recover from each of their first four relapses, irrespective of which relapse it was[167]. Finally, a subset of patients (23%) can even be treatment resistant at the time of illness onset, even before the first relapse[168].

It is important to note that, beyond the controversies regarding disease progression after each relapse, it is clear that each relapse is a traumatic experience associated with potentially serious psychosocial and functional consequences that are impacting the quality of life of the patient and the caregiver. Unfortunately, no clear interventions have been developed and validated for the tertiary prevention of disease progression from stage 3a to stage 3b (prevention of relapse recurrences), because second relapses are not consistently associated with robust modifiable risk factors such as non-adherence[119]. Similarly, there are no approved treatments to prevent progression to clinical stage 4. Overall, these data are in line with the limited evidence for substantial protective effects of antipsychotics on relapse prevention in the long term and highlight a clear need for further prospective research elucidating the role of relapse on illness progression in early psychosis.

Challenges and future directions

A new test to identify non-response to antipsychotics and reduce delay to clozapine usage

Recent studies suggest that, among treatment-resistant first-episode schiz-

ophrenia patients, 70% never experienced any symptomatic remission from the time of their first presentation, while 30% had achieved a symptomatic remission before developing treatment resistance during the first 5 years of illness[168]. Therefore, for the majority of cases, treatment resistance could be most appropriately addressed with clozapine at an early stage of its presentation, particularly given that early treatment with clozapine is effective[157], and that worse outcomes are seen with a delayed use of the drug[169]. In standard mental health services, the mean delay in initiating clozapine is 4 years[170].

A further possibility to accelerate the use of clozapine for treatment-resistant patients may be to use a diagnostic test to predict non-response to antipsychotics. A meta-analysis of 34 studies (N = 9,460) found that a <20% PANSS or BPRS reduction at week 2 of antipsychotic treatment predicted non-response at 12 weeks, with a specificity of 86% and a positive predictive value of 90%[171]. The use of this test in early intervention services can facilitate the switch to a second antipsychotic (ideally LAIs in patients with risk factors for relapse) and therefore minimize the delay to clozapine.

Another possibility could be to identify treatment-resistant patients at baseline. Research in this field is in its infancy, but a recent study suggested that it is possible to identify specific predictors of treatment-resistant schizophrenia[172].

Can we prevent negative symptoms?

The presence of prominent negative symptoms at baseline is one of the strongest predictors of poor outcome in first-episode patients[173,174]. Negative symptoms are twice as likely to become non-responsive to treatments than positive symptoms[140]. A recent meta-analysis found that no available treatment for negative symptoms reached the threshold for robust clinically meaningful improvement[175].

Poor social functioning, disorganized symptoms and schizophrenia diagnosis are baseline risk factors that can be used to identify first-episode patients at risk of developing negative symptoms[140]. Negative symptoms are also predicted by longer DUP[176], suggesting that programmes aimed at shortening DUP might reduce the prevalence of negative symptoms and improve prognosis of first-episode psychosis[177].

LIMITATIONS OF THE CLINICAL STAGING MODEL

Staging models have been widely adopted in oncology, because stages are defined by clear pathophysiological boundaries associated with discrete changes in mortality risk and treatment choices [174,178]. On the contrary, the example of ventricular enlargements highlights the lack of utility of current neurobiological measures to inform prognosis and treatment decisions in psychosis[179]. Translation from clinical to pathophysiological staging is not yet available in psychosis.

Variation in cancer severity within a stage (e.g., tumor size or number of metastases) has fewer implications for prognosis and treatment than variation between stages. This is not the case for psychosis, where high heterogeneity and variations within each stage (e.g., stage 2)[58] play a substantial role. Additional robust evidence is needed to support the incremental clinical utility of the discrete stages proposed (e.g., from stage 3 to stage 4)[178,180].

TOWARDS AN INTERNATIONAL COORDINATED SPECIALTY PROGRAMME FOR EARLY PSYCHOSIS

In conclusion, we show here that to improve outcomes of a complex, heterogeneous syndrome such as psychosis, it is necessary to globally adopt complex models integrating a clinical staging framework and coordinated specialty care programmes[133] that offer preemptive interventions to high-risk groups identified across the early stages of the disorder[181].

It is possible to improve outcomes of first-episode psychosis using stage-specific interventions that are comprehensive[182], i.e. ranging from the universal prevention of psychosis to strategies for overcoming treatment-resistant psychosis, and transdiagnostic, i.e. spanning broader spectra during the clinical stage 1 and the psychosis spectrum during the clinical phase 2.

Although we have detailed the key clinical strategies for improving outcomes at each clinical stage, it is clear that only a systematic implementation of these cost-effective[132] models of care in the national health care systems will render these strategies accessible to the 23 million people worldwide suffering from the most severe psychiatric disorders.

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What are the key ingredients of optimal psychosocial treatment for persons recovering from a first episode of psychosis?

In their comprehensive synthesis of what is known and remains to be learned about the treatment of first-episode psychosis, Fusar-Poli et al[1] offer an intriguing staging model and highlight several important challenges to the field. However, one topic to which they give relatively little attention is identifying the key components of the psychosocial treatments that are essential to comprehensive specialty care for these persons.

Just as pharmacotherapists must adapt what they have learned from treating long-term consumers to those experiencing a first episode of psychosis, so psychosocial researchers are expected to tailor interventions found effective for those who have been ill for years to meet the needs of those receiving treatment for the first time. In this commentary, we briefly outline two key issues that are yet to be resolved in defining optimal psychosocial treatment for persons experiencing an initial episode of psychosis.

The first key issue is: does cognitive-behavioral therapy for psychosis (CBTp) alone meet the needs of individuals diagnosed with a first episode of psychosis, or is a broader intervention required?

Most multi-component interventions referenced by Fusar-Poli et al have included CBTp, but the defining elements of that therapy are unclear across these studies[2]. Although there are similarities in the CBTp strategies, the models that have been used with consumers who have been ill for several years incorporate a wide degree of heterogeneity, and not all first-episode programs have employed individual interventions based on CBT.

Persons who experience their first episode of psychosis are typically in their late teens or early 20s, and often have a diverse set of developmental needs to be addressed in individual therapy. Therefore, a comprehensive yet individualized approach which is more encompassing than a typical course of CBTp may be desirable. For example, the individual resiliency training component of the NAVIGATE program[3] incorporates many elements of CBT, but also includes bolstering individuals' personal resiliency, education about psychosis, processing the psychotic episode, teaching illness self-management strategies, social skills training, substance abuse treatment, and health and wellness promotion.

A broad-based model such as this one may offer young people a wider range of options and empirically supported strategies for addressing their individual needs and helping them make progress towards their goals. At this point, we are lacking trials comparing more comprehensive individual interventions to CBTp in first-episode psychosis, so the optimal breadth of the individual intervention with this consumer group is unclear.

The second key issue is: does the prevailing evidence-based model of supported employment in psychiatric illness, i.e. individual placement and support, meet the needs of those recovering from a first episode of psychosis?

There is little agreement across the specialized integrated early intervention programs cited by Fusar-Poli et al in terms of the vocational supports required to help individuals return to school or work following a first episode of psychosis. Although three of the programs cited by the authors refer to vocational help or support, and one program refers to supported employment and education, it is unclear to what extent any of these approaches are suited to address the unique needs of individuals recovering from an initial episode of psychosis.

Recently, it has been suggested that early intervention programs for psychosis should include a component that places a premium on rapid job search or school enrollment for individuals with such goals, and the provision of follow-along supports to facilitate job retention or completion of educational degrees[4], based on the success of the individual placement and support model at improving competitive employment outcomes in persons with (typically longer term) severe mental illness[5].

However, there are many developmental challenges commonly experienced by most adolescents and young adults. Identifying and pursuing an appropriate career or educational path can be daunting and involve many false starts, even under the best circumstances. With regard to those recovering from a first episode of psychosis, it is unclear what proportion endorse work or school as an immediate goal[6], and individuals frequently cite barriers to returning to work or school[7].

Many young people who have developed a psychosis experience a profound sense of loss which further interferes with their ability to articulate work or school goals during early recovery. Most individuals entering a first episode of psychosis are enduring heightened psychiatric symptoms and are new to mental health care. They may be experiencing significant medication side effects and often require time to become socialized into treatment.

These issues can all impact on the "rapid job search" approach. For example, in the trial of the NAVIGATE program, at study entry all participants were assigned a supported employment and education specialist who was a member of their treatment team, but only 68% engaged in that component of the program (defined as meeting with their specialist three or more times)[8]. Furthermore, about one-half of the individuals who eventually engaged in that component did so after more than six months into the program.

The NAVIGATE results and other findings raise questions about the emphasis on rapid job search or school enrollment in supported employment and education programs, and suggest that more attention is needed early in the course of treatment to harnessing individuals' motivation by facilitating the exploration of work, school and career options to foster their ability to articulate specific personal goals related to role functioning.

Resolution of the differing vocational perspectives and goals of the consumer and involved family members may also

be required. While individual placement and support may have much to offer to first-episode consumers, even Bond et al[8] note that its effect sizes for competitive employment are smaller in first-episode samples and are not significant for educational pursuits.

A greater recognition and acknowledgement of the confusion and ambivalence of people who have recently experienced a first episode of psychosis, and a willingness to "meet the person where he or she is at" in order to instill hope and a sense of purpose for one's future, while permitting time for recovery, may be critical to enhancing the successful uptake of supported employment and education services before the mounting pressures of applying for disability become too great, and countervailing financial disincentives to work become a reality[9].

The questions posed in this commentary are not meant to be comprehensive. There are other important issues to be resolved in our understanding of optimal psychosocial treatment for first-episode psychosis, such as defining the role of peer providers, clarifying the necessary elements and ideal formats for family interventions, determining the need to include training in life skills as standard care, and resolving concerns about requisite intensity and duration of treatment to promote recovery. This is an exciting time to be supporting recovery in first episode and there is much to learn.

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Taking care of the carers: support for families of persons with early psychosis

A decade ago, we published research on the experience of families seeking treatment for loved ones with early psychosis in the Northeastern US[1]. Our sample was ethnically diverse, consisting of mostly mothers, a few fathers, a brother and an aunt. The resounding message was frustration, especially in respect to encounters with the mental health system.

The family of a young African-American woman described calling for help, and being met by a team of armed officers yelling and breaking down their door, then handcuffing their daughter. One mother described being told she had "three kids, two were good but one was not", and that she should "get used to it", as her son would "be like that the rest of his life". Another mother described waiting weeks to speak to the head psychiatrist, and then "the big cheese doctor came out and gave me the luxury of his presence for a few moments".

After discharge, families described psychiatrists declining care as their loved one was "too sick to treat", struggles with third-party payers and bills, and difficulty in convincing their loved one to go to appointments.

These themes were echoed in a contemporaneous qualitative research study with families of individuals with early psychosis in the Southeastern US, all African-American: they also described encounters with the law as the frequent first contact, grappling with stigma, and difficulty in accessing care[2].

In our study, across the board, families described a hunger for information and education: "a chance to ask questions would have been nice". Those families who reported getting useful information from doctors and staff expressed gratitude. They also welcomed the message of recovery: "I want any parent who has to hear for the first time that their beloved son or daughter is developing this illness to know that yes, they can become well"[1].

In the ensuing decade, the importance of including family members in early psychosis services has been increasingly recognized. In Europe, Australia and the Americas, there has been a concerted effort to develop specialty services for early psychosis that truly involve families. Among the earliest of these was the OPUS project in Denmark, initiated in 2000, for which integrated intervention comprises assertive community treatment, family involvement and social skills training. OPUS led to a decreased sense of burden among families, and greater satisfaction[3].

Researchers in Australia showed that, compared with "treatment as usual", combined individual and family cognitive behavioral therapy with psychoeducation led to less stress among family members and a greater sense of making "a positive contribution to the care of their relative"[4].

In the Northeastern US, early psychosis services have been developed and implemented by Dixon, Lieberman and colleagues, specifically the "Recovery After an Initial Schizophrenia Episode" RAISE Connection Program, that comprises two

years of coordinated specialty care promoting engagement, participation, and recovery[5]. Key elements include shared decision making, assistance in education and employment, social skills training, outreach, crisis services and, for families, engagement, psychoeducation, family nights, and as-needed consultation.

RAISE is collaborative, person-centered and sensitive to cultural and developmental issues. It improves symptoms and occupational/social function among participants. Families benefit as well. Families' experiences with RAISE were assessed in a recent qualitative research study[6], using similar methods as our studies from a decade earlier, also with an ethnically diverse cohort of mostly mothers, a few fathers, a sibling and a cousin. The contrast in themes over time was dramatic, illustrating the beneficial effects of caring also for the carers.

In RAISE, families described fear, worry, guilt, and a sense of helplessness before they arrived[6]. They were relieved to meet RAISE staff, who were warm, friendly and supportive, putting them at ease. Staff were seen as responsive, going above and beyond to help, showing they really cared, and increasing trust. Families in RAISE valued the outreach and support, frequent communication, flexibility and individualization of care, including concrete and practical assistance, and expressed a desire for individual counseling. And they wanted even more of this, in what the authors describe as "yes but more".

Families in RAISE also valued the flexibility and tailoring of services to client and family needs, including time and location, and the shared decision-making, including for medications, which were provided onsite without cost. Families described that it made a big difference to be listened to. As in the earlier studies, families also grappled with the tension of respecting autonomy, while also wanting to help and protect their loved ones, but now they were actively engaged in care and the promotion of recovery.

From these and other studies in Australia, Europe and the Americas, and now also Asia, we know that, for early psychosis, we can succeed in caring for families as well. The question then is how to broaden access to early psychosis services. It is important to demonstrate to policy makers that early psychosis programs are cost-effective, and RAISE Connection now has many sites across New York State.

Also, barriers to access, including stigma and geographical distance, must be addressed. In Australia, Orygen has moved its youth mental health services, including early psychosis services, out of medical centers and into the community, with great success (see oyh.org.au). Another proposal is to engage religious institutions, including churches, temples, mosques and synagogues[7]. Religious centers provide support for young people and families, including activities and networks, and often exist where mental health resources are minimal, including rural areas.

Another promising option is to use manuals or web-based services to help families of individuals with early psychosis. This has proven effective in Hong Kong, with the delivery of psychoeducation to a large number of families, in a culturally sensitive manner that reduces stigma, leading to reduced family burden and improved patient outcome[8].

In low- and middle-income countries, including in Africa, families might best be helped through a public health approach of population-level psychoeducation to reduce stigma, integration of services into existing health care, free access to medications, and practical support and training that enables families to care for their loved ones[9]. In Chile, for example, the GES (Garantías Explícitas en Salud) program, backed by a state law, has provided global access to free care for schizophrenia, including "suspected cases", leading to lower rates of rehospitalization, and better outcomes for patients and families[10].

These are successful and promising approaches to caring for families of young people with early psychosis. Our task is to broaden access to these services worldwide in a culturally sensitive and cost-effective manner. As clinicians, we must be willing to listen to patients and families and learn from them, and provide them with material support and information, doing so in a flexible, respectful and empowering manner. We must also fight stigma, and advocate for and promote recovery for our patients.

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Taking a Bleulerian perspective: a role for negative symptoms in the staging model?

In their well-wrought overview of the evidence on interventions to improve the outcomes of first-episode psychosis, Fusar-Poli et al[1] adopt a revised staging approach. One of the most prominent new features of this model is the distinction of three different clinical stages of high risk for psychosis, starting with a stage defined by negative and

cognitive symptoms (1a), followed by one characterized by attenuated psychotic symptoms (1b), and one of short-lived remitting psychotic episodes (1c). These stages precede the stage 2 full-blown first-episode psychosis, defined by early full recovery.

Though the authors acknowledge the lack of a pathogenetically driven staging model, and imply that the joints of nature could have to be carved at different places the more pathogenesis is clarified, their revised model does account for the early initial prodromal state as delineated in German literature, starting with early cognitive and negative symptoms, even before the first positive symptoms emerge. The transition rate at 2-year follow-up from stage 1a to full-blown psychosis (stage 2) has been shown to amount to 3%, while it is 19% from stage 1b and 39% from stage 1c[2].

Stage 1a seems a valuable addition to the staging model, on several grounds. Negative symptoms are the most important predictor of outcome in first-episode and early-onset psychosis according to a number of studies[3,4]. Long-term functional outcome of first-episode psychosis is highly correlated to negative symptomatology, much more so than to positive symptom severity or duration of untreated psychosis[5]. In spite of the relatively low transition rate to a full-blown psychotic stage (symptomatic outcome), due to the poor specificity of sole negative symptoms, the prediction of diminished functional capacity irrespective of diagnosis might be stronger than transition rate to psychosis would suggest.

Maybe the emphasis on positive symptomatology in the current staging models has something to do with the different treatment perspectives of the two symptom dimensions: as Fusar-Poli et al emphasize, there is still not much we can do against negative symptoms, while positive symptoms are far more amenable to treatment, particularly with antipsychotic drugs. The less complicated operationalization of criteria for and assessment of positive vs. negative symptoms may also have contributed to the less prominent role of the latter in staging and operationalized criteria.

Fusar-Poli et al provide one more argument to emphasize the importance of negative symptoms. They cite the literature showing that recovery rates (one in seven) and associated disability (11th cause of disability worldwide in 2013) have not improved over the past 70 years, and that antipsychotics can reduce some symptoms, but have little impact on the outcome of the illness[6]. This is in line with the lack of stringent evidence for a robust effect of antipsychotics on relapse prevention on the long term[7].

If the dopamine blockade exerted by antipsychotics is now mostly considered a symptomatic therapy, not really altering the course of the disease, one might wonder whether the derangement of the dopamine system during florid psychotic episodes is at the core of the disease, or mainly a consequence of primary derangements higher upstream, e.g. in the GABA-ergic parvalbumin interneuron system, and/or the glutamatergic input into that and other systems[8]. If this is the case, there might be other trajectories leading to dopamine derangement, perhaps more benign and self-limited[9], not based on a more fundamental interneuron deficiency, but on environmental factors such as cannabis use or traumatic experiences.

Following this somewhat speculative reasoning, the lack of specificity of the stages 1b and 1c, mainly based on positive symptoms, would be the consequence of the heterogeneous causes of excessive dopamine activity (associated with positive symptoms), of which the more persistent negative symptom-related lack of inhibitory power due to GABA-ergic deficits would be only one. In a brain with a primary dysfunctional excitation-inhibition balance, episodes of positive symptoms might represent a decompensated stress-adaptive mechanism driven by dopamine.

Thus, the occurrence of positive episodes embedded in a negative syndrome is probably what should really warn us for prognostic risks. The poor prognosis associated with the diagnosis of schizophrenia might be mainly attributable to this combination. After all, the negative symptom dimension is one of the main constituents of the operational criteria for a schizophrenia diagnosis, with its persistence in time, association to relapse proneness and functional decline, and poor response to treatment.

Though essential knowledge is lacking to refute or confirm this hypothesis, it might be worthwhile for research purposes to suggest a staging approach using both symptom dimensions, with negative symptoms not limited to stage 1a, but also running along the other stages, at least including stage 2, that are currently only operationalized by positive symptoms and relapse.

Regarding the treatment recommendations for stage 2, the first episode with full recovery, the authors do acknowledge the symptomatic nature of antipsychotic treatment. Though the persistence or not of negative symptoms is not mentioned, most first-episode psychosis samples include patients with persisting negative symptoms after treatment response. Fusar-Poli et al mention the conceivable advantages of the recommendation by ourselves and a number of other authors[10] to individually adjust dosage reduction of antipsychotics to the lowest dose that is still effective to redress positive symptoms. This is aimed to prevent not only extrapyramidal and metabolic side effects, but also the induction of subjective side effects due to dopamine blockade in the ventral striatum and reward circuits, which may be denoted as subtle extrapyramidal side effects.

The authors argue in favour of research into the characteristics of patients who will do better on low doses or even discontinuation of antipsychotics. However, their suggestion to exclude patients with a schizophrenia diagnosis might have been worded better by suggesting research across all non-affective psychosis categories, investigating the role of baseline negative symptoms as a very suspect candidate for predicting unsuccessful dosage reduction, more relapses and shorter time to first relapse with respect to symptomatic outcome, and failure to regain functional capacity with respect to functional outcome.

At present, it is unknown whether higher maintenance doses of antipsychotics would lead to better outcomes in

patients with more severe negative symptoms, since antipsychotics tend to worsen these symptoms, probably also affecting functional outcome. However, the dopamine system, in a number of these patients, might be so brittle that dosage reduction inevitably leads to relapse. On the other hand, patients who use cannabis at baseline might have a more important environmental causation of their dopamine derangement, tend to show less negative symptoms, and may be less likely to respond unfavourably to dosage reduction[11]. Several trials are now underway to clinically evaluate dosage reduction in remitted first-episode schizophrenia patients, that will hopefully answer some of these questions.

Finally, the authors' view that in later stages (3 and 4) dosage reduction will probably not be an answer, while the still underused and often delayed antipsychotic drug clozapine might substantially improve outcome, though convincing, requires a more substantial research support.

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Early intervention in psychosis: p-values, policy, and politics

Psychosis is among the most disabling, persistent and poorly understood medical conditions. The staging of psychotic illness outlined in Fusar-Poli et al's paper[1] is innovative, but is only as useful as the *magnitude* of the effectiveness of available treatments at each stage and of the differences in effectiveness between stages. While some statistically significant experimental data support "stage 1" interventions targeting people at high risk but without manifest psychosis, and "stage 2" interventions for patients with recent-onset psychosis, there is no evidence to suggest that treatments are more effective at one stage than another and thus are stage-specific. The authors call for the global implementation of early intervention in psychosis, and of the staged approach more specifically, but p-values do not by themselves justify policies or suggest their political salience.

It is sometimes mistakenly expected that statistically significant scientific findings have, by themselves, policy and political importance. Although there is a logical sequence leading from scientific findings to policy proposals and then to political action, there is no tight link between the three, because each represents only one of many inputs into the next. Good science does not always find a practical policy application, and rational policy is not assured of political success. The discovery of effective HIV treatment, by itself, generated neither a credible policy for making it available, nor political agreement about how to do so.

Following the example of cancer research, long-term prospects for early intervention studies are based on the hope that incremental steps will eventually add up to major gains. Data from numerous rigorous studies show statistically significant positive outcomes of early intervention for symptoms, quality of life, employment and school participation, reduced hospitalization, substance use, depression and others. There is also evidence that potentially mediating indicators can be significantly improved such as delayed onset of psychosis, reduced duration of untreated psychosis, lowered family burden, and increased retention, trust and satisfaction.

But we are also faced with sobering counter-observations[1]. Three trials of interventions at stage 1 had negative findings, possibly because of the difficulty of prospectively identifying patients who will develop psychosis, or low statistical power. Small trials in stage 2 showed "minimal beneficial effects or no effects at all on clinical outcomes"[1], and in large trials benefits have rarely been shown to last beyond two years. Further, Fusar-Poli et al's systematic review of randomized controlled trials[1] failed to show statistically significant benefits of early intervention on preventing relapse or rehospitalization. The paper's section on antipsychotics suggests that these medications, while undoubtedly beneficial, may delay, but do not prevent, relapse. The presentation of both enthusiasm for positive results and candor about negative results, while jarring at times, ultimately reflects a high level of scientific integrity.

In the end, the authors conclude that "to improve outcomes... it is necessary to globally adopt complex models integrating a clinical staging framework and coordinated specialty care programs"[1]. This conclusion, however, represents a leap from the realm of p-values to advocacy for a global initiative encompassing "national health care systems", a bold proposal that would likely require a level of political commitment similar to that which has characterized the global fight against the HIV epidemic.

Effective intervention in psychosis is, without doubt, desperately needed worldwide. The 2015 Global Burden of Disease Study estimates the disability-adjusted life years (DALYs) attributable to schizophrenia as 15,020,500 years, more than three times the 3,989,900 DALYs for HIV[2]. But the available data suggest that, in spite of this immense need, early

intervention may not yet be a scientifically supportable or politically practical path. When we move from the realm of experimental outcome research to that of political action, we leave the realm of p-values (tests that show only that observed benefits in specific experimental studies are not simply due to chance) to a realm of policy analysis, in which large magnitude effects and grossly favourable balance sheets of benefits and costs may be needed to carry the day. For example, the RAISE Early Treatment Program, sponsored by the National Institute of Mental Health, perhaps the largest US study of intervention for early psychosis[3], showed that the intervention was superior to usual care at $p<0.05$, but the effect size (Cohen's d) for quality of life gains was 0.31 and for symptom reduction was −0.29, reflecting small to moderate effects.

At several points Fusar-Poli et al's paper assures readers that early intervention is cost-effective. However, of the three studies cited, one is a modelling effort based on judgments of clinical experts and selected publications[4]; a second is based on a "narrative review"[5]; and only the third is based a large randomized trial[6]. That study found increased benefits but also increased costs and concluded that the benefits, when converted to quality adjusted life years and then to dollars, were indeed greater than the costs. These three studies are not likely to be sufficiently robust to attract major national or international support and funding. The negative findings of the authors' systematic review on relapse and re-hospitalization make it unlikely that savings can be realized that would be sufficient to pay for intensive early intervention.

Taking the proposed initiative at face value, it may be informative to consider the process, beautifully described by H. Varmus[7], that led President G.W. Bush to initiate the President's Emergency Plan For AIDS Relief (PEPFAR). By 2014 PEPFAR had provided antiretroviral treatment to over 7.7 million people, supported HIV testing for more than 57 million people, and seen commitments of $70 billion from Presidents Bush and Obama[8]. Could PEPFAR be a model for the proposed worldwide early intervention effort? At a minimum, it is a lesson on the political and scientific complexities involved in moving a global initiative into practice. According to Varmus, President Bush was highly skeptical about foreign aid, but impressed by the remarkable advances in HIV treatment, with life expectancy for an HIV positive 20-year old increasing from 39 years of age in 1996 to 73 by 2011[9]. Bush further insisted on a high level of accountability and his support seems to have been won by the promise that changes in HIV mortality could be readily tracked.

If the data reviewed here do not seem strong enough to support a "PEPFAR" for early intervention in psychosis, they may yet inspire more modest but exceptionally defensible, albeit challenging, objectives for stages 3 and 4 interventions. These objectives would include: a) making antipsychotic medication available with appropriate supervision to all who need it, worldwide, b) assuring respect for basic human rights of people with psychosis, and c) reducing stigma, an extraordinarily challenging goal that may, nevertheless, be the key to achieving objectives a) and b).

The optimism engendered by early intervention studies has inspired wealthy countries such as Australia, the UK, Denmark, and recently the US, to publish recommendations for and funding to support early intervention programs. Even if not yet robustly justified by outcome or cost-effectiveness data, such initiatives provide humane, trust-engendering support to patients and families at a moment of heartbreak in their lives. By drawing attention to the unquestioned need for expanded intervention for psychosis across the globe, and to the hope for further advances in early intervention, Fusar-Poli et al's paper reminds us of the urgency of laying solid foundations for a much-needed "PEPFAR" for psychosis in the years to come.

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An international response to improving outcomes for first-episode psychosis is warranted, but more needs to be done to make it happen

Fusar-Poli et al[1] propose a staging model for first episode of non-affective psychosis and put together an impressive summary of the current state of evidence in relation to interventions matched to these stages. They also highlight the effectiveness and limitations of current prevention strategies for people at risk of developing psychosis, outline some of key issues in relation to improving interventions for people with an overt episode of psychosis, and flag important risk factors that influence their outcomes. Finally, they stress upon the need to develop coordinated specialty programs globally that

are integrated within national health systems.

However, as they point out, the current evidence does not suggest that primary prevention strategies have any reliable impact on attenuating the longer-term course of the illness, even though they positively impact some important treatment-related outcomes. What is even more concerning is the limited uptake of screening, detection and referral to specialist services of people with emergent psychosis (stage 1c) in existing secondary services, where such strategies might be the most effective.

On the other hand, the evidence base around the effectiveness of early engagement and treatment with people with an overt psychotic episode (stage 2) through multi-component interventions is more robust in terms of reducing the duration of untreated psychosis and improving treatment-related variables and functional outcome for both the person and caregivers. However, these interventions again do not seem to reduce the chance of relapse and thus a progression into stage 3. While strategies like early initiation of long-acting injectable antipsychotics, reduction of illicit substance abuse and a longer duration of engagement with specialist services can potentially improve outcomes, their impact on the longer-term course of the illness continues to be limited.

Any disease staging process is based on the assumption that the defining variable(s) chosen to measure progression of the illness are closely linked to the underlying pathophysiology and strongly predictive of outcomes. As the authors point out, neither of these conditions is satisfied in the case of first-episode psychosis, where heterogeneity between and within the stages is common. The absence of reliable neurobiological measures of psychosis is a critical gap in developing targeted stage-specific interventions and, till these are available, the staging outlined in Fusar-Poli et al's paper should be considered as provisional in nature. In the short term, the staging process can be progressively refined by future research that specifically examines potential neurobiological mechanisms underlying the functional outcomes, an explicit focus on the elucidation of more robust moderating and mediating variables, and efforts to include population-based cohorts to reduce selection bias that limit the generalizability of findings.

It needs to be emphasized that the evidence presented in support of the staging process and matched interventions is derived from selected cohorts receiving dedicated treatments in high-income settings, where substantial investments have been made to make specialist first-episode psychosis services available. Thus, the essential precondition in making comprehensive, stage-specific, matched interventions more widely available is the presence of a well-functioning health system that can provide accessible, affordable, comprehensive and continued care.

Globally, the overwhelming majority of people who experience a first episode of psychosis live in low- and middle-income countries and, in many of them, community-based mental health systems are either non-existent or rudimentary[2]. Thus, the majority of such persons are unlikely to receive any treatments; for example, the recent national mental health survey in India has estimated that the treatment gap for people with a current diagnosis of psychosis is more than 75%[3].

In such situations, it is extremely unlikely that rolling out resource intensive and specialist driven interventions for people at clinical high risk for psychosis will be feasible or become a national health priority in the face of scarce human and financial resources. A more realistic option might be to develop locally feasible and culturally appropriate methods for the early identification and treatment of people with a first episode of psychosis (stage 2 onwards) through a combination of wide community engagement methods and task sharing with other trained and supervised non-specialist health workers and community volunteers.

There is no doubt that, given the enormous unmet need and therapeutic potential of services for people with a first episode of psychosis, there is an urgent need to develop and evaluate adaptations and innovations that are feasible, acceptable and cost-effective in low- and middle-income country settings. The ongoing Jan Man Swasth (People's Mental Health) program in India shows that early intervention is feasible in rural Indian settings by adopting a three pronged approach: firstly, through intensive community engagement using culturally adapted methods; secondly, through the availability of trained accredited social health activists who are embedded in the local community as the first point of contact; and third, through effective linkages with community-based treatment teams which provide need-based comprehensive treatments.

Making services for first-episode psychosis more widely available beyond high-income country settings is necessary but challenging, and an area where dedicated research attention is warranted as a matter of priority.

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Early intervention services are effective and must be defended

Three world leading researchers in the field have written a comprehensive review[1] of the current evidence for improving outcomes in first-episode psychosis. As they point out, based on the Global Burden of Disease study, there are currently 23 million people worldwide living with schizophrenia. Half of these people are untreated, and the majority of the other

half are likely to receive suboptimal treatment. Schizophrenia is ranked as number 12 among conditions leading to years lost to disability. This summary of the current evidence was highly needed, and the obvious next step could be a set of recommendations launched by World Health Organization and endorsed by health ministers all over the world. The main focus of our commentary is to identify which findings call for immediate implementation.

Interventions to shorten duration of untreated psychosis should certainly be implemented. Partly due to lack of agreement on operationalized criteria, this duration varies widely among studies, but it has consistently been found to be a predictor of short- and long-term outcome after a psychotic disorder. The effect of duration of untreated psychosis on outcome could both be biological (permanent changes in brain function) and of a psychosocial nature (as the disintegration of the patient's social network prior to treatment could have a long-term effect).

A short duration of untreated psychosis means that treatment is provided within the early course of illness. Patients suffer from severe social and clinical consequences of absent or insufficient treatment in early phases of psychosis, and therefore can be especially receptive to interventions in these early years. If the now established specialized early intervention teams want to exert their maximal effects, widespread interventions to reduce the duration of untreated psychosis should be implemented. The Treatment and Intervention in Psychosis (TIPS) study showed how society level interventions could reduce that duration and affect the long-term outcome[2], and we are awaiting the results of a German study testing the effect of society level awareness campaigns combined with specialized early intervention teams[3].

Fusar-Poli et al[1] conclude that there is sufficient evidence to recommend that specialized early intervention programs be implemented. It is beyond doubt that the current huge variation in implementation worldwide cannot be justified by lack of evidence. Even in high-income countries with large health budgets there are large variations, spanning from almost complete nationwide coverage in Denmark and England to almost no services available in many other European countries. These differences are likely due to local traditions more than scientific evidence.

Health economic analyses of specialized early intervention find it to be cost-effective on the long term[4], but this intervention requires more resources "up front" and this leads to its achievements always having to be defended from cuts in funding by politicians and health administrators. This is why it is imperative to have high-quality research proving its efficacy.

Further, we need to protect the specialized early intervention teams from "drifting back to ordinariness". This drift could be due to political pressure regarding measurable productivity goals, but also the sentiment of the team members. It is therefore important to engage the clinical staff in an ongoing debate both with researchers and among themselves. To ensure that the treatment provided still lives up to the standards originally tested, it is central to develop fidelity measures. Fidelity scales work as a safety mechanism and should also be viewed as a tool to empower the clinical staff in defending the treatment from cuts in funding and inauspicious reorganizations.

The duration of specialized early intervention programs is an important issue. The Early Assessment Service for Young People with Early Psychosis (EASY) trial, comparing 3 vs. 2 years of specialized early intervention, has recently published 5-year follow-up data and, while there was initial evidence that the prolonged intervention had effect on negative and depressive symptoms, these gains were, as in prior trials, lost when the intervention was terminated[5].

We have recently published data from our trial (OPUS II) comparing 2 vs. 5 years of specialized early intervention[6], and there are further ongoing trials testing similar prolonged interventions[7,8]. In the first OPUS trial (OPUS I), we found that participants randomized to the intervention group relapsed when transferred to standard treatment after 2-year OPUS intervention. We therefore anticipated that this relapse could be prevented by prolonging the intervention in the second trial (OPUS II). Surprisingly, we found no sign of relapse neither in the control nor in the intervention group, and the overall pattern in both groups was that participants improved over time on most functional, psychopathological and cognitive outcomes. The prolonged intervention did not improve further on this already positive trajectory, except for better user satisfaction and working alliance. The most likely explanation for this finding is improvements in the treatment-as-usual arm. Participants randomized to this arm were in most cases referred to community health centres after termination of their 2-year OPUS treatment, and 20% of them received assertive community treatment. We therefore concluded that the early gains seen in treatment of first-episode psychosis by specialized early intervention teams can be upheld either by prolonging the treatment or by providing high-resource standard care with the possibility of assertive treatment for the most debilitated patients.

Regarding the duration of antipsychotic medication for remitted patients, Fusar-Poli et al[1] mention that treatment reduction may be an option for first-episode psychosis patients who have achieved clinical remission and are not at high risk of relapse. Recent studies based on long-term results from the OPUS trial document that such patients exist, and that a proportion of remitted patients with schizophrenia and schizophrenia-like psychosis will discontinue antipsychotic medication with or without doctors being involved in their decision[9,10]. In order to protect patients from side effects, further studies are necessary focusing on the identification of the subgroup of patients who can stay in remission without antipsychotic medication.

Finally, we want to point out that the early intervention services now provided in many countries have been part of a very significant change in the view of mental disorders and mental health care. The evidence supporting the introduction of these services is strong and should lead to even more widespread implementation. What is needed is a long-term,

high-resource commitment by policy makers to develop and uphold the positive gains obtained. It is time to rally behind the banners, protect the ground already covered, and push forward.

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Advances and challenges in early intervention in psychosis

Fusar-Poli et al[1] offer a "state of the art" account of what is possible to do for prevention and early intervention in psychotic disorders. As they correctly point out, "indicated prevention" directed at individuals at an elevated clinical high risk for developing a psychotic disorder is at present the closest we can get to any level of prevention.

However, the specificity of the clinical high risk state for psychotic disorders may depend partly on the service context within which such cases are defined and followed. While it may hold for clinical high risk patients in specialty clinics, the same may not be true in services for general psychiatric populations. This is suggested by two streams of evidence: first, childhood psychotic symptoms are not associated exclusively with the later onset of psychotic disorders[2]; second, the relationship between psychotic experiences and a variety of mental disorders has been shown to be bidirectional in a large international population based study[3]. Thus, psychotic disorders may not be the only consequence of early psychotic experiences, while clinical high risk for psychosis may be something other than a "diluted" form of psychosis[4].

An equally, if not more, important consideration is the inverse question that remains unaddressed: whether most first-episode psychosis cases emerge via a clinical high risk state. Initial reports suggest that less than half of cases have gone through such a state prior to onset of psychosis[5], leaving a substantial proportion who may have experienced only non-psychotic symptoms. There are different lenses through which a staging model of psychosis is viewed: one that considers a first episode of psychosis as a progressive enrichment of an earlier "psychosis-like" state; and the other as a transdiagnostic model in which early stages have pluripotential outcomes[6]. Further, a staging model that relies almost exclusively on symptoms may miss some earlier stages where the presenting problems may be more social and functional[7].

The difficulties associated with identifying all or even the majority of individuals with clinical high risk for psychosis are well recognized. However, this challenge may be better addressed by structuring services around a transdiagnostic staging model. To facilitate a higher rate of penetration into the true prevalence across all clinical high risk states, the entrance point for mental health services needs to be made more easily accessible rather than being embedded in the current multi-layered systems. An enhanced primary care system with direct connection to speciality programs, such as early intervention services for psychosis, is more likely to achieve a higher yield of cases at both at-risk as well as first-episode psychosis stages, aided by the use of digital and mobile technologies favoured by young people.

As the authors suggest, selective intervention for clinical high risk subjects may promote better outcome for first-episode psychosis, beyond delaying or preventing psychosis through better service engagement. On the other hand, there is some evidence that individuals with clinical high risk states who develop psychosis despite interventions known to reduce conversion to psychosis may, in fact, have a worse course and outcome[8]. Such variation in outcome will also depend on whether the clinical high risk state is ultimately found to be a common phase *en route* to a first episode psychosis: if not, then interventions aimed at those states, however effective at the individual level, will ultimately have limited ability to improve outcomes for the first-episode psychosis population as a whole.

The authors also quite correctly emphasize the importance of preventing further decline following treatment of first-episode psychosis. However, an exclusive emphasis on relapse to gauge clinical outcomes may not be adequate, for several reasons, including variation in the definition of what constitutes a relapse, reliance on hospitalization as a proxy for relapse and, most importantly, variation in the length of a relapse. It may be better to monitor and sustain longer periods of remission of both positive and negative symptoms, given the consensus on an operational definition of remission[9] and the very high proportion of variance in functional outcome explained by the length of remission[10].

While earlier use of long-acting injectable antipsychotic medications, as suggested by the authors, may improve chances of symptom remission, their use within the context of multi-component psychosocial interventions provided in early intervention services may add further benefits. Despite this, nearly half of

fully remitted patients may not achieve a satisfactory functional outcome[11], due to several reasons, including persistent negative symptoms, untreated comorbidity (e.g., social phobia), substance abuse, unstable housing and self-stigmatization. These impeding factors are likely to require targeted psychological interventions. For example, for negative symptoms, pharmacological interventions are likely to have limited effect, while several specific psychological and psychosocial interventions are likely to be more effective[12].

Two other considerations may facilitate improvement of outcomes in first-episode psychosis and in clinical high risk states. A greater emphasis on patient and family perspectives and processes involved in facilitating recovery is needed to improve outcome. Further, in the current environment, digital technologies are being increasingly investigated for additional benefits to promote recovery and prevent relapse following treatment of a first episode of psychosis. Last, but not least, the enormous global burden of psychosis, that the authors quite rightly refer to, will need a global effort that involves understanding of suitable models of care for populations that differ on culture, economy, geography and politics.

To summarize, early interventions for psychosis may be best conceptualized as comprising two components, one attached closer to an enhanced primary care mental health service designed for this age group and a second of more specialized care for both at-risk states and full fledged serious mental disorders, such as psychoses. The former would provide an entry point for those at risk for not only psychosis but also other moderate to severe mental disorders, while the latter would assure a state-of-the-art multiple component treatment framework with established evidence of effectiveness. Further research is needed to identify methods that would assist in matching patients to appropriate intensity and length of service based on the stage of illness.

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Moving interventions from after to before diagnosis

Some twenty years ago, the onset of psychosis was seen as the first sign of a schizophrenia spectrum disorder. Large scale epidemiological studies have since shown that, before the first psychotic episode, several deviations of normal development take place in (at least part of) the youngsters who later develop schizophrenia. While in childhood there is an average delay in reaching milestones such as walking, talking and reading, the most salient deviation during the teens is the decreased interaction with peers and decreased academic performance[1].

Children who later develop a psychotic disorder may have some deviant behavior, with schizotypal or schizoid features, which is expressed as few (or no) close friends and fewer social connections in sports, teams or hobbies. Occasional perceptual aberrations and magical beliefs are experienced by some 40% of children who later develop schizophrenia[2,3]. In the second decade, cognitive decreases become apparent, which can be observed as lower school level than that of sibs and parents, doubling of classes or even quitting school[4,5]. Finally, after puberty, subclinical psychotic symptoms emerge (or increase), which indicates the ultra high risk (UHR) period.

Of course there are many exceptions, and some youngsters will develop a first psychosis out of the blue, with perfect social and cognitive skills antedating it. Yet, at least half of psychotic patients show a trajectory which provides clues for early recognition and interventions. All larger cohorts of UHR individuals show that cognitive decline is the clearest predictor of transition to psychosis[5-7], together with severity of subclinical psychotic complaints.

Animal models, genetic information, imaging studies in high risk groups, studies in children with 22q11 deletion syndrome, and post-mortem studies have shed light on neurobiological deviations that take place in these early phases, before the so-called first psychotic episode. Decreases in GABA functioning, especially of Chandelier cells, reduced NMDA receptor activity, increased oxidative stress and insufficient scavengers (especially glutathione), increased pro-inflammatory status of the brain and lower mitochondrial functioning add to varying degree to an individual's susceptibility towards developing schizophrenia. Some of these neurobiological deviations can be measured *in vivo* (i.e., glutathione and GABA concentrations by magnetic resonance spectroscopy; inflammatory status by positron emission tomography), whilst others cannot (density of Chandelier cells). This knowledge provides a basis for potential targeted treatment of specific susceptible subgroups of individuals with the same phenotype, but is not yet ready for clinical use.

Epidemiology, cohort and case-control studies provide evidence of several risk factors occurring in the teenage period that can further increase risk of onset of psychosis. Among them are drug abuse, bullying, social exclusion, sleep deprivation, stressful events, inflammatory conditions and immigration.

At the same time, pilot studies on interventions in the preclinical period have been performed, that showed efficacy of cognitive behavioural therapy (CBT) (although not compared to an active control condition)[8] and of nutritional supply of omega-3 fatty acids (although not replicated in a larger group)[9].

At present, we do not know everything we would like to know to act early to prevent transition to psychosis in vulnerable youngsters, but we do have some basic clues on which we can act already. Each year we wait to complete our knowledge, many youngsters go on to develop a schizophrenia spectrum disorder. This topic should be a high priority in psychiatric research, as even UHR individuals who do not develop psychosis tend to manifest (other) severe psychiatric problems. A psychiatric disease affecting an adolescent or young adult has a large impact on the person himself, but also on his family, surrounding and society at large.

There are several ways forward, both for researchers and for health care workers. For the latter, schools are the most important partners for collaboration, since cognition is such an important risk factor. Cognitive decline is first detected at school, and lower functioning than in previous years, with a prominent deviation from sibs, should be a reason to contact health care workers who can screen for (subclinical) psychotic features. When these are present, a working alliance between mental care workers, family and school should be made to prevent further hits, i.e. prevent the youngster from starting to abuse drugs, actively avoid (or stop) being bullied and socially isolated, regulate exposure to stress and sleep.

For researchers, individual neurobiological deviations at the UHR stage need to be tested for correction with specific interventions, such as supplementation with n-acetylcysteine to restore glutathione function, glutamatergic or GABA-ergic agents to improve signaling of the inhibitory interneurons, and omega-3 fatty acids or anti-inflammatory agents to restore optimal brain condition. In addition, CBT for UHR needs to be compared to other psychosocial interventions, and efficacy has to be tested at group level and in specific patient groups.

In short, there is much work to do for all of us in order to prevent transition to psychosis of vulnerable youngsters, and we need to make haste.

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Early intervention in psychosis: much done, much more to do

While the term dementia praecox is usually credited to Kraepelin, it was B.A. Morel who first used it in 1852 to describe a 14-year-old: "His brilliant intellectual faculties underwent in time a very distressing arrest. A kind of torpor akin to hebetude replaced the earlier activity. In the hospital, the adolescent improved physically, worsened mentally and eventually was considered a hopeless case"[1].

Morel was describing a presentation rather than a diagnostic category. The "hopeless", chronic and progressively deteriorating course became for Kraepelin the unifying feature of some mental disorders included in the category of dementia praecox. Bleuler broadened the scope of the diagnosis, identifying a set of basic symptoms (the four As, now considered negative symptoms). We now know that neither chronicity nor any set of basic symptoms is pathognomonic of schizophrenia. Our understanding of many aspects of the condition remains uncertain; we can claim neither accuracy nor precision in our diagnosis. Schizophrenia seems to capture Pearson's concept of uncertainty not due to limits of technology or measurement but inherent in the nature of the phenomenon being studied[2].

Fusar-Poli et al[3] remind us of many areas of uncertainty that still linger in the diagnosis, management and outcome prediction of first-episode psychosis, where the development of early intervention services has raised several new questions while partially answering some old ones. These services improve short- to medium-term outcomes of first-episode psychosis. Some forms of targeted interventions for "at risk mental states" appear to delay the emergence of frank psychosis. A staging approach to the broad category of psychosis might offer new opportunities and avenues for research and clinical practice. Of all this we can be certain. The rest is in a state of equipoise, and we are some way from understanding this most human of all conditions. Psychosis (including schizophrenia) is basically a disorder of the self. The subjective self remains elusive to the observer, just like disorders of the self do.

Despite the uncertainties and contentious debates about the boundaries and limits of diagnostic categories of psychosis, we can still be proud of some of the changes heralded by the early interven-

tion movement. We were lucky in the UK to receive significant new investment for the establishment of early intervention services in 2004 and have recently been set a highly ambitious target to reduce the duration of untreated psychosis. From April 1, 2016, more than 50% of people experiencing first-episode psychosis should commence on the package of care recommended by the National Institute for Health and Care Excellence (NICE) within two weeks of referral.

In the intervening decade, we have learnt interesting and unexpected lessons from the development of early intervention services. A surprising contributor to duration of untreated psychosis is delays within generic secondary mental health services, especially if sufferers have first sought help from child and adolescent mental health services[4]. Duration of untreated psychosis is malleable; developing a direct care pathway combined with a public awareness campaign can almost halve its length[5]. Just developing early intervention services, even when these do not have a specific early detection function, can reduce duration of untreated psychosis and hence ensure prompt and early treatment of first-episode psychosis[6].

We should not be surprised by how much remains uncertain. Kraepelin thought that schizophrenia was a single disease entity, akin to tertiary syphilis with its progressive decline and deterioration. Bleuler recognized the heterogeneity of the disorder, regarding it as a genus rather than a species[7]. Early intervention services deal with broad psychosis rather than narrow schizophrenia. No wonder that this has increased areas of uncertainty. We are at the same stage of our understanding of the pathophysiology of psychosis as the ancient world was about dropsy, which for centuries was treated by mechanical removal of fluids from the body (bleeding, leeching, lancing, etc.)[8]. It was only when the renal and cardiac causes of dropsy were differentiated that medicine started developing treatments specific to aetiology. Psychosis is very likely the final common outcome of a number of different psychopathological processes. If our current treatments are symptomatic rather than curative, this simply reflects our limited understanding of the underlying causes. Dopamine dysfunction is a mechanism of symptom production, not a cause of psychosis, hence antipsychotics only relieve symptoms. Fundamentally altering the course of the disorder or preventing it in the first place will take several new advances in neuroscience. Social epidemiology has confirmed several environmental factors that increase the risk of psychosis. The biological underpinnings of psychosis are likely to be epigenetic rather than DNA sequence based, and the "prism of epigenetics" may yield clues where traditional genetic or environmental paradigms have fallen short[9].

Early intervention services have had a profound impact on clinical practice and user experience, which is rarely measured, often intangible, not factored into trial designs and hence rarely commented upon, but one that is evident to those who have worked before and after these services have become available. We no longer consider a 14-year-old with emerging psychosis as a "hopeless case". The UK Schizophrenia Commission Report[10] noted: "We have seen what can be achieved with the approaches to care and treatment in the early intervention in psychosis services which focus on solutions. Today, instead of a life sentence, young people in early intervention services are given hope. They are supported to recover, with many returning to college or the workplace to live an ordinary life like everyone else".

This is a fundamental clinical, conceptual and philosophical shift, and its effect is experiential, like psychosis itself.

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Comparing three-year extension of early intervention service to regular care following two years of early intervention service in first-episode psychosis: a randomized single blind clinical trial

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This study aimed to determine if, following two years of early intervention service for first-episode psychosis, three-year extension of that service was superior to three years of regular care. We conducted a randomized single blind clinical trial using an urn randomization balanced for gender and substance abuse. Participants were recruited from early intervention service clinics in Montreal. Patients (N=220), 18-35 years old, were randomized to an extension of early intervention service (EEIS; N=110) or to regular care (N=110). EEIS included case management, family intervention, cognitive behaviour therapy and crisis intervention, while regular care involved transfer to primary (community health and social services and family physicians) or secondary care (psychiatric outpatient clinics). Cumulative length of positive and negative symptom remission was the primary outcome measure. EEIS patients had a significantly longer mean length of remission of positive symptoms (92.5 vs. 63.6 weeks, t=4.47, p<0.001), negative symptoms (73.4 vs. 59.6 weeks, t=2.84, p=0.005) and both positive and negative symptoms (66.5 vs. 56.7 weeks, t=2.25, p=0.03) compared to regular care patients. EEIS patients stayed in treatment longer than regular care patients (mean 131.7 vs. 105.3 weeks, t=3.98, p<0.001 through contact with physicians; 134.8 ± 37.7 vs. 89.8 ± 55.2, t=6.45, p<0.0001 through contact with other health care providers) and received more units of treatment (mean 74.9 vs. 39.9, t=4.21, p<0.001 from physicians, and 57.3 vs. 28.2, t=4.08, p<0.001 from other health care professionals). Length of treatment had an independent effect on the length of remission of positive symptoms (t=2.62, p=0.009), while number of units of treatment by any health care provider had an effect on length of remission of negative symptoms (t=−2.70, p=0.008) as well as total symptoms (t=−2.40, p=0.02). Post-hoc analysis showed that patients randomized to primary care, based on their better clinical profile at randomization, maintained their better outcome, especially as to remission of negative symptoms, at the end of the study. These data suggest that extending early intervention service for three additional years has a positive impact on length of remission of positive and negative symptoms compared to regular care. This may have policy implications for extending early intervention services beyond the current two years.

Key words: First-episode psychosis, extension of early intervention service, regular care, positive symptoms, negative symptoms, outcome, remission

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Psychotic disorders, comprised primarily of schizophrenia spectrum and affective psychoses, have a lifetime median prevalence of 4%[1,2] and enormous negative personal, social and economic consequences[3,4].

Outcome trajectories are generally established during the "critical period" (i.e., the early years of psychosis)[5-7]. This has fuelled the development of specialized early intervention services in many parts of the world[8,9]. Such services are characterized by comprehensive, multi-modal and phase-specific treatment of patients with a first episode of psychosis, typically centred around assertive case management with access to multiple psychosocial interventions in addition to use of medications[9] and, in some cases, efforts at reducing delay in treatment[10].

The short-term benefits of early intervention services compared to regular care for treatment of first-episode psychosis have been reported in a number of studies measuring syndromal and functional outcomes as well as substance abuse, aggression and/or suicidal behaviour, re-hospitalization and cost-effectiveness[10-13]. While these studies are very encouraging, these gains may not be retained once patients are transferred to regular care after the first two years of early intervention services[14], as reported by the OPUS I study[15].

Another uncontrolled trial, using a substantially lower intensity of early intervention service following two years of full intensity service, produced more encouraging results. This study showed higher rates of full remission of positive symptoms for the last two of five years of follow-up than the OPUS I study (54.3% vs. 41.3%, respectively)[16].

Two recent studies have produced mixed results. A study from Hong Kong reported benefits of a third year extension of early intervention service[17]. Another randomized controlled trial, just published from Denmark (OPUS II study), failed to find any benefit of extending early intervention service from two to five years when compared to two years of early intervention service followed by three years of regular care, using severity of negative symptoms as the primary outcome[18].

The objective of the present trial, similar to the OPUS II study just published, was to examine if extending treatment in an early intervention service over the entire five-year "critical period" produces better outcomes than two years of early intervention service followed by regular care, using a randomized controlled single blind design.

METHODS

Design and participants

The central postulate tested in this study was that the experimental group, that is, individuals receiving early intervention service for an extended period (five years), will show a significantly longer remission of positive and negative symptoms than the control group (individuals receiving early intervention service for two years followed by regular care for three years).

The study was carried out between 2008 and 2015. We used an open-label randomized controlled design. Prior to randomization, all patients had received two years of treatment for their first episode of psychosis in one of the early intervention services included within the McGill University network. These services follow guidelines incorporating modified assertive case management, lowest effective dose pharmacotherapy, family intervention, group interventions to facilitate recovery, cognitive behaviour therapy when indicated, and crisis intervention[9,19,20].

We included patients able to provide informed consent, meeting DSM-IV criteria for a psychotic disorder (schizophrenia spectrum psychoses or affective psychosis) confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition[21], and having completed 24 (±3) months of treatment in one of the above-mentioned early intervention services. Patients were included irrespective of their remission status and presence or not of comorbid substance abuse.

Exclusion criteria were inability to provide informed consent or to speak either English or French fluently, and an IQ below 70 as assessed using the short form of the Wechsler Adult Intelligence Scale[22].

Randomization and patient allocation

All patients receiving treatment for first-episode psychosis in an early intervention service of the McGill University Network were approached for participation in the study, usually following the 18-month review. At month 24 (±3 months), patients who met inclusion and exclusion criteria and signed an informed consent were allocated to either the experimental or the control intervention using a computerized urn randomization protocol[23] carried out by a trial statistician not connected with any of the services. This procedure improves upon chance allocation by adjusting assignment probabilities based on key intake characteristics (gender and comorbid diagnosis of substance abuse) that could influence outcomes. Group allocation was concealed in sealed opaque envelopes.

Randomization results were revealed to the patient and, if he/she was randomized to regular care, the transfer process was initiated within two weeks. Baseline assessments were conducted by the research coordinator prior to randomization. Outcome evaluations were carried out in a setting different from the clinical ones by a trained researcher who was blinded to treatment assignment, was not involved in patient care and did not have access to patients' clinical records. Patients were instructed and reminded not to reveal the nature of treatment they were receiving or the name and location of their treating clinicians. In addition, data collected from each patient's case files by the project co-ordinator were re-coded to remove any information that would identify the treatment allocation.

Primary outcome measure

Clinical remission is among the most desirable outcomes and is also strongly associated with functional recovery[24-26]. Length of remission of positive, negative and both positive and negative symptoms (i.e., total remission) is reported here as the primary outcome as per the trial registration. We also report the proportion of patients who were in remission for at least three months during the follow-up period.

Remission was measured by administering the Scale for Assessment of Positive Symptoms (SAPS)[27] and the Scale for Assessment of Negative Symptoms (SANS)[28] every three months. Patients scoring 2 or less on all of the global (subscale) items of either scale were considered to be in remission for that scale, and those with scores of 2 or less on all global items of both scales were considered to be in total remission.

Demographic and clinical data at the time of randomization were obtained from the program database and confirmed with patients during the baseline interview. Treatment contact was defined as face-to-face professional interventions by either a physician or another health care provider (e.g., case manager). Second generation antipsychotic medications were used invariably and the dosage was expressed as chlorpromazine equivalents[29]. Adherence to antipsychotic medications was self-reported and not confirmed with any assays or through verification with treating clinicians in order not to break the blind assessment. Attempts were made to verify with the dispensing pharmacy whenever possible.

The study was approved by McGill University Human Ethics Committee. Patients in both conditions were paid compensations for travel expenses ($20) for each study assessment.

Sample size was calculated based on findings of the previous uncontrolled study of extension of early intervention service[16] for length of positive symptom remission. Taking into consideration attrition over time, we estimated that a sample of 220 patients randomized to the two treatment conditions and 167 evaluable patients would have sufficient power to detect significant group differences on the primary outcome measure.

Trial interventions

Experimental intervention

The experimental intervention – extended early intervention service (EEIS) for three years following two years of early intervention service – comprised the elements detailed below.

Modified assertive case management tailored to meet the needs of younger patients in the early phase of illness[9] was continued as the primary mode of service delivery, with a case load of 20-22 cases per case manager. During this extended phase, the case manager provided continued emphasis on appropriate treatment goals, such as adherence to treatment, reintegration into employment and/or educational activities, improving patients' understanding about their illness, reducing dependence on hospital services, providing crisis intervention and promoting independence.

The case manager continued to facilitate maintenance of remission primarily through encouraging adherence to medication, controlling substance use, and teaching skills for identifying early warning signs of relapse. Based on each patient's profile of early (prodromal) signs observed prior to onset of first episode and over the first 24 months of treatment, a signature profile of early warning signs[30] was created. At each contact, case managers evaluated the status of the early warning signs, and patients were trained by the case manager to monitor these signs to prevent future relapses. Use of relapse prevention strategy and early warning signs was monitored continuously through monthly meetings between the case managers and the research team.

Families of EEIS patients were offered booster sessions of structured family education and multiple family group interventions[31]. A family self-help support group was active throughout the study period.

Cognitive behaviour therapy was provided using the same criteria as in the pre-randomization phase (a major depressive episode, anxiety disorder or residual psychotic and/or negative symptoms). Therapists received weekly peer supervision, and recordings from the sessions were reviewed for quality assurance.

Severity of alcohol and drug consumption in the previous six months was assessed with the timeline follow-back procedure and followed by brief intervention to reduce substance abuse, if indicated[32]. Interventions lasting up to 20 minutes were undertaken, using motivational interviewing principles, Case managers had received training and ongoing supervision from one of the co-investigators.

Control intervention

The control intervention – early intervention service for two years followed by regular care for three years – was implemented as follows.

Patients randomized to regular care received treatment in general medical or regular psychiatric services available to them in the absence of participation in the trial. Transfers were made to two levels of regular care in the community: "primary care" (which in Québec includes community health and social service centres and family physicians with variable support from psychiatric services) or "secondary care" (through outpatient services attached to a hospital where most of the care is provided by psychiatrists often with nursing or other professional involvement).

Prior to randomization, clinicians – in collaboration with patients and their families – decided on the best choice within the regular care system based on the complexity of patient's needs as emerging during the two years of initial treatment in the early intervention service. Those with a more complex course were recommended follow-up with secondary care, while patients who had been stable for a lengthy period of time were advised transfer to primary care. Each patient randomized to regular care was transferred to the new service with a personalized meeting involving the patient, his/her early intervention service case manager, and the new clinician taking charge of the patient's care, accompanied by relevant documentation.

Data analysis

We estimated the length of time patients stayed in treatment with their respective services and compared the number of total treatment exposures received by patients for both groups.

Multiple regression was the main approach to analysis. The length of remission of (positive, negative and total) symptoms was the principal variable of interest. Site and number (and length) of treatments received from any health care provider were tested as possible covariates and entered in that order. Because of high co-linearity between number and length of treatments, these were entered alternately.

These covariates were selected because of their potential to confound the primary outcome. For example, greater frequency of treatment interventions is expected in EEIS, as case managers are required to have contact with their patients with a minimum frequency of once per month and usually every two weeks, and to increase this frequency if the clinical condition so requires. The frequency of treatment may, therefore, have a confounding effect on outcome irrespective of the treatment model. Given the difference in the length of stay in the study across the two conditions, it was important also to determine if the length of exposure to treatment had an independent effect.

We also compared the proportion of patients who were in a state of remission for a minimum of three months (over one period of assessment) at any time during the study between those randomized to EEIS and regular care. This analysis was performed in all patients who had a minimum of one assessment post-randomization.

Information on the primary outcome variable, if missing as a result of patients not completing some interviews, was supplemented by clinical data derived from case files from all services within regular care as well as those in EEIS. An experienced research assistant was trained to reconstruct remission of positive and negative symptoms from the case files. Ratings were then reviewed with the project coordinator. Data were included in the analysis until time of completion of the study or withdrawal.

RESULTS

The patient recruitment, randomization process and patient allocation to treatment group have been described in the paper

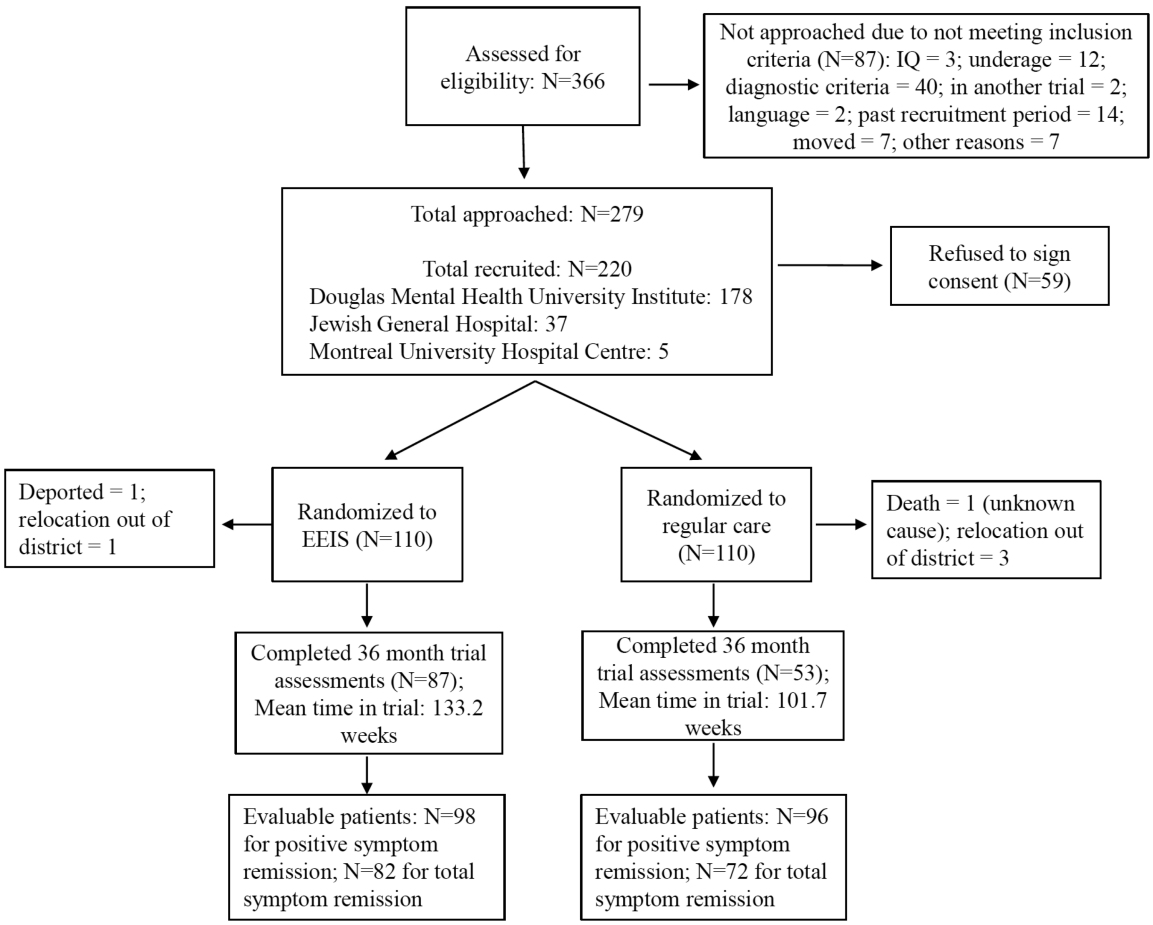

Figure 1 CONSORT flow diagram. EEIS – extended early intervention service

presenting the study protocol[33]. An updated consort flow diagram (Figure 1) shows patient allocation on randomization, number of patients receiving treatment in the assigned condition (EEIS vs. regular care), study withdrawals and number of patients included in the analyses.

Table 1 shows that there were no significant differences between the two groups – EEIS (N=110) and regular care (N=110) – on any demographic or clinical variables, including remission status, at the time of randomization.

Patients randomized to regular care were transferred in almost equal proportions to "primary care" (N=51, 46.4%) and "secondary care" (N=48, 43.6%), with 11 (10%) patients dropping out after randomization before they could be transferred. While transfer to regular care was started within two weeks of randomization, it was dependent on the ability and policies of receiving services and often involved considerable delays (mean 25.7 ± 16.1 weeks). EEIS patients, on the other hand, continued with their previous case managers and psychiatrists in the same early intervention service as prior to randomization.

Over the course of the study, one patient randomized to regular care died of unknown causes (at 30 weeks), one patient randomized to the EEIS got deported (at 23.2 weeks), and four patients (three on regular care, at 84.0, 139.2 and 91.5 weeks, and one on EEIS, at 50.7 weeks, respectively) moved out of town. No suicides were reported from either group. Data on these patients were included in the analyses until the time of withdrawal from the study.

The mean dose of antipsychotic medication was comparable (299.9 ± 350.1 and 329.7 ± 342.9 chlorpromazine equivalent mg/day, respectively, for EEIS and regular care). Nine and seven patients were prescribed clozapine, respectively, in the EEIS and regular care groups over the course of the study. Self-reported adherence rates, based on 103 patients for EEIS and 73 patients for regular care groups, were extremely high (95% and 97%, respectively).

At the end of the study, 49 patients had lost their blind assessment status. Most of them (N=40) were from the EEIS group, almost invariably as a result of patients inadvertently stating their place of treatment or the name of their case manager during their assessment by the research staff.

Patients were considered withdrawn from the study if they missed three consecutive assessments. The number of patients who completed research assessments as per the protocol for the entire 36-month period was significantly higher in the EEIS than the regular care group (N=87, 79.1% and N=53, 48.2%, respectively, χ^2=22.7, p<0.001). The length of stay in the study (time to

Table 1 Demographic and clinical characteristics at randomization

	Total (N=220)	EEIS (N=110)	Regular care (N=110)
Age at onset of first-episode psychosis (years, mean±SD)	22.4 ± 4.4	21.9 ± 4.1	22.9 ± 4.7
Gender (N male, %)	151 (68.6%)	75 (68.2%)	76 (69.1%)
Marital status (N single, %)	200 (90.9%)	103 (93.6%)	97 (88.2%)
Education (N high school or less, %)	103 (46.8%)	53 (48.2%)	50 (45.4%)
Duration of untreated psychosis (weeks, mean±SD)	49.3 ± 123.6 (median=11.6 weeks)	52.4 ± 148.8 (median=8.3 weeks)	46.3 ± 92.7 (median=12.7 weeks)
Primary diagnosis of schizophrenia spectrum (N, %)	143 (65.0%)	74 (67.3%)	69 (62.7%)
Secondary diagnosis of substance abuse/dependence (N, %)	105 (47.7%)	52 (47.3%)	53 (48.2%)
Antipsychotic dose in chlorpromazine equivalents (mg, mean±SD)	314.6 ± 332.6	299.9 ± 350.1	329.7 ± 342.9
SAPS total score (mean±SD)	6.5 ± 9.7 (N=216)	7.1 ± 10.4 (N=107)	6.0 ± 8.9 (N=109)
SANS total score (mean±SD)	13.8 ± 11.6 (N=204)	13.6 ± 10.4 (N=103)	14.0 ± 12.8 (N=101)
Positive symptom remission (N, %)	161 (73.2%)	81 (73.6%)	80 (72.7%)
Negative symptom remission (N, %)	107 (48.6%)	53 (48.2%)	54 (49.1%)
Total symptom remission (N, %)	92 (41.8%)	45 (40.9%)	47 (42.7%)

EEIS – extended early intervention service, SAPS – Scale for the Assessment of Positive Symptoms, SANS – Scale for the Assessment of Negative Symptoms

Table 2 Clinical care received during follow-up

	Number of interventions (mean±SD)		Length of treatment (weeks, mean±SD)	
	EEIS	Regular care	EEIS	Regular care
Physicians	74.9 ± 43.6*	39.9 ± 69.1	131.7 ± 37.4*	105.3 ± 51.5
Other health care providers	57.3 ± 37.3*	28.2 ± 59.6	134.8 ± 37.7**	89.8 ± 55.2

EEIS – extended early intervention service
*p<0.001, **p<0.0001

withdrawal) was significantly higher for EEIS (mean 133.2 ± 43.4 weeks) than for regular care (mean 101.7 ± 53.9 weeks, t=4.76, df=218, p<0.001). Complete data for the primary outcome (remission), from the time of randomization to end of study (or withdrawal), was available in 98 (89.1%) patients for positive symptom remission, and 82 (74.5%) patients for both positive and negative symptom remission for the EEIS group. The respective numbers for the regular care group were 96 (87.2%) and 72 (65.5%).

Table 2 shows that patients treated in EEIS stayed in treatment for significantly longer time than patients in regular care (131.7 ± 37.4 vs. 105.3 ± 51.5 weeks through contact with physicians, t=3.98, p<0.001; 134.8 ± 37.7 vs. 89.8 ± 55.2 weeks through contact with other health care providers, t=6.45, p<0.0001). Patients in EEIS received a significantly higher number of interventions either from a physician or another health care provider compared to the regular care group (74.9 ± 43.6 vs. 39.9 ± 69.1, t=4.21, p<0.001; and 57.3 ± 37.3 vs. 28.2 ± 59.6, t=4.08, p<0.001, respectively).

Remission status

Patients in the EEIS experienced remission of positive symptoms for a significantly longer period than patients in regular care (mean 92.5 ± 41.9 vs. 63.6 ± 46.7 weeks, standardized beta=0.34, t=4.47, p<0.001). Neither site nor number of times seen by any health care provider added any significant effect. However, length of treatment showed an independently significant effect on length of positive symptom remission (standardized beta=0.20; t=2.62, p=0.009), suggesting that longer stay in treatment was associated with longer remission of positive symptoms (Table 3).

For negative symptom remission, the effect of treatment condition was significant favouring EEIS (mean 73.4 ± 43.7 vs. 59.6 ± 47.0 weeks, standardized beta=0.15, t=2.84, p=0.005). While site had no independent effect, the number of units of treatment with any health care provider showed a significant effect (standardized beta=−0.25, t=−2.70, p=0.008), suggesting that higher number of interventions was associated with shorter length of remission (Table 3). The length of treatment had no effect (standardized beta=0.12, t=1.46, p=0.15).

Table 3 Variables affecting length of remission (regression analysis)

	Beta	SE	Standardized beta	t	p
Positive symptom remission					
Treatment group	31.58	7.06	0.34	4.47	<0.001
Site	−4.35	9.82	−0.03	−0.44	0.66
Length of treatment	0.20	0.08	0.20	2.62	0.009
Negative symptom remission					
Treatment group	13.79	6.98	0.15	2.84	0.005
Site	−9.18	8.00	−0.08	−1.65	0.10
Number of interventions	0.25	0.09	−0.25	−2.70	0.008
Positive and negative symptom remission					
Treatment group	19.80	8.80	0.23	2.25	0.03
Site	−10.40	11.03	−0.08	−0.94	0.35
Number of interventions	0.28	0.12	−0.25	−2.40	0.02

For total remission (of both positive *and* negative symptoms), treatment group (EEIS vs. regular care) showed a statistically significant difference (mean 66.5 ± 41.6 vs. 56.7 ± 45.0 weeks, standardized beta=0.23, t=2.25, p=0.03). While site had no effect on the outcome, number of treatment interventions did (standardized beta=−0.25, t=−2.40, p=0.02), suggesting that higher number of treatment encounters was associated with shorter length of total remission of both positive and negative symptoms (Table 3). The length of treatment had no such effect (standardized beta=−0.01, t=−0.12, p=0.90).

The proportion of patients who met criteria for positive, negative and total symptom remission (extending a minimum of three months) at any time during the study was not significantly different between the two groups (see Table 4). It is important to note that at randomization (Table 1) the proportion of patients allocated to EEIS and regular care who were in remission for positive symptoms (73.6% and 72.7%), negative symptoms (48.2% and 49.1%) and both positive and negative symptoms (40.9% and 42.7%) were lower than that reported at the end of the study (82.7% and 78.1%, 62.5% and 60.5%, 58.5% and 58.3%, respectively). However, these differences were not statistically significant.

Post-hoc analyses

As indicated above, patients randomized to regular care were transferred either to primary care (N=51) or secondary care (N=48). This selection of type of care was made very carefully with the intention of matching patients' needs to the level of care in order to maximize the benefits of treatment.

At baseline (time of randomization), patients transferred to primary care had a higher level of education, while patients transferred to secondary care had a higher level of positive and negative symptoms, a lower rate of positive, negative and total symptom remission, and a more common comorbid diagnosis of substance abuse (Table 5). There were no other differences between the two groups on any other characteristics, including duration of untreated psychosis.

Table 4 Proportion in remission at any time during the trial

	EEIS	Regular care	X^2	p
Positive symptom remission	81/98 (82.7%)	75/96 (78.1%)	0.63	0.47
Negative symptoms remission	55/88 (62.5%)	49/81 (60.5%)	0.07	0.87
Total remission	48/82 (58.5%)	42/72 (58.3%)	0.01	1.00

EEIS – extended early intervention service

During follow-up, secondary care patients received a significantly higher number of treatment interventions from either a physician or another health care provider (p<0.001). There was no difference in the overall length of time patients stayed in treatment, but secondary care patients received treatment from other health care providers for longer periods (mean 101.4 ± 49.5 vs. 76.5 ± 58.8 weeks, t=−2.08, p=0.04) and more frequently (mean 45.5 ± 84.0 vs. 12.1 ± 13.9 weeks, t=−2.48, p=0.01). This most likely reflects a combination of greater clinical needs as well as availability of other health care providers for those in secondary care.

At the end of follow-up, primary care patients had been in negative symptom remission for significantly longer periods (p<0.01). The differences on positive symptom remission, although in the same direction, did not reach statistical significance. A significantly higher proportion of primary care patients had met criteria for positive, negative and total symptom remission at any time during the course of follow-up (p<0.001) (Table 5).

DISCUSSION

The principal finding of this study is that, following two years of early intervention service, patients with first-episode psychosis randomized to continue in that service (EEIS) were in remission of positive, negative and total (both positive and negative) symptoms for significantly longer time during the subsequent three-year period than were patients randomized to regular care.

The longer periods of remission of both positive and negative symptoms in EEIS is likely related to significant efforts by case managers to keep patients engaged in treatment, follow them closely with a flexible approach including community and clinic based appointments, involve them in monitoring their own risk of relapse, provide access to psychosocial interventions when needed (e.g., family intervention, cognitive behaviour therapy), and include management of substance abuse in the treatment

Table 5 Post-hoc analyses in patients transferred to primary or secondary care

	Primary (N=51)	Secondary (N=48)	Test	p
Baseline				
Post-secondary education (N, %)	31 (60.8%)	18 (39.1%)	χ^2=4.53	0.03
Substance abuse (N, %)	20 (46.5%)	28 (68.3%)	χ^2=4.06	0.05
SAPS total score (mean±SD)	2.4 ± 3.5	9.7 ± 10.1	z =−4.37	<0.001
SANS total score (mean±SD)	10.7 ± 10.4	19.9 ± 14.4	t =−3.39	<0.001
Positive symptom remission (N, %)	45 (88.2%)	26 (54.2%)	χ^2=14.15	<0.001
Negative symptom remission (N, %)	32 (62.7%)	16 (33.3%)	χ^2=8.54	<0.001
Total symptom remission (N, %)	31 (60.8%)	10 (20.8%)	χ^2=16.26	<0.001
Follow-up and outcome				
Number of treatment interventions (mean±SD)	20.8 ± 24.8	60.1 ± 94.9	z =3.90	<0.001
Length of treatment (weeks, mean±SD)	102.3 ± 55.3	107.7 ± 48.8	t =−0.47	0.64
Positive symptom remission length (weeks, mean±SD)	75.2 ± 48.6	57.2 ± 42.2	t =1.90	0.07
Negative symptom remission length (weeks, mean±SD)	73.9 ± 47. 8	47.0 ± 41.6	t=2.52	<0.01
Total symptom remission length (weeks, mean±SD)	66.1 ± 46.4	46.9 ± 40.6	t=1.66	0.10
Positive symptom remission at any time (N, %)	44 (86.3%)	24 (50.0%)	χ^2 =15.12	<0.001
Negative symptom remission at any time (N, %)	33 (64.7%)	11 (22.9%)	χ^2=17.49	<0.001
Total symptom remission at any time (N, %)	31 (60.8%)	7 (14.6%)	χ^2=22.32	<0.001

SAPS – Scale for the Assessment of Positive Symptoms, SANS – Scale for the Assessment of Negative Symptoms

program. In addition, patients had ready access to the assigned psychiatrist, often facilitated by their respective case managers, for unscheduled appointments. The extra effort involved in early intervention services in considering patient's psychosocial needs and the ready access to psychosocial interventions may have led to sustained negative symptom remission, given the documented, albeit modest, impact of psychosocial interventions on negative symptoms[34,35]. The inverse association between number of treatment interventions and length of remission of negative symptoms, as well as total remission, most likely reflects the need for greater frequency of treatment contacts for patients who were not in remission.

It appears that, over the study period, patients randomized to both interventions not only maintained the status of remission, but that rates of all types of remission increased (see Tables 1 and 4). This suggests that even for patients transferred to regular care some gains from the first two years of early intervention service may be maintained. However, what seems particularly relevant is how long such remission of positive or negative symptoms was sustained, given the strong association of the length of remission with functional outcome[24,25]. Results from a previous study of patients with first-episode psychosis (N=159) showed that, at the end of two years, the length of positive and negative symptom remission had contributed 15% and 13%, respectively, of the 38% of explained variance in functional outcome (employment and social relationships)[27].

A comparison with a previous study of patients with first-episode psychosis, followed up in a low intensity early intervention service after two years of full intensity early intervention service, may provide some context for the relevance of the findings reported here[16]. Although the measures of outcome are not identical, the results of the current study confirm the superior outcome on positive symptoms in EEIS reported in that study[16]. However, our study also shows an advantage of EEIS in its impact on length of negative symptom remission and, as a consequence, on total remission of both positive and negative symptoms. The previous study did not have a control sample of an alternate service. A recent study from Hong Kong also showed an independent effect of an extension of one year following the initial two years of early intervention service[17], although there are significant differences in the cultural and resource contexts between that study and the current one.

The most recent trial from the OPUS program in Denmark has reported the absence of any significant differences in the level of negative symptoms between a three-year extension of early intervention service and regular care following two years of early intervention service[18]. The differences in the results of our study and the new OPUS study can be explained at several levels. The OPUS study assessed the level of negative symptoms only at two time points, post-randomization and the end of the study, while we used three-monthly assessments of positive and negative symptoms over the study period. The differences cannot be attributed to a higher intensity of treatment in our EEIS, given our case manager to patient ratio of 22:1, compared to 15:1 in the OPUS trial. However, there are likely differences in the intensity of care available in regular care between the two studies, with the OPUS study reporting a higher intensity of services such as case management provided in regular care in Denmark. Last, but not

least, length of remission of symptoms may be a more robust measure of outcome because of its strong association with functional outcome than level of symptoms at any given time.

One of the limitations in a trial with a long follow-up is attrition rate, which was greater for regular care (51.8%) than for EEIS (20.9%) in our study. While adding methodological rigour, thirteen detailed evaluations may have increased the risk of attrition due to burden of repeated assessments, as well as led to loss of blinding of assessments over time. Despite this, our completion rate at 3-year post-randomization is comparable to the new OPUS study (66% vs. 71%). Further, patients in each treatment condition stayed in the research protocol for considerable time (mean 133.2 weeks for EEIS and 101.7 for regular care). We were able to utilize data for 65-89% of patients for evaluation of the primary outcome measures through additional data being derived from the clinical files. Since the quality of records available varied across services and was likely better in the EEIS, this may have biased some of the results. Every attempt was made by the project coordinator to verify the accuracy of the data retrieved by the research staff. This additional information was only required for one third of the cases. This may be more accurate than imputing data for a missing assessment from a previous one conducted three months earlier. Such imputation may not capture the change in symptoms occurring over such a long period.

The lower attrition rate of patients in EEIS may reflect a higher level of engagement for patients compared to regular care, one of the objectives of most early intervention services. This is likely explained by the central role of case management and continuity of care in the EEIS. Patients randomized to regular care often had to make a difficult transition to another service, despite strong efforts by the early intervention service staff to assertively engage with regular care to facilitate such transfers. Sustained engagement in treatment may be an important outcome in itself. It is possible, therefore, that continuity of care was an important ingredient for the superiority of outcome in EEIS.

Although our study was conducted within a network of three early intervention services that used an identical service model, it is still possible that differences in staffing and culture of treatment may have had an effect on outcome. However, our results show a lack of any effect of site on outcome. For regular care, all patients had access to the same system of care across the three clinical sites.

While the results of this study suggest an overall superior outcome measured by the length of symptomatic remission for patients treated in an EEIS, it is likely that extension of early intervention service may be particularly beneficial to certain patients and that such an extension may not be necessary to all. In other words, some patients with a better prognostic profile may do well if transferred to an appropriate level of regular care. In order to examine this possibility, we have reported post-hoc analyses on patients who were transferred to regular care. Our results suggest that after careful matching, achieved through consensus with patients and their families and based on their progress over the preceding two years of early intervention service, a substantial proportion of patients did well following transfer to primary care. The latter patients had a higher education level, a lower rate of substance abuse and were clinically stable at the time of randomization. As expected these patients received lower intensity of care, while those transferred to specialist regular care received higher frequency of care from psychiatrists and other health care providers. It should, however, be emphasized that the transition of patients to a different form and level of care needs very careful management and requires considerable effort by the early intervention service, as was done in this study.

In conclusion, in this randomized controlled trial, we explored whether an extension of early intervention service beyond the first two years is likely to provide greater benefits than transfer to regular care. Our results suggest that, for the entire group of patients with first-episode psychosis receiving care in an early intervention service, an extension of additional three years is beneficial to obtain better clinical outcomes. However, as suggested by our post-hoc analysis, a subgroup of patients with good prognostic characteristics achieved following two years of early intervention service may do well in a lower intensity system of care.

Our findings have potential significance for policies regarding length of early intervention services to be recommended for patients with first-episode psychosis beyond the first two years. This will, however, need to be supported by sound health economic data, which will be examined in a subsequent report.

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The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials

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The rapid advances and adoption of smartphone technology presents a novel opportunity for delivering mental health interventions on a population scale. Despite multi-sector investment along with wide-scale advertising and availability to the general population, the evidence supporting the use of smartphone apps in the treatment of depression has not been empirically evaluated. Thus, we conducted the first meta-analysis of smartphone apps for depressive symptoms. An electronic database search in May 2017 identified 18 eligible randomized controlled trials of 22 smartphone apps, with outcome data from 3,414 participants. Depressive symptoms were reduced significantly more from smartphone apps than control conditions (g=0.38, 95% CI: 0.24-0.52, p<0.001), with no evidence of publication bias. Smartphone interventions had a moderate positive effect in comparison to inactive controls (g=0.56, 95% CI: 0.38-0.74), but only a small effect in comparison to active control conditions (g=0.22, 95% CI: 0.10-0.33). Effects from smartphone-only interventions were greater than from interventions which incorporated other human/computerized aspects along the smartphone component, although the difference was not statistically significant. The studies of cognitive training apps had a significantly smaller effect size on depression outcomes (p=0.004) than those of apps focusing on mental health. The use of mood monitoring softwares, or interventions based on cognitive behavioral therapy, or apps incorporating aspects of mindfulness training, did not affect significantly study effect sizes. Overall, these results indicate that smartphone devices are a promising self-management tool for depression. Future research should aim to distil which aspects of these technologies produce beneficial effects, and for which populations.

Key words: Smartphone technology, mental health interventions, depression, e-health, mhealth, apps, cognitive training, mood monitoring, cognitive behavioral therapy, mindfulness training

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Depression is now recognized as a leading cause of global disability, impacting over 300 million people around the world[1]. In countries like the US, 9% of the population may have depression at any one time[2]. Beyond the personal suffering, depression is associated with unemployment, poor physical health, impaired social functioning and, in its most severe forms, suicide[3]. Thus, the disorder carries a high cost for both the individual and the society, particularly when considering the economic burden incurred through clinical care and lost productivity[4].

Depression is a potentially treatable condition, with a range of available medications and psychological interventions that are supported by robust clinical evidence. While the choice of pharmacotherapy or psychotherapy depends on many factors, for most individuals with mild or moderate depression they may be nearly equivalent[5].

However, there are many barriers towards both of these treatment methods. For instance, access to mental health care remains limited, as almost half of the world's population lives in countries where there is less than one psychiatrist per 100,000 people[6], and continued shortage in mental health care staff is expected for both the near and long term future[7,8]. Additionally, medications and psychotherapies may carry some level of stigma (particularly among younger people), which further limits their effectiveness[9,10].

Furthermore, although these therapies demonstrate high clinical efficacy for reducing symptoms, they may not always bring about full and sustained remission in those treated. Finally, many people experience either subclinical depression or residual depressive symptoms even after achieving clinical response to treatment. Therefore, novel primary and/or adjunctive methods for reducing depression on a population scale are urgently needed.

Digital technologies may represent a novel and viable solution. Mobile phones are among the most rapidly adopted innovations in recent history, and smartphone ownership continues to increase in both developed and developing countries[11]. Through providing ubiquitous Internet connectivity, along with the capacity to download and run externally created applications ("apps"), smartphone technology presents an opportunity to transform mobile phones into devices which could provide global, cost-effective and evidence-based mental health services on demand and in real time[12].

This clear therapeutic potential has triggered a wave of interest and investment in mental health apps from governments, technology companies, advocacy groups, and research groups internationally[13,14]. But in the enthusiasm to realize the potential of apps for depression, it has become difficult to separate actual efficacy from overzealous aspirational claims[15]. With thousands of mental health apps readily available through Apple or Google marketplaces, finding a useful tool supported by robust evidence to manage one's depression is clearly a challenge for a lay person[16,17]. The increasing media promotion and accessibility of apps for mental health now presents a "duty of

care" issue towards ensuring that people have information and understanding of evidence-based digital treatments for depression.

Recent meta-analyses have documented that various smartphone interventions can have positive effects on physical diseases, such as diabetes[18], and mental health conditions, such as anxiety[19]. However, the clinical effect of smartphone interventions on symptoms of depression has yet to be established. Thus, our aim was to examine the efficacy of delivering mental health interventions via smartphones for reducing depressive symptoms in both clinical and non-clinical populations. We also sought to use subgroup and meta-regression analyses in order to explore which aspects of smartphone interventions are associated with greater or lesser efficacy for depressive symptoms. The results of these meta-analyses provide the first overall estimate of effects from such interventions, along with informing treatment choices and future research in this area.

METHODS

This systematic review and meta-analysis followed the PRISMA statement for transparent and comprehensive reporting of methodology and results[20]. In order to eliminate researcher bias, the search strategy, inclusion criteria and data extraction, as well as the overall and pre-planned subgroup analyses, strictly adhered to those adopted in a previous systematic review of smartphone interventions for anxiety[19], as specified in a registered online protocol (CRD42017064882).

Search strategy

We conducted an electronic search of the following databases: Cochrane Central Register of Controlled Trials, Health Technology Assessment Database, Allied and Complementary Medicine (AMED), Health Management Information Consortium (HMIC), Ovid MEDLINE, Embase, and PsycINFO, from inception to May 1, 2017. The search applied the PICO framework[21], using a range of relevant terms to capture all potentially eligible results relating to smartphone mental health interventions for depressive symptoms. An additional search of Google Scholar was implemented, and reference lists of retrieved articles were checked to identify any further eligible studies.

Eligibility criteria

Only English-language articles were included. Eligible studies were all randomized controlled trials (RCTs) examining the effects of mental health interventions delivered via smartphone devices with at least one outcome measure for depressive symptoms. We aimed to examine the effects of smartphone interventions on primary depression, comorbid depression and subclinical depressive symptoms. No restrictions were placed on diagnosis or any other clinical or demographic characteristics of eligible samples.

Three independent investigators judged article eligibility (JF, JN and JT), with any disagreements resolved through discussion. "Smartphones" were defined as mobile phones with 3G or 4G Internet connectivity, along with the ability to download, install and run external applications ("apps"). RCTs of interventions delivered solely or in part via smartphone devices matching this definition, aimed at improving mental health or well-being (with depression as a primary or secondary outcome), were included in the review.

Studies using either "inactive" or "active" control groups were eligible for inclusion. "Inactive" control groups were classified as those in which participants received no intervention during the trial period (or were put into a waitlist until pre-and-post measures had been collected from both groups). "Active" control groups were categorized as those which attempted to control for the time and attention given to people in the smartphone intervention condition, by using apps not aimed at treating depression, in-person interventions, or other forms of activities or patient contact. RCTs comparing smartphone interventions to antidepressant medications were also eligible for inclusion. All eligible studies had a duration of at least one week (thus excluding studies measuring changes in mood following a single use of smartphone apps).

Data extraction

A systematic extraction form was used for each article to collect the following data: a) study information (sample size, mean age of participants, diagnostic information or relevant inclusion criteria, study length and trial quality); b) intervention features (app/program name, regularity of instructed use, smartphone program summary, any additional intervention components, details of the control condition); c) effects on depressive symptoms (changes in total depressive symptoms scored before and after smartphone and control interventions using any clinically validated rating scale). For studies which used more than one measure of depression, a mean total change was calculated by pooling outcomes from each measure.

Statistical analyses

All analyses were conducted by Comprehensive Meta-Analysis 2.0[22], using a random-effects model[23] to account for between-study heterogeneity. The total difference in changes in depressive symptoms between smartphone interventions and control conditions were pooled to compute the overall effect size of the former (as Hedges' g), with 95% confidence intervals (CI). For RCTs comparing smartphone interventions to both inactive and active control conditions, the comparative effects with active control groups were used in the primary

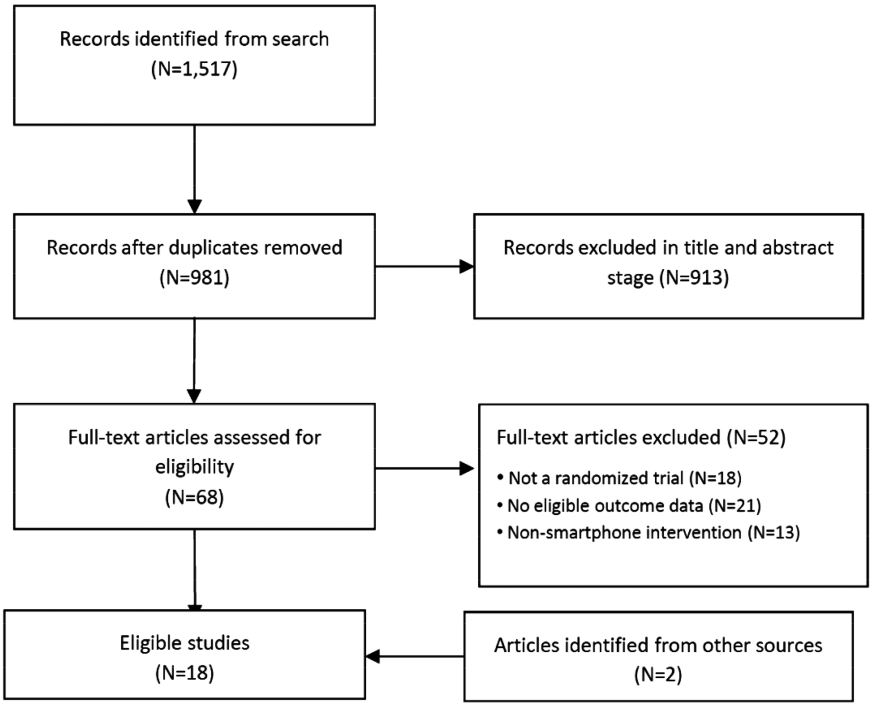

Figure 1 PRISMA flow chart of study selection

analysis. After computing main effects, a sensitivity analysis was applied to investigate effects of smartphone interventions in RCTs which used intention-to-treat analyses or had complete outcome data.

To quantify the degree to which statistical heterogeneity in the meta-analyses arose due to between-study differences, rather than due to chance, Cochran's Q (with p value) and I^2 were used. Included studies were also assessed using the Cochrane Collaboration's Risk of Bias tool. This examined study quality in six areas of trial design (sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting), ranking each area as high, low or unknown for risk of bias[24].

Risk of publication bias was examined using a funnel plot of study effect sizes, and Egger's regression test was applied to all aforementioned analyses. Furthermore, a Duval and Tweedie's trim-and-fill analysis was conducted to re-calculate the pooled effect size after removing any studies which may introduce publication bias (i.e., small studies with large effect sizes from the positive side of the funnel plot). Additionally, a "fail-safe N" was used to account for the file draw problem[25], estimating the number of non-significant unpublished trials which would be needed to cause the observed p value to exceed 0.05.

Pre-planned subgroup analyses were conducted to examine whether effects of smartphone interventions differed when comparing them to inactive or active control conditions. Additionally, we carried out a range of exploratory post-hoc subgroup and meta-regression analyses in order to examine which factors may impact the effectiveness of smartphone interventions, particularly with regards to sample details (i.e., clinical population, age, gender) and treatment characteristics (i.e., psychological basis, technological features and length of smartphone interventions).

RESULTS

The search returned a total of 1,517 records; 981 after duplicates were excluded. Title and abstract screening removed a further 913 articles. Full versions were retrieved for 68 papers, of which 16 met eligibility criteria. Two further articles were retrieved following an additional search of Google Scholar. Thus, 18 unique RCTs were included in the meta-analysis, assessing the effects of 22 different smartphone-delivered mental health interventions. The article inclusion/exclusion process is shown in Figure 1.

Characteristics of included studies

Full details of each study are displayed in Table 1. Outcome data were available from 18 RCTs. Two papers reported outcome data in a format not suited for meta-analysis, but the corresponding authors provided the raw data to enable inclusion[26,30]. Mean sample ages ranged from 18 to 59 years (median 39 years). All but two studies[32,34] used some indication of mental health issues as inclusion criteria. For clinical populations, two studies

Table 1 Details of included studies

Study	Sample type	N (each condition)	Age (years, mean)	Design	Other intervention aspects	Outcome measure
Arean et al[26]	Self-reported mild-to-moderate depression	211,209,206	33.9	12 weeks of Project EVO (cognitive training app) vs. iPST (problem-solving therapy app) vs. Health Tips control app	None	PHQ-9
Birney et al[27]	Self-reported mild-to-moderate depression	150,150	40.7	6 weeks of MoodHacker (CBT-based depression app) vs. links to approved depression websites	Daily e-mails to provide additional digital content and prompt engagement	PHQ-9
Depp et al[28]	DSM-IV bipolar disorder	41,41	47.5	10 weeks of PRISM (mood monitoring and self-management app) vs. paper and pencil equivalent	Both groups received four sessions of individual therapy	MADRS
Enock et al[29]	Self-reported high social anxiety	158,141	34.8	4 weeks of CBM Active (cognitive bias modification training app) vs. inactive training or waitlist control	None	DASS
Faurholt-Jepsen et al[30]	ICD-10 bipolar disorder	33,34	29.3	6 months of MONARCA (self-monitoring app) vs. regular smartphone use	Patients could also contact their clinicians directly using the smartphone, in case of deterioration	HAM-D
Horsch et al[31]	Self-reported mild insomnia	74,77	39.7	6 to 7 weeks of Sleepcare (CBT-based insomnia app) vs. waitlist control	None	CES-D
Howells et al[32]	General population	57,64	40.3	10 days of Headspace (mindfulness app) vs. list-making app control	None	CES-D
Ivanova et al[33]	Self-reported social anxiety	50,51,51	35.3	10 weeks of guided ACTsmart (acceptance and commitment therapy app) vs. unguided ACTsmart vs. waitlist control	Participants also provided with pen-and-paper booklet for completing written assignments and a CD with ACT exercises	PHQ-9
Kahn et al[34]	US veterans	44, 41,42, 46	NA	16 weeks of Mission Reconnect program (using mindfulness and awareness techniques) vs. Prevention and Relationship Enhancement program vs. both programs together vs. waitlist control	Strategies for applying learnt techniques in challenging situations, and additional audio exercises	BDI-II
Kuhn et al[35]	Self-reported traumatic event + PTSD symptoms	62,58	39	3 months of PTSD Coach (app providing psychoeducation, symptom tracking and self-management strategies) vs. waitlist control	None	PHQ-8
Ly et al[36]	DSM-IV major depression	46,47	30.6	10 weeks of Behavioral Activation app plus 4 face-to-face behavioral activation sessions vs. 10 face-to-face behavioral activation sessions	None	BDI-II
Moell et al[37]	Self-reported data to diagnose ADHD	26,27	36.8	6 weeks of LivingSMART (app facilitating life organization and improving attentional control) vs. waitlist control	Computer-aided training on how to use the apps; participants were also allocated a coach to help with app usage	HADS

Table 1 Details of included studies *(continued)*

Study	Sample type	N (each condition)	Age (years, mean)	Design	Other intervention aspects	Outcome measure
Oh et al[38]	Older adults with self-reported memory complaints	18,19,16	59.3	8 weeks of SMART vs. Fit Brains (two cognitive training apps) vs. waitlist control	None	CES-D
Proudfoot et al[39]	Self-reported mild-to-moderate depression	126,195, 198	39	7 weeks of MyCompass (app enabling self-monitoring of problematic moods, thoughts and behaviors, tracking their severity, and receiving feedback advice and mental health management tips by SMS) vs. attention-matched and waitlist control	Computer modules provided to deliver evidence-based interventions	DASS
Reid et al[40]	Youth mental health patients	68,46	18	2 to 4 weeks of MobileType (app tracking mental health relevant thoughts and behaviors) vs. using a control app which tracks irrelevant behaviors	Participants reviewed information gathered by MobileType with their general practitioner, and were given guides for managing mental health	DASS
Roepke et al[41]	Clinically significant depression	93,97,93	40.2	1 month of SuperBetter (app supporting self-esteem and self-acceptance) vs. SuperBetter Plus (app adopting principles of CBT and positive psychology) vs. waitlist control	None	CES-D
Tighe et al[42]	Recent suicidal thoughts	31,30	26.3	6 weeks of ibobbly (app based on acceptance and commitment therapy principles) vs. waitlist control	24-hour helpline details available through the app in case of suicidality	PHQ-9
Watts et al[43]	DSM-IV major depression	10,15	41	8 weeks of Get Happy (CBT-based depression app) vs. computerized CBT program	Clinician contact during first two weeks to check and promote adherence	BDI-II PHQ-9

CBT – cognitive behavioral therapy, PTSD – post-traumatic stress disorder, ADHD – attention-deficit/hyperactivity disorder, PHQ – Patient Health Questionnaire, MADRS – Montgomery-Åsberg Depression Rating Scale, DASS – Depression Anxiety Stress Scale, HAM-D – Hamilton Rating Scale for Depression, CES-D – Center for Epidemiological Studies – Depression, BDI-II – Beck Depression Inventory II, HADS – Hospital Anxiety Depression Scale, NA – not available

recruited people with major depression[36,43], two individuals with bipolar disorder[28,30], one young people in primary care with any mental health condition[40]. Others recruited individuals from the general population with self-reported mild-to-moderate depression[26,27,39,41], suicidal thoughts/tendencies[42], probable attention-deficit/hyperactivity disorder (ADHD)[37], anxiety disorders[29,33], insomnia[31], or symptoms of post-traumatic stress disorder (PTSD)[35]. One further study examined older adults with memory complaints[38].

Smartphone interventions lasted between 4 and 24 weeks. Depressive symptoms were measured as a primary outcome in 12 studies, and as a secondary outcome in six. The following tools were used: the Depression Anxiety Stress Scale[44] depression subscale in three studies[29,39,40]; the Center for Epidemiological Studies Depression scale[45] in four[31,32,38,41]; the Beck Depression Inventory II[46] in three[34,36,43]; the Patient Health Questionnaire[47] in six[26,27,33,35,42,43]; the Hamilton Rating Scale for Depression[48] in one[30]; the Hospital Anxiety Depression Scale[49] in one[37]; and the Montgomery-Åsberg Depression Rating Scale[50] in one[28].

The results from the Cochrane Risk of Bias assessments are displayed in Table 2. This shows that the most frequent risk factor for bias was inadequate blinding of participants, with only five of 18 studies using intervention-matched comparators for which the participants would not be aware of their treatment/control status or of the hypothesized outcomes of the trial.

Overall effects of smartphone interventions on depressive symptoms

Figure 2 displays the pooled effect size from smartphone interventions on depressive symptoms, along with individual

Table 2 Quality assessment in included studies

Study	1	2	3	4	5	6	7
Arean et al[26]	+	+	+	+	+	+	–
Birney et al[27]	+	+	–	+	+	+	–
Depp et al[28]	+	+		+	+	+	+
Enock et al[29]			+	+	+	+	+
Faurholt-Jepsen et al[30]	+	+	–	+	+	+	+
Horsch et al[31]	+	+	–	–	+	+	–
Howells et al[32]	+	+	+	+	–	+	
Ivanova et al[33]	+	+			+	+	–
Kahn et al[34]	+			+	+	+	–
Kuhn et al[35]	+	–	–		+	+	
Ly et al[36]	+	+	+	+	+	+	
Moell et al[37]			–	+	+	+	
Oh et al[38]			–		–	+	+
Proudfoot et al[39]	+	+		+	+	+	+
Reid et al[40]	+	+	+	+	+	+	+
Roepke et al[41]	+	+	–	+	+	+	–
Tighe et al[42]	+	+	–	–	+	+	+
Watts et al[43]	+	+			–	+	

1 – random sequence generation, 2 – allocation concealment, 3 – blinding of participants and personnel, 4 – blinding of outcome assessment, 5 – incomplete outcome data, 6 – selective outcome reporting, 7 – other bias

effects from each app trialled. A random-effects meta-analysis revealed a small-to-moderate positive effect size of smartphone mental health interventions for reducing depressive symptoms in comparison to control conditions (18 studies, N=3,414, g=0.383, 95% CI: 0.24-0.52, p<0.001).

Although there was heterogeneity across the study data (Q=80.8, p<0.01, I^2=74.0%), there was no evidence of publication bias (p=0.255 in Egger's regression test), and the fail-safe N was 567 (estimating that 567 unpublished "null" studies would need to exist for the actual p value to exceed 0.05). A trim-and-fill analysis identified no outlier studies, and thus did not change the observed effect size.

When considering only the studies which used intention-to-treat analyses and/or reported complete outcome data, we found a similar effect of smartphone interventions on depressive symptoms (16 studies, N=3,320, g=0.399, 95% CI: 0.25-0.55, p<0.001; Q=80.0, I^2=77.5%).

In our pre-planned subgroup analyses, we found that effect sizes were significantly greater when comparing smartphone interventions to inactive conditions than when using active control conditions (Q=9.76, p=0.002; Figure 3). Compared to inactive control conditions, the pooled effect size across 13 smartphone interventions (N=1,674) was g=0.558 (95% CI: 0.38-0.74), indicating a moderate effect on depressive symptoms. However, when compared to active control conditions, smartphone interventions had only a small effect size on depressive symptoms (12 studies, N=2,381, g=0.216, 95% CI: 0.10-0.33). Both studies with active and inactive controls had significant heterogeneity, but no evidence of publication bias (Table 3).

Population characteristics and effects on depressive symptoms

We also applied post-hoc subgroup analyses to studies that had used mood disorder inclusion criteria, in order to explore which populations smartphone interventions may be most effective for. As shown in Table 4, the only populations in which smartphone interventions significantly reduced depressive symptoms were those with self-reported mild-to-moderate depression (5 studies, N=1,890, g=0.518, 95% CI: 0.28-0.75, p<0.001; Q=36.6, I^2=83.6). There was no significant effect among the smaller samples with major depressive disorder, bipolar disorder and anxiety disorders (two studies each).

Mixed-effects meta-regressions were applied to explore whether continuous moderators of average age, gender distribution and sample size affected study findings, but found no indication that these factors influenced observed effect sizes (all p>0.2).

Intervention characteristics and effects on depressive symptoms

In order to gain insight into which aspects of smartphone interventions make them effective for depressive symptoms, we performed further comparative subgroup analyses after separating studies on the basis of common characteristics, such as intervention components, feedback types, and therapeutic approaches applied. The common features examined, and the results of all subgroup comparisons, are detailed in full in Table 5.

These analyses showed that smartphone interventions which involved "in-person" (i.e., human) feedback had small, non-significant effects on depressive symptoms (g=0.137, 95% CI: −0.08 to 0.35, p=0.214), whereas those which did not use in-person feedback had moderate positive effects (g=0.465, 95% CI: 0.30-0.63, p<0.001). The difference between these subgroups was statistically significant (p=0.017).

Additionally, the effects of smartphone interventions which were delivered entirely via the smartphone device (10 studies, N=2,178, g=0.479, 95% CI: 0.27-0.69, p<0.001) appeared larger than those which were not self-contained smartphone-only interventions (8 studies, N=1,236, g=0.241, 95% CI: 0.09-0.39, p=0.002), although the difference between these subgroups fell short of significance (p=0.07).

Similarly, interventions which provided "in-app feedback", such as summary statistics and progress scores, had greater effect sizes (g=0.534, 95% CI: 0.26-0.81, p<0.001) than those which did not have in-app feedback (g=0.266, 95% CI: 0.14-0.39, p<0.001), although again the difference between subgroups was non-significant (p=0.082).

The only other notable finding was that the studies of cognitive training apps had a significantly (p=0.004) smaller effect size on depression outcomes (four studies, N=836, g=0.123,

Study	App name	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z	p	Sample size: Smartphone	Sample size: Control
Arean et al[26]	iPST	0.417	0.099	0.010	0.224	0.611	4.224	<0.001	211	206
Arean et al[26]	Project EVO	0.112	0.098	0.010	-0.080	0.304	1.142	0.253	209	206
Birney et al[27]	MoodHacker	0.287	0.116	0.013	0.060	0.514	2.477	0.013	150	150
Depp et al[28]	PRISM	0.568	0.223	0.050	0.130	1.005	2.543	0.011	41	41
Enock et al[29]	CBM Active	0.069	0.116	0.013	-0.158	0.295	0.593	0.553	158	141
Faurholt-Jepsen et al[30]	MONARCA	0.045	0.242	0.058	-0.429	0.518	0.185	0.853	33	34
Horsch et al[31]	Sleepcare	1.027	0.172	0.030	0.689	1.365	5.956	<0.001	74	77
Howells et al[32]	Headspace	0.378	0.183	0.033	0.021	0.736	2.073	0.038	57	64
Ivanova et al[33]	ACTsmart - guided	0.533	0.201	0.040	0.139	0.927	2.652	0.008	50	51
Ivanova et al[33]	ACTsmart - unguided	0.259	0.197	0.039	-0.127	0.646	1.314	0.189	51	51
Kahn et al[34]	Mission Reconnect	-0.082	0.153	0.023	-0.382	0.218	-0.536	0.592	86	41
Kuhn et al[35]	PTSD Coach	0.596	0.186	0.034	0.233	0.960	3.214	0.001	62	58
Ly et al[36]	Behavioral Activation	0.019	0.206	0.042	-0.384	0.422	0.091	0.927	46	47
Moell et al[37]	LivingSMART	0.496	0.275	0.076	-0.043	1.035	1.804	0.071	26	27
Oh et al[38]	Fit Brains	0.122	0.332	0.110	-0.529	0.772	0.367	0.713	19	16
Oh et al[38]	SMART	0.161	0.336	0.113	-0.498	0.820	0.479	0.632	18	16
Proudfoot et al[39]	MyCompass	0.435	0.115	0.013	0.209	0.661	3.771	<0.001	126	195
Reid et al[40]	MobileType	-0.012	0.190	0.036	-0.384	0.360	-0.064	0.949	68	46
Roepke et al[41]	SuperBetter	1.118	0.156	0.024	0.814	1.423	7.191	<0.001	97	93
Roepke et al[41]	SuperBetter Plus	0.518	0.148	0.022	0.227	0.809	3.488	<0.001	93	93
Tighe et al[42]	ibobbly	1.006	0.269	0.072	0.479	1.533	3.743	<0.001	31	30
Watts et al[43]	Get Happy	0.332	0.398	0.158	-0.447	1.112	0.836	0.403	10	15
Overall		***0.383***	***0.072***	***0.005***	***0.242***	***0.524***	***5.312***	***<0.001***	***1,716***	***1,698***

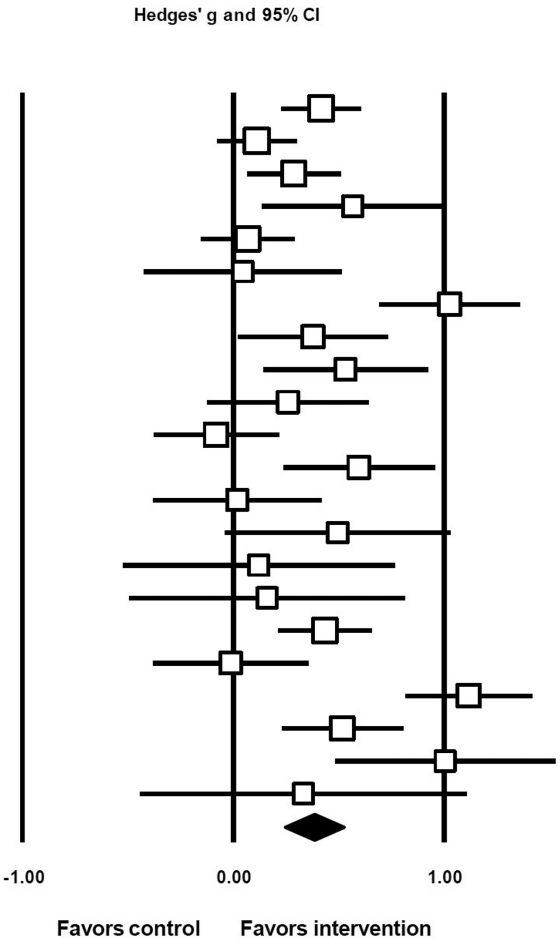

Figure 2 Meta-analysis of the effects of smartphone interventions on depressive symptoms. Box size represents study weighting. Diamond represents overall effect size and 95% CI.

Study	Appname	Control group	Hedges' g	Standard error	Variance	Upper limit	Lower limit	Z	p	Sample size
			Statistics for each study							
Arean et al[26]	iPST	Health Tips app	0.417	0.099	0.010	0.224	0.611	4.224	<0.001	417
Arean et al[26]	Project EVO	Health Tips app	0.112	0.098	0.010	-0.080	0.304	1.142	0.253	415
Birney et al[27]	MoodHacker	Depression websites	0.287	0.116	0.013	0.060	0.514	2.477	0.013	300
Depp et al[28]	PRISM	Pen and paper monitoring	0.568	0.223	0.050	0.130	1.005	2.543	0.011	82
Enock et al[29]	CBM Active	Placebo app	0.069	0.116	0.013	-0.158	0.295	0.593	0.553	299
Faurholt-Jepsen et al[30]	MONARCA	Smartphone without app	0.045	0.242	0.058	-0.429	0.518	0.185	0.853	67
Howells et al[32]	Headspace	List-making app	0.378	0.183	0.033	0.021	0.736	2.073	0.038	121
Kahn et al[34]	Mission Reconnect	Relationship therapy	-0.082	0.153	0.023	-0.382	0.218	-0.536	0.592	127
Ly et al[36]	Behavioral Activation app	In-person behavioral activation	0.019	0.206	0.042	-0.384	0.422	0.091	0.927	93
Proudfoot et al[39]	MyCompass	E-mail + SMS support	0.435	0.115	0.013	0.209	0.661	3.771	<0.001	321
Reid et al[40]	MobileType	Placebo app	-0.012	0.190	0.036	-0.384	0.360	-0.064	0.949	114
Watts et al[43]	GetHappy	Home-computer version	0.332	0.398	0.158	-0.447	1.112	0.836	0.403	25
Overall active controls			***0.216***	***0.060***	***0.004***	***0.098***	***0.334***	***3.587***	***<0.001***	***2,381***
Enock et al[29]	CBM Active	Waitlist	0.227	0.208	0.043	-0.180	0.634	1.094	0.274	185
Horsch et al[31]	Sleepcare	Waitlist	1.027	0.172	0.030	0.689	1.365	5.956	<0.001	151
Ivanova et al[33]	ACTsmart - guided	Waitlist	0.533	0.201	0.040	0.139	0.927	2.652	0.008	101
Ivanova et al[33]	ACTsmart - unguided	Waitlist	0.259	0.197	0.039	-0.127	0.646	1.314	0.189	102
Kahn et al[34]	Mission Reconnect	Waitlist	0.268	0.150	0.023	-0.026	0.562	1.787	0.074	132
Kuhn et al[35]	PTSD Coach	Waitlist	0.596	0.186	0.034	0.233	0.960	3.214	0.001	120
Moell et al[37]	LivingSMART	Waitlist	0.496	0.275	0.076	-0.043	1.035	1.804	0.071	53
Oh et al[38]	FitBrains	Waitlist	0.122	0.332	0.110	-0.529	0.772	0.367	0.713	35
Oh et al[38]	SMART	Waitlist	0.161	0.336	0.113	-0.498	0.820	0.479	0.632	34
Proudfoot et al[39]	MyCompass	Waitlist	0.572	0.116	0.013	0.345	0.800	4.939	<0.001	324
Roepke et al[41]	SuperBetter	Waitlist	1.118	0.156	0.024	0.814	1.423	7.191	<0.001	190
Roepke et al[41]	SuperBetter Plus	Waitlist	0.518	0.148	0.022	0.227	0.809	3.488	<0.001	186
Tighe et al[42]	ibobbly	Waitlist	1.006	0.269	0.072	0.479	1.533	3.743	<0.001	61
Overall inactive controls			***0.558***	***0.091***	***0.008***	***0.379***	***0.736***	***6.119***	***<0.001***	***1,674***

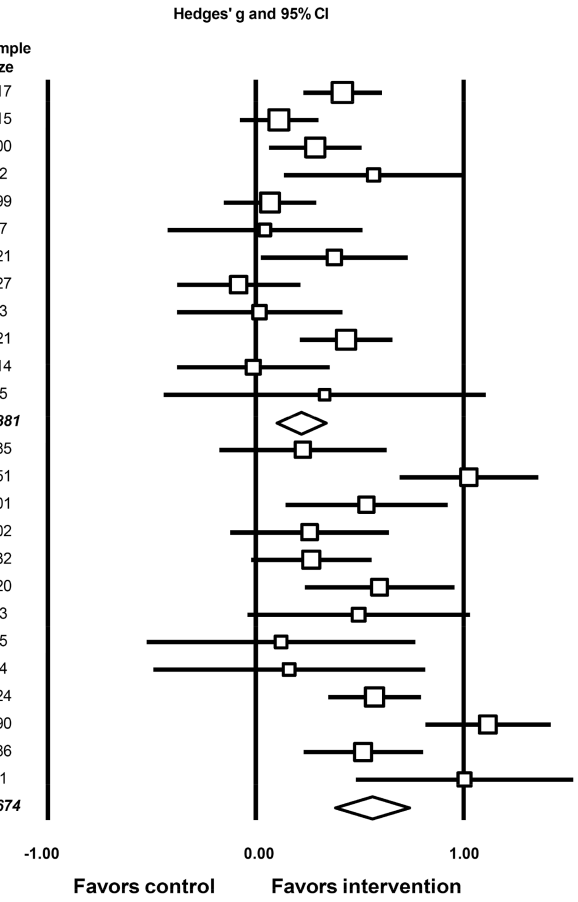

Figure 3 Meta-analysis showing effects of smartphone interventions on depressive symptoms in comparison to active and inactive controls. Box size represents study weighting. Diamonds represent overall effect size and 95% CI.

Table 3 Effects of smartphone-delivered mental health interventions on depressive symptoms: pre-planned subgroup analyses

	Studies	Sample size (smartphone/control)	Meta-analysis				Heterogeneity			Publication bias (Egger's regression)	
			Hedges' g	95% CI		p	Q	p	I^2	Intercept	p
Main analysis	18	1,716/1,698	**0.383**	0.242	0.524	**<0.001**	80.8	**<0.01**	74.0	0.80	0.26
Intent-to-treat or complete outcome data	16	1,669/1,651	**0.399**	0.248	0.550	**<0.001**	80.0	**<0.01**	77.5	1.68	0.15
Smartphone vs. active control	12	1,195/1,186	**0.216**	0.098	0.334	**<0.001**	20.8	**0.03**	47.2	−0.49	0.34
Smartphone vs. inactive control	13	891/783	**0.558**	0.379	0.736	**<0.001**	34.9	**<0.01**	65.6	0.25	0.25

Significant values are highlighted in bold prints

Table 4 Post-hoc analyses: mood disorder samples

	Studies	Sample size (smartphone/control)	Meta-analysis				Heterogeneity		
			Hedges' g	95% CI		p	Q	p	I^2
Self-reported mild-to-moderate depression	5	917/973	**0.518**	0.282	0.754	**<0.001**	36.6	**<0.001**	83.6
Major depressive disorder	2	56/62	0.085	−0.273	0.443	0.642	0.49	0.484	0.00
Bipolar disorder	2	74/75	0.314	−0.198	0.827	0.229	2.53	0.112	60.4
Anxiety disorders	2	259/242	0.250	−0.023	0.523	0.073	4.13	0.127	51.6

Significant values are highlighted in bold prints

Table 5 Post-hoc analyses: intervention features

	Studies	Sample size (smartphone/control)	Meta-analysis				Heterogeneity			Between groups tests	
			Hedges' g	95% CI		p	Q	p	I^2	Q	p
Delivered solely via smartphone	10	1,103/1,075	**0.479**	0.271	0.687	**<0.001**	62.05	**<0.01**	80.66		
Not delivered solely via smartphone	8	613/623	**0.241**	0.088	0.394	**0.002**	13.38	**<0.01**	40.22	3.277	0.070
In-app feedback	8	750/816	**0.534**	0.258	0.810	**<0.001**	54.41	**<0.01**	85.02		
No in-app feedback	11	966/882	**0.266**	0.143	0.389	**<0.001**	18.95	**<0.01**	36.68	3.02	0.082
In-person feedback	6	309/246	0.137	−0.079	0.353	0.214	8.66	0.12	42.25		
No in-person feedback	13	1,407/1,452	**0.465**	0.302	0.627	**<0.001**	61.6	**<0.01**	75.645	**5.654**	**0.017**
Mental health focused apps	15	1,286/1,292	**0.438**	0.276	0.601	**<0.001**	2.09	0.72	0.00		
Cognitive training apps	4	430/406	0.123	−0.012	0.258	0.074	63.6	**<0.01**	74.83	**8.517**	**0.004**
Mood monitoring features	9	653/709	**0.336**	0.182	0.489	**<0.001**	16.6	0.06	82.81		
No mood monitoring	9	1,063/989	**0.418**	0.191	0.645	**<0.001**	64.0	**<0.01**	45.71	0.348	0.555
CBT-based intervention	7	541/615	**0.531**	0.339	0.722	**<0.001**	13.5	0.04	55.58		
Not CBT-based	12	1,175/1,083	**0.311**	0.130	0.493	**0.001**	59.0	**<0.01**	76.26	2.661	0.103
Mindfulness aspects	6	615/573	**0.487**	0.214	0.760	**<0.001**	38.3	**<0.01**	81.716		
No mindfulness aspects	12	1,101/1,125	**0.321**	0.160	0.482	**<0.001**	38.9	**<0.01**	66.549	1.049	0.306

CBT – cognitive behavioral therapy
Significant values are highlighted in bold prints

95% CI: −0.012 to 0.26, p=0.074) than those which focused on mental health (15 studies, N=2,578, g=0.438, 95% CI: 0.28-0.60, p<0.001).

The use of mood-monitoring softwares, cognitive behavioral therapy (CBT)-based interventions and mindfulness training did not appear to influence study effect sizes (all p>0.1 between subgroups with vs. without these features).

A mixed-effects meta-regression of study effect size with intervention length (in weeks) found indication of a slight negative relationship between the two, with smaller effects observed from longer interventions, although this correlation fell short of statistical significance (B=–0.025, SE=0.014, Z=−1.72, p=0.086).

DISCUSSION

To our knowledge, this is the first meta-analysis to examine the efficacy of smartphone interventions for depressive symptoms. Our systematic search identified 18 RCTs, examining 22 mental health interventions delivered via smartphone devices, across a total of 3,414 participants. Thus, the literature base for this particular area has evolved swiftly, and is considerably larger than that found for smartphone interventions in other conditions. Around twice the number of eligible interventions and participants were identified compared to recent meta-analyses of smartphone interventions for diabetes and anxiety[18,19]. Furthermore, 14 of the 18 eligible studies were published within the last two years, which may reflect both the increased research interest in using apps for mental health[13] and the increased ownership, access and use of mental health apps by patients and health care organizations.

The main analysis found that smartphone interventions had a moderate positive effect on depressive symptoms, with no indication of publication bias affecting these findings. However, our subgroup analyses found that the effects of smartphone interventions were substantially larger when compared to inactive (g=0.56) than active (g=0.22) control conditions. The same pattern of effect sizes was observed in our meta-analysis of smartphone interventions for anxiety[19]. Previous reviews of other technological interventions for mental health conditions have reported similar findings, as a meta-analysis of virtual reality interventions for treating anxiety found significant effects in comparison to inactive controls, but no difference from traditional psychological treatments[51]. The extent to which the observed effects on depressive symptoms arise from using the device itself, rather than the psychotherapeutic components of the intervention, should be examined and quantified in future research, to further explore the notion of a "digital placebo" influencing findings[52].

We also explored other factors which may drive the effects of smartphone interventions for depressive symptoms, using a range of post-hoc subgroup analyses. With regards to population type, significant benefits of smartphone apps were only found for those with self-reported mild-to-moderate depression. This may be due to variations in subgroup sample sizes, as the majority of studies were conducted in non-clinical populations, thus leaving the analyses for major depression and bipolar disorder underpowered to detect significant effects. Nonetheless, the nature of smartphone interventions does appear to position them as an ideal self-management tool for those with less severe levels of depression. The observed effects indicate that these interventions are well-placed for delivering low-intensity treatment within a stepped-care approach[53], or even prevention of mild-to-moderate depression among the millions of people affected by subclinical symptoms[54]. The findings that neither age nor gender had any relationship with study effect size indicate that smartphone interventions may be applicable to a broad range of individuals.

With regards to intervention features, we found that those delivered entirely via smartphone devices had significantly greater effects than those which also involved other human/computerized aspects. Similarly, those using "in-person feedback" components had significantly smaller effects than those which did not. It seems counterintuitive that additional features/human feedback would decrease smartphone effectiveness. However, this relationship is likely due to the fact that apps not relying on external components have been designed as more comprehensive and self-contained tools. Indeed, we found some indication that studies which provided in-app feedback were more effective than those without. It should also be noted that the single study which compared a therapist-guided smartphone intervention to the same intervention without therapist support found equal effects across the two groups[33].

Smartphone interventions based on CBT significantly reduced depressive symptoms, as did those which incorporated aspects of mindfulness training or mood monitoring. However, we were not able to elucidate which of the features were most effective. A previous study which directly compared smartphone apps based on principles of either behavioral activation or mindfulness also found no overall difference between the two approaches[55]. Nonetheless, results showed that those with more severe depression experienced greater benefits from the behavioral activation app, whereas those with mild depression benefitted more from the mindfulness app. Understanding both which psychological interventions are best delivered via a smartphone and which patient populations will most benefit from smartphone-based interventions will require further research. As smartphone apps for mental health are becoming easier to create, focusing research on specific populations will enable more personalized and likely effective uses.

The trend-level negative correlation between effectiveness and length of intervention indicates that another factor to consider when designing optimal apps is user engagement[56]. Lower rates of user engagement over time have been found in numerous other mental health app studies[57-59]. Higher rates of engagement have also been associated with those apps designed for brief interactions[60], suggesting the need to customize interventions to the ways people use smartphones. While there is early

research on the optimal design and presentation of telehealth platforms[61,62], the impact on patient engagement and outcomes remains an area of nascent exploration. Understanding other factors related to app use, such as socioeconomic status, health literacy[63], technology literacy and health status[64,65], also remain important targets for further research.

A major strength of this meta-analysis is the strict adherence to a registered protocol which exactly described the search strategy, inclusion criteria, data extraction and analytic procedures. However, one drawback is that we only included smartphone interventions which have been evaluated in RCTs. Given the wide availability of mental health apps, ensuring that consumers and clinicians have access to evidence-based interventions is vital for informed decision making. While the sheer number of apps available, and their frequent updating[14,66], makes rating each impossible, research elucidating the components of effective apps and highlighting best practices may offer information immediately useful for clinical care. Of note, future studies must identify and report safety concerns regarding the use of smartphone interventions[67]. The ability of smartphones to immediately register entered mood data, compute if responses exceed a certain threshold, and if so activate emergency response systems, offer real time safety monitoring absent from traditional depression treatment.

Another limitation is the significant heterogeneity found across the analyses. Although this heterogeneity was statistically accounted for by the random-effects models when computing the effect size and respective p values, this still does indicate that significant between-study differences existed, even when subgrouping by sample/intervention type. Due to the extent of differences between studies, it was difficult to establish the single most effective components of smartphone interventions, or determine which populations these interventions are best suited for. Future studies which directly test alternative approaches against each other in non-inferiority controlled trials, while assessing outcome variation between subsamples of participants[55], would add great value to our understanding of what would constitute the optimal smartphone app for depressive symptoms, and in which populations these methods may be most effective.

In conclusion, the evidence to date indicates that mental health interventions delivered via smartphone devices can reduce depressive symptoms. However, delivering treatments via a smartphone introduces several new aspects which need to be considered, beyond the platform change alone. Specifically, we have yet to establish the ways in which user engagement, feedback loops, expectancy effects, and individual patient characteristics influence intervention outcomes. Rather than a barrier, these variables represent new opportunities for further research to optimize and personalize smartphone-based interventions.

Given the early indication of efficacy, and rapidly growing empirical research base, it is possible to envisage that continued technological advances will ultimately lead to scalable and cost-effective digital treatments for depressive symptoms[56,68]. Thus, along with continuing to design and evaluate optimal apps, further research should also be dedicated towards establishing feasible methods for implementing smartphone-based interventions within health care systems.

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Estimating treatment coverage for people with substance use disorders: an analysis of data from the World Mental Health Surveys

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Substance use is a major cause of disability globally. This has been recognized in the recent United Nations Sustainable Development Goals (SDGs), in which treatment coverage for substance use disorders is identified as one of the indicators. There have been no estimates of this treatment coverage cross-nationally, making it difficult to know what is the baseline for that SDG target. Here we report data from the World Health Organization (WHO)'s World Mental Health Surveys (WMHS), based on representative community household surveys in 26 countries. We assessed the 12-month prevalence of substance use disorders (alcohol or drug abuse/dependence); the proportion of people with these disorders who were aware that they needed treatment and who wished to receive care; the proportion of those seeking care who received it; and the proportion of such treatment that met minimal standards for treatment quality ("minimally adequate treatment"). Among the 70,880 participants, 2.6% met 12-month criteria for substance use disorders; the prevalence was higher in upper-middle income (3.3%) than in high-income (2.6%) and low/lower-middle income (2.0%) countries. Overall, 39.1% of those with 12-month substance use disorders recognized a treatment need; this recognition was more common in high-income (43.1%) than in upper-middle (35.6%) and low/lower-middle income (31.5%) countries. Among those who recognized treatment need, 61.3% made at least one visit to a service provider, and 29.5% of the latter received minimally adequate treatment exposure (35.3% in high, 20.3% in upper-middle, and 8.6% in low/lower-middle income countries). Overall, only 7.1% of those with past-year substance use disorders received minimally adequate treatment: 10.3% in high income, 4.3% in upper-middle income and 1.0% in low/lower-middle income countries. These data suggest that only a small minority of people with substance use disorders receive even minimally adequate treatment. At least three barriers are involved: awareness/perceived treatment need, accessing treatment once a need is recognized, and compliance (on the part of both provider and client) to obtain adequate treatment. Various factors are likely to be involved in each of these three barriers, all of which need to be addressed to improve treatment coverage of substance use disorders. These data provide a baseline for the global monitoring of progress of treatment coverage for these disorders as an indicator within the SDGs.

Key words: Substance use disorders, alcohol, drugs, treatment coverage, World Health Organization, United Nations Sustainable Development Goals

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Substance use is one of the biggest risk factors for burden of disease globally, accounting for 11% of total health burden[1]. There is increasing recognition of the need for a public health rather than a criminal justice approach to substance use disorders[2], to reduce current burden and prevent future health loss. This is evident in the United Nations' Sustainable Development Goals for 2030, where prevention and treatment of substance use disorders feature in the targets[3]. Two targets are of particular relevance to the current report: 3.5 - Strengthen prevention and treatment of substance use disorders including opioid use and harmful use of alcohol, and 3.8 - Universal health coverage.

There is considerable concern about barriers to treatment for mental and substance use disorders[4], and treatment coverage is thought to be far too low globally[5]. However, few data currently exist to shed light specifically on treatment coverage of substance use disorders. The World Health Organization (WHO)

published its Atlas on Substance Use in 2010[6], which compiled survey responses from member state focal points on levels of service provision for treatment of substance use disorders. Responses indicated a low perceived coverage of services for people with these disorders[6]: 40% of participants (in 115 countries) indicated that they believed that less than 10% of people with alcohol use disorders received outpatient counseling, and 45% of participants (in 95 countries) perceived a similarly low level for drug use disorders[6], but these reports were based on expert judgments rather than actual data.

Empirical data have been lacking to date. This paper presents findings from WHO's World Mental Health Surveys (WMHS) on levels of treatment received by people with substance use disorders, across countries with varied income and social characteristics, examining: a) the 12-month prevalence of DSM-IV substance use disorders in 26 countries worldwide; b) the proportion of people with these disorders who recognize a need for treatment for their condition; c) the proportion of those with perceived need who receive any treatment; and d) the proportion of treatment received that meets minimal standards for adequacy ("minimally adequate treatment").

METHODS

Data come from 26 countries participating in the WMHS (N=28 surveys). These included 12 countries classified by the World Bank[7] as low or middle income (Brazil, Bulgaria, Colombia, Iraq, Lebanon, Mexico, Nigeria, People's Republic of China, Peru, Romania, South Africa and Ukraine) and 14 as high income (Argentina, Belgium, France, Germany, Israel, Italy, Japan, The Netherlands, New Zealand, Northern Ireland, Poland, Portugal, Spain, and the United States). The first study in Colombia (2003) was conducted when that country was classified as lower-middle income, while the second (2011-2012) took place when it was classified as upper-middle income. The majority of surveys (N=19) were based on nationally representative household samples; three were representative of urban areas (Colombia, Mexico, Peru); two were representative of selected regions (Japan, Nigeria); and four were representative of selected metropolitan areas (São Paulo in Brazil; Medellin in Colombia; Murcia in Spain; Beijing and Shanghai in People's Republic of China).

Substance use disorders were assessed using the WHO Composite International Diagnostic Interview (CIDI) Version 3.0[8], a fully-structured lay-administered interview generating lifetime and 12-month prevalence estimates of mood, anxiety, behavioural and substance use disorders. The interview translation, back-translation and harmonization protocol required culturally competent bilingual clinicians to review, modify and approve key phrases describing symptoms[9]. Blinded clinical reappraisal interviews using the Structured Clinical Interview for DSM-IV (SCID-I)[10] were carried out in four WMHS countries. Good concordance was found with diagnoses based on the CIDI[11].

Trained lay assessors administered the interviews face-to-face in the homes of participants aged 18 years or older. Standardized interviewer training and quality control procedures were used in each survey. Informed consent was obtained before administering interviews. Ethics committees of the organizations coordinating the surveys approved the procedures for informed consent and protecting human subjects. Full details of the methodology are available elsewhere[12].

To reduce participant burden, the interview was divided into two parts. Part 1 was administered to all participants and included the core diagnostic assessment of mood and anxiety disorders. Part 2 was administered to all respondents with a certain number of mood and anxiety symptoms, and to a random proportion of those who had none, and included questions about disability and additional mental disorders as well as information on physical conditions. Part 2 individuals were weighted by the inverse of their probability of selection to adjust for differential sampling, and therefore provide representative data on the target adult general population. Further details about sampling and weighting are available elsewhere[12].

Substance use disorders in this paper are defined as meeting past 12-month DSM-IV diagnostic criteria for alcohol or drug abuse or dependence. For some countries in the earlier-conducted WMHS, a skip existed whereby those who did not endorse any symptoms of abuse of a substance were not assessed for dependence. In a separate exercise, we imputed data for these countries using data from nine more recently completed surveys without the skip pattern. Full details of this process are described elsewhere[13].

Participants with substance use disorders were asked if they had ever received treatment for emotional or substance use problems and if they had done so in the past year. Those who had received past-year treatment for emotional or substance use problems were asked if they had consulted a specialty mental health provider (psychiatrist, psychologist, other mental health professional in any setting, social worker or counsellor in a mental health specialty treatment setting, or a mental health hotline); a general provider (primary care doctor, other medical doctor, any other health care professional in a general medical setting); a non-medical provider (religious or spiritual advisor, social worker or counselor in a non-medical setting, any other type of healer); or a self-help group (e.g., alcoholics anonymous, narcotics anonymous). The treatment provider categories offered were consistent across countries. A more detailed description of WMHS 12-month treatment measures is presented elsewhere[14].

The definition of past-year "minimally adequate treatment" focused on the minimum number of visits typically required for psychosocial treatments. We assumed that pharmacological treatments were less common than psychosocial ones, but questions were not included in the survey that allowed us to determine which type of treatment was received[14]. The number of sessions used as the minimally adequate treatment threshold was four for people reporting treatment from a specialty mental health or general medical provider and six for those receiving treatment from non-medically trained professionals, based on

Table 1 World Mental Health Surveys: characteristics of the samples

Country	Sampling	Field dates	Age range	Sample size			Response rate
				Part 1	Part 2	Part 2 and age ≤44	
Low and lower-middle income countries							
Colombia	All urban areas of the country (about 73% of the total national population)	2003	18-65	4,426	2,381	1,731	87.7%
Iraq	Nationally representative	2006-7	18-96	4,332	4,332	-	95.2%
Nigeria	21 of the 36 states in the country (about 57% of the national population)	2002-4	18-100	6,752	2,143	1,203	79.3%
People's Republic of China	Beijing and Shanghai metropolitan areas	2001-3	18-70	5,201	1,628	570	74.7%
Peru	All urban areas of the country	2004-5	18-65	3,930	1,801	1,287	90.2%
Ukraine	Nationally representative	2002	18-91	4,725	1,720	541	78.3%
Total				**29,366**	**14,005**	**5,332**	**82.8%**
Upper-middle income countries							
Brazil	São Paulo metropolitan area	2005-8	18-93	5,037	2,942	-	81.3%
Bulgaria	Nationally representative	2002-6	18-98	5,318	2,233	741	72.0%
Colombia	Medellin metropolitan area	2011-12	19-65	3,261	1,673	-	97.2%
Lebanon	Nationally representative	2002-3	18-94	2,857	1,031	595	70.0%
Mexico	All urban areas of the country (about 75% of the total national population)	2001-2	18-65	5,782	2,362	1,736	76.6%
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%
Total				**28,927**	**16,913**	**3,072**	**78.5%**
High income countries							
Argentina	Nationally representative	2015	18-98	3,927	2,116	-	77.3%
Belgium	Nationally representative	2001-2	18-95	2,419	1,043	486	50.6%
France	Nationally representative	2001-2	18-97	2,894	1,436	727	45.9%
Germany	Nationally representative	2002-3	19-95	3,555	1,323	621	57.8%
Israel	Nationally representative	2003-4	21-98	4,859	4,859	-	72.6%
Italy	Nationally representative	2001-2	18-100	4,712	1,779	853	71.3%
Japan	Eleven metropolitan areas	2002-6	20-98	4,129	1,682	-	55.1%
The Netherlands	Nationally representative	2002-3	18-95	2,372	1,094	516	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	2010-11	18-65	10,081	4,000	2,276	50.4%
Portugal	Nationally representative	2008-9	18-81	3,849	2,060	1,070	57.3%
Spain	Nationally representative	2001-2	18-98	5,473	2,121	960	78.6%
Spain	Murcia region	2010-12	18-96	2,621	1,459	-	67.4%
United States	Nationally representative	2001-3	18-99	9,282	5,692	3,197	70.9%
Total				**77,303**	**39,962**	**10,706**	**63.5%**
Overall sample				**135,596**	**70,880**	**19,110**	**69.9%**

Table 2 12-month prevalence (% and standard error) of substance use disorders, perceived need for treatment, receipt of any treatment, and receipt of minimally adequate treatment

	12-month diagnosis of substance use disorders	Perceived need for treatment among those with substance use disorders	Any 12-month treatment among those with perceived need	Minimally adequate treatment among those with any treatment	Minimally adequate treatment among all those with substance use disorders	N
Low and lower-middle income						
Colombia	2.9 ± 0.4	42.7 ± 5.9	18.8 ± 6.5	18.9 ± 4.7	1.5 ± 1.0	90
Iraq	0.2 ± 0.1	61.5	84.7	0.0	0.0	7
Nigeria	0.9 ± 0.2	21.3 ± 5.5	95.4 ± 0.1	0.0	0.0	37
People's Republic of China (Beijing/Shanghai)	1.7 ± 0.4	21.8 ± 2.3	37.2 ± 3.9	0.0	0.0	52
Peru	2.3 ± 0.4	44.2 ± 5.8	26.5 ± 4.3	20.0	2.3 ± 1.8	50
Ukraine	6.6 ± 0.8	21.3 ± 2.9	38.8 ± 4.8	7.3 ± 6.8	0.6 ± 0.6	153
Total	**2.0 ± 0.2**	**31.5 ± 2.2**	**35.6 ± 3.1**	**8.6 ± 2.1**	**1.0 ± 0.4**	**389**
Upper-middle income						
Brazil (São Paulo)	3.8 ± 0.4	38.0 ± 5.0	51.0 ± 7.4	49.0 ± 6.8	9.5 ± 2.9	164
Bulgaria	1.2 ± 0.3	12.9 ± 6.0	30.6	59.6	2.4 ± 0.2	39
Lebanon	1.3 ± 0.8	27.0 ± 1.2	42.3	43.0	4.9 ± 0.2	12
Colombia (Medellin)	4.1 ± 0.6	31.3 ± 5.9	37.8 ± 11.7	26.8 ± 10.2	2.6 ± 1.3	85
Mexico	2.6 ± 0.4	41.0 ± 3.9	45.3 ± 3.1	13.8 ± 0.2	2.6 ± 1.3	80
Romania	1.0 ± 0.2	14.0 ± 8.7	100.0	100.0	10.2 ± 8.0	20
South Africa	5.8 ± 0.6	39.3 ± 3.9	72.0 ± 3.1	8.1 ± 0.6	2.3 ± 1.0	214
Total	**3.3 ± 0.2**	**35.6 ± 2.2**	**59.1 ± 2.9**	**20.3 ± 1.9**	**4.3 ± 0.8**	**614**
High income						
Argentina	2.4 ± 0.3	37.1 ± 5.8	59.5 ± 4.6	19.1 ± 4.9	4.2 ± 1.8	73
Belgium	2.7 ± 0.8	28.7 ± 4.1	66.4 ± 8.1	35.8 ± 16.5	6.8 ± 1.5	30
France	1.5 ± 0.3	44.4 ± 9.2	75.9 ± 9.1	44.4 ± 2.4	14.9 ± 3.8	31
Germany	1.6 ± 0.5	12.8 ± 0.8	63.5 ± 25.5	100.0	8.2 ± 3.0	25
Israel	1.4 ± 0.2	23.8 ± 4.4	54.9 ± 5.8	10.6 ± 0.8	3.4 ± 1.4	70
Italy	0.4 ± 0.1	27.2 ± 9.2	58.1	25.8	4.1 ± 0.6	11
Japan	1.0 ± 0.2	29.5 ± 4.2	55.5 ± 9.4	0.0	0.0	29
The Netherlands	1.8 ± 0.4	28.3 ± 6.7	81.4 ± 0.1	18.0 ± 0.1	4.2 ± 0.9	32
New Zealand	3.7 ± 0.3	51.4 ± 2.7	66.0 ± 2.8	30.4 ± 2.9	10.3 ± 1.6	474
Northern Ireland	3.5 ± 0.5	50.6 ± 3.8	85.3 ± 2.0	16.4 ± 4.3	7.1 ± 2.0	68
Poland	3.6 ± 0.3	24.9 ± 4.1	62.8 ± 3.2	39.6 ± 3.4	6.2 ± 1.8	181
Portugal	1.6 ± 0.3	35.5 ± 8.0	77.7 ± 8.4	37.5 ± 17.0	10.3 ± 6.2	40
Spain	1.1 ± 0.3	13.3 ± 2.9	78.8 ± 17.3	48.6 ± 1.9	5.1 ± 1.2	25
Spain (Murcia)	1.0 ± 0.4	53.6	78.2	83.9	35.2	17
United States	4.2 ± 0.4	59.9 ± 2.6	66.1 ± 2.8	43.9 ± 3.2	17.4 ± 2.0	314
Total	**2.6 ± 0.1**	**43.1 ± 1.4**	**67.5 ± 1.4**	**35.3 ± 1.8**	**10.3 ± 0.8**	**1,420**
Overall sample	**2.6 ± 0.1**	**39.1 ± 1.1**	**61.3 ± 1.3**	**29.5 ± 1.4**	**7.1 ± 0.5**	**2,423**
Chi-square tests						
Across all surveys (χ^2, df=27)	727.2 (p<0.0001)	241.2 (p<0.0001)	259.5 (p<0.0001)	63.2 (p<0.0001)	96.4 (p<0.0001)	
Across country income groups (χ^2, df=2)	50.2 (p<0.0001)	19.5 (p<0.0001)	68.4 (p<0.0001)	16.8 (p<0.0001)	43.5 (p<0.0001)	
Across high income countries (χ^2, df=14)	254.2 (p<0.0001)	188.5 (p<0.0001)	35.1 (p=0.0014)	16.5 (p<0.0001)	34.2 (p<0.0001)	
Across upper-middle income countries (χ^2, df=6)	176.4 (p<0.0001)	16.9 (p=0.0084)	46.2 (p<0.0001)	28.9 (p<0.0001)	13.4 (p=0.0073)	
Across low/lower-middle income countries (χ^2, df=5)	271.8 (p<0.0001)	48.9 (p<0.0001)	102.9 (p<0.0001)	0.3 (p=0.7816)	0.5 (p=0.7680)	

Table 3 12-month prevalence (% and standard error) of receipt of minimally adequate treatment using a broader definition including people who required treatment for substance use or emotional problems

	Minimally adequate treatment among those with any treatment	Minimally adequate treatment among all those with substance use disorders	N
Low and lower-middle income			
Colombia	47.2 ± 11.2	3.8 ± 1.7	90
Iraq	17.2	9.0	7
Nigeria	0.0	0.0	37
People's Republic of China (Beijing/Shanghai)	50.4	4.1 ± 1.0	52
Peru	42.9	5.0 ± 2.5	50
Ukraine	36.3 ± 9.9	3.0 ± 1.3	153
Total	**32.3 ± 3.6**	**3.6 ± 0.8**	**389**
Upper-middle income			
Brazil (São Paulo)	51.3 ± 5.0	9.9 ± 2.6	164
Bulgaria	59.6	2.4 ± 0.2	39
Lebanon	66.3	7.6 ± 0.3	12
Colombia (Medellin)	78.6 ± 5.6	9.3 ± 3.5	85
Mexico	23.7 ± 0.4	4.4 ± 1.4	80
Romania	100.0	10.2 ± 8.0	20
South Africa	26.0 ± 3.4	7.4 ± 1.8	214
Total	**36.4 ± 2.3**	**7.7 ± 1.1**	**614**
High income			
Argentina	77.6 ± 6.7	17.1 ± 4.7	73
Belgium	57.9 ± 22.7	11.1 ± 2.1	30
France	67.8 ± 5.5	22.8 ± 5.6	31
Germany	100.0	8.2 ± 3.0	25
Israel	80.0 ± 5.2	10.5 ± 3.2	70
Italy	53.2	8.4 ± 1.2	11
Japan	80.5	13.1 ± 2.7	29
The Netherlands	61.6 ± 0.3	14.2 ± 3.1	32
New Zealand	68.5 ± 2.5	23.3 ± 2.0	474
Northern Ireland	58.2 ± 9.4	25.1 ± 4.8	68
Poland	71.8 ± 2.8	11.2 ± 2.4	181
Portugal	81.7 ± 8.7	22.5 ± 6.5	40
Spain	92.9 ± 6.8	9.7 ± 4.4	25
Spain (Murcia)	47.1	19.8	17
United States	74.9 ± 4.4	29.6 ± 3.0	314
Total	**70.6 ± 2.1**	**20.5 ± 1.2**	**1,420**
Overall sample	**58.9 ± 1.7**	**14.1 ± 0.8**	**2,423**
Chi-square tests			
Across all surveys (χ^2, df=27)	102.6 (p<0.0001)	159.2 (p<0.0001)	
Across country income groups (χ^2, df=2)	72.2 (p<0.0001)	98.0 (p<0.0001)	
Across high income countries (χ^2, df=14)	12.2 (p=0.0324)	46.8 (p<0.0001)	
Across upper-middle income countries (χ^2, df=6)	14.6 (p<0.0001)	3.6 (p=0.5474)	
Across low/lower-middle income countries (χ^2, df=5)	2.3 (p=0.0399)	1.5 (p=0.4990)	

evidence from randomized controlled trials[15-18]. Any participant who was still in treatment at the time of interview was regarded as having met this definition, even if he/she had not yet had the required number of sessions.

Participants with substance use disorders were asked if they had ever talked to a "medical doctor or other professional (e.g. psychologists, counselors, spiritual advisors, herbalists, acupuncturists, and other healing professionals) about their use of alcohol/drugs/alcohol or drugs", and if they had done so in the past year. They were also asked if they had attended a self-help group focusing on alcohol or drugs in the past year. Those who reported any of these in the past year, and who had had at least the above-mentioned number of sessions of treatment, or those receiving such treatment at the time of interview, were defined as having received "minimally adequate treatment".

Since substance use disorders are often comorbid with various mental disorders, we also used a broader definition of "minimally adequate treatment". This included people receiving treatment for substance use or emotional problems in the past year for at least the above-mentioned number of sessions, or those receiving such treatment at the time of interview.

Survey sampling weights were applied in all analyses to make samples representative of target populations in terms of sociodemographic and geographic characteristics. Standard errors were estimated using Taylor series linearization implemented in Statistical Analysis System (SAS) to account for weighting and clustering[19]. To test for differences between countries; between high, upper-middle and low/lower-middle income country groups; and between countries within each of the three income groups, χ^2 tests were applied.

RESULTS

The characteristics of the study sites are shown in Table 1. The weighted average response rate across all surveys was 69.9%. A total of 70,880 participants were assessed for substance use disorders.

Across all countries, 2.6% of participants met 12-month criteria for a DSM-IV substance use disorder (Table 2). The prevalence was higher in upper-middle (3.3%) than in high (2.6%) and low/lower-middle (2.0%) income countries.

Across surveys, 39.1% participants with 12-month substance use disorders reported that they perceived a need for treatment. Levels of perceived need were higher in high (43.1%) than in upper-middle (35.6%) and low/lower-middle (31.5%) income countries.

Among people with substance use disorders who perceived a need for treatment, 61.3% had any contact with a service provider or self-help group in the past year. Again, the proportions were higher in high and upper-middle (67.5% and 59.1% respectively) than in low/lower-middle (35.6%) income countries.

Among people with substance use disorders who received any treatment, 29.5% received minimally adequate treatment. Levels were lower in low/lower-middle (8.6%) and upper-middle (20.3%) than in high (35.3%) income countries.

Among all people with substance use disorders, only 7.1% had received at least minimally adequate treatment in the past year (10.3%, 4.3% and 1.0%, respectively, in high, upper-middle, and low/lower-middle income countries) (Table 2). This was a joint function of only around one-third (39.1%) of those with such disorders perceiving that they needed treatment; two-thirds of the latter (61.3%) receiving any treatment; and around one in three of those with any treatment (29.5%) receiving a level of treatment that was minimally adequate (i.e., $0.391 \times 0.613 \times 0.295 = 7.1\%$). The two components driving this level down in particular were the proportion of people with substance use disorders perceiving a need for treatment and the proportion of those receiving any intervention who had a minimally adequate exposure to treatment. Nonetheless, it is important to recognize that it is the conjunction of all three components being considerably lower than 100% that leads to the very low overall prevalence of minimally adequate treatment.

The differences across all surveys and across country income groups with respect to the above variables were all significant at the $p<0.0001$ level. There were also significant differences within each country income group. Exceptions to this included that in low and middle income countries there was no variation in what were very low levels of minimally adequate treatment coverage.

Using the broader definition of minimally adequate treatment, which could have been for emotional or substance use problems, estimated levels of minimally adequate treatment were around two times higher (see Table 3). Among all people with past-year substance use disorders, using this broader definition, 14.1% had received minimally adequate treatment in the past year (20.5%, 7.7% and 3.6%, respectively, in high, upper-middle and low/lower-middle income countries).

DISCUSSION

Substance use disorders are prevalent in many countries, yet there have been no estimates of treatment coverage for these disorders cross-nationally. We found that, even using a definition of minimally adequate treatment that required relatively low levels of treatment exposure, coverage was extremely low: one in ten people with these disorders in high income countries, one in 24 people in upper-middle income countries, and only one percent of people in low/lower-middle income countries. Few countries, even in high income settings, had high coverage of minimally adequate treatment.

Several limitations of our study need to be considered. There might be differential social, religious and legal contexts across countries that affected willingness to report substance use. Several strategies were used to maximize the likelihood of honest reporting. First, pilot testing was carried out to determine the best way to describe the study in order to increase willingness to respond honestly and accurately. Second, in countries that do not have a tradition of public research, and where concepts of

anonymity and confidentiality are less familiar, community leaders were contacted to explain the study and obtain formal endorsement; these leaders announced the study and encouraged participation. Third, interviewers were centrally trained in use of non-directive probing, which is designed to encourage thoughtful, honest responding. Finally, especially sensitive questions were asked in a self-report rather than an interviewer-report format (among those who could read). These strategies were probably not effective in removing all cross-national differences in willingness to report, and remaining differences that could have contributed to reporting biases should be borne in mind. Nonetheless, the cross-national variations we found in the prevalence of substance use disorders are consistent with other global and country-level reports on substance use epidemiology[20-23].

We focused on psychosocial treatments, and did not include pharmacotherapies. However, although there is good evidence for the efficacy and effectiveness of opioid substitution therapy for opioid dependence[24,25], the evidence concerning other substance use disorders is less compelling. Evidence is mixed as regards pharmacotherapies for cannabis dependence[26] and lacking for psychostimulant dependence[27-29]. Medications for alcohol dependence (by far the most prevalent substance use disorder), such as naltrexone, have evidence of efficacy[30], but uptake and adherence are very low.

The available information suggests that pharmacotherapies may be even less frequently utilized to treat substance use disorders than psychosocial interventions we included here. For example, a systematic review found that only 8 per 100 people who inject drugs received opioid substitution therapy in the previous year[31]. In Australia, only around 0.5% of alcohol dependent people are estimated to have been prescribed naltrexone or acamprosate for the recommended 3-month duration[32].

We have not examined the role of comorbid disorders in affecting recognition of treatment need and access to services. This is not really a limitation of our study, in that we were primarily interested in treatment coverage among all people with substance use disorders. It is nonetheless important to acknowledge that these people, when they have additional mental disorders, may seek treatment for those other disorders, presumably increasing the likelihood of recognition of substance use disorders and the relevant treatment need.

The data we presented here are on self-reported service use. WMHS attempted to minimize inaccuracies in self-report by using commitment probes (i.e., questions measuring a subject's commitment to the survey), and excluding respondents who did not endorse such probes. Without studies that involve linkage to routine administrative or facility-based datasets on substance use treatment, there is no viable alternative. In many countries no such study designs are yet feasible, particularly in those with more limited infrastructure, due to both clinical and technological reasons.

Some surveys were conducted over a decade ago, raising the possibility that treatment rates in the relevant countries have changed since. We consider this unlikely, since more recent data on service provision collected for the WHO Atlas on Substance Use[6], and as part of the work of the Reference Group to the United Nations on HIV and Injecting Drug Use[31], similarly revealed very low perceived[6] and actual[31] coverage of services.

Response rates in the WMHS varied widely. We attempted to control for differential response through post-stratification adjustments, but it remains possible that survey response was related to the presence and severity of substance use disorders or treatment in ways that were not corrected. Having said that, existing evidence suggests that household and community-based surveys produce underestimates of problematic substance use for a number of reasons[20,33,34], suggesting that the estimates of prevalence reported here are conservative, and estimates of coverage potentially higher than actual levels.

The issue of perceived need for treatment is important. Even if treatment were easily available to all people with substance use disorders, our findings suggest that only one in three across countries would feel they need help, with slightly lower levels in low income settings. This strongly indicates that efforts to improve treatment coverage for substance use disorders will need to address both scaling up of services as well as supporting people with these disorders to recognize need for help and seek treatment. The latter is challenging, and complex public health interventions may be required that increase recognition of and willingness to address the problem among those living with these disorders, as well as their family and community.

Even among those who recognized the problem, a significant proportion did not access any services. This is likely to be the result of a complex array of individual, social and structural level barriers to seeking help. These include treatment availability, awareness of and access to effective treatment[35], fear of stigma (from family and community), financial barriers in contexts where treatment must be paid for by the individual, as well as legal, policy, service and even law-enforcement barriers to people with substance use disorders being able to access services[36-39].

Treatment access *per se* is not sufficient. There is a need to ensure treatment quality, which includes delivery of effective interventions in sufficient doses. There may be alternative methods of defining minimally adequate treatment within the constraints of the WMHS measure. It is clear, however, that most people needing treatment did not receive a minimally adequate level, even though our definition involved a relatively small number of service contacts. Overall, only one in 14 people with substance use disorders were receiving minimally adequate treatment.

Quality improvement initiatives, such as adoption of the evidence-based WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide[40-42] and work of the United Nations Office for Drug and Crime and the WHO in improving treatment quality in low and middle income countries (Treatnet)[43,44] are important efforts in this regard. However, significant investment in service systems and capacity building will need to occur in countries that currently have little to no formal treatment services or where substance use disorders are addressed outside of the health system.

Improving treatment coverage will hence require action at several levels: low rates of recognition of treatment need by people with substance use disorders, low rates of consultation by people who do recognize that they have a problem, and finally, inadequate treatment exposure when it is received. There is a need to act across all these levels to improve the coverage and quality of treatment for people with these disorders.

CONCLUSIONS

The United Nations Sustainable Development Goals reflect political commitment to scale up treatment coverage of substance use disorders. We have presented unique person-level data on services use by people with these disorders cross-nationally, demonstrating very low treatment coverage. This is true across country income levels, but worryingly, lowest in lower income countries, which also include the greatest share of the world's population.

Access to services is not the only barrier. A combination of limited recognition of treatment need, barriers to accessing treatment, and inadequacy of treatments delivered are all responsible for this low coverage.

These data might be considered as a baseline measure of this key sustainable development goal (and indeed for the WHO's Mental Health Action Plan 2013-2020, which aims to increase service coverage for severe mental disorders by 20% by the year 2020[45]). Given how poor current coverage is, it seems clear that substantial efforts across the above levels are needed to achieve the goal set by the United Nations for the year 2030. Regular review of this coverage indicator will be crucial.

APPENDIX

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Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis

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People with severe mental illness (schizophrenia, bipolar disorder or major depressive disorder) die up to 15 years prematurely due to chronic somatic comorbidities. Sedentary behavior and low physical activity are independent yet modifiable risk factors for cardiovascular disease and premature mortality in these people. A comprehensive meta-analysis exploring these risk factors is lacking in this vulnerable population. We conducted a meta-analysis investigating sedentary behavior and physical activity levels and their correlates in people with severe mental illness. Major electronic databases were searched from inception up to April 2017 for articles measuring sedentary behavior and/or physical activity with a self-report questionnaire or an objective measure (e.g., accelerometer). Random effects meta-analyses and meta-regression analyses were conducted. Sixty-nine studies were included (N=35,682; 39.5% male; mean age 43.0 years). People with severe mental illness spent on average 476.0 min per day (95% CI: 407.3-545.4) being sedentary during waking hours, and were significantly more sedentary than age- and gender-matched healthy controls (p=0.003). Their mean amount of moderate or vigorous physical activity was 38.4 min per day (95% CI: 32.0-44.8), being significantly lower than that of healthy controls (p=0.002 for moderate activity, p<0.001 for vigorous activity). People with severe mental illness were significantly less likely than matched healthy controls to meet physical activity guidelines (odds ratio = 1.5; 95% CI: 1.1-2.0, p<0.001, I^2=95.8). Lower physical activity levels and non-compliance with physical activity guidelines were associated with male gender, being single, unemployment, fewer years of education, higher body mass index, longer illness duration, antidepressant and antipsychotic medication use, lower cardiorespiratory fitness and a diagnosis of schizophrenia. People with bipolar disorder were the most physically active, yet spent most time being sedentary. Geographical differences were detected, and inpatients were more active than outpatients and those living in the community. Given the established health benefits of physical activity and its low levels in people with severe mental illness, future interventions specifically targeting the prevention of physical inactivity and sedentary behavior are warranted in this population.

Key words: Physical activity, sedentary behavior, severe mental illness, schizophrenia, bipolar disorder, major depressive disorder, physical activity guidelines, cardiovascular disease, premature mortality

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People with severe mental illness (schizophrenia, bipolar disorder or major depressive disorder) have higher levels of somatic comorbidities and premature mortality than the general population[1-3]. A recent meta-analysis[4] documented that mortality rates are approximately two to three times increased in these people. The higher premature mortality rates are largely attributable to cardiovascular disease[5].

In the general population, there is evidence that physical activity and its structured form, exercise, are broadly as effective as pharmacological interventions in preventing cardiovascular disease and reducing mortality[6]. However, people with severe mental illness experience a range of barriers to engaging in physical activity and exercise, such as high levels of perceived stress, somatic comorbidities, low mood, and a lack of self-confidence and of social support[7-11].

More recently, the impact of prolonged periods of sedentary behavior on risk of cardiovascular disease and mortality has also been noted. A large meta-analysis of general population studies[12] reported that sedentary behavior (e.g., sitting or lying down during waking hours) is independently associated with increased risk of developing cardiovascular disease, type 2 diabetes, and all-cause mortality.

Given that reduction in sedentary behavior and an active lifestyle are related to lower cardiovascular disease risk, understanding sedentary behavior, physical activity levels and their correlates among people with severe mental illness may aid in tailoring efforts to improve their long-term physical health outcomes[13]. Next to this, there is a substantial body of evidence that physical activity may have important mental health benefits in people with severe mental illness, reducing depression and improving social and cognitive functioning[14-19].

Despite growing recognition of the importance of reducing sedentary behavior and increasing physical activity levels to improve the health and wellbeing of people with severe mental illness, several important questions remain unanswered[20]. For instance, although people with major depressive disorder, bipolar disorder and schizophrenia have been found to be more sedentary and less physically active than controls[21-24], it is unclear whether differences between diagnostic subgroups exist. Identifying whether there are differences in sedentary behavior and

physical activity levels between these clinical groups may assist in developing rehabilitation priorities to prevent or reduce the risk for somatic comorbidities and premature mortality.

Pooling data across major diagnostic categories also allows for a large-scale investigation of the role of demographic and clinical variables (gender, age, illness duration, employment status, educational level, marital status), physical health measures (body mass index, cardiorespiratory fitness levels), other lifestyle (smoking, alcohol use) and treatment-related factors (psychotropic medication use), geographical differences, differences between treatment settings (e.g., outpatients versus inpatients) and differences in physical activity and sedentary behavior assessment (e.g., subjective versus objective assessments). Outcomes of these analyses will assist identification of specific vulnerable subgroups, environmental factors (e.g., differences in health-related policies or available facilities) and assessment methods.

The aims of the present global systematic review and meta-analysis were to: a) establish the mean time people with severe mental illness spend being sedentary or physically active (at light, moderate and high intensity) per day, b) investigate differences between clinical subgroups, c) investigate predictors of physical activity and sedentary behavior using meta-regression analyses and d) explore differences in physical activity and sedentary behavior between people with severe mental illness and age- and gender-matched healthy comparison subjects.

METHODS

This systematic review was conducted in accordance with the MOOSE guidelines[25] and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard[26].

Eligibility criteria

We included studies: a) with observational (cross-sectional, retrospective or prospective) and clinical or randomized controlled trial designs having baseline data; b) in adults with a diagnosis – established through standard procedures (e.g., structured or semi-structured diagnostic interviews) – of schizophrenia or related psychotic disorders, bipolar disorder or major depressive disorder according to DSM or ICD, irrespective of clinical setting (inpatient, outpatient, community or mixed); c) measuring physical activity and sedentary behavior using either self-report questionnaires (e.g., the International Physical Activity Questionnaire, IPAQ[27]) or objective measures (e.g., accelerometer).

Physical activity was defined as any activity that involved bodily movement produced by skeletal muscles and that required energy expenditure[28], while sedentary behavior was defined as an energy expenditure $\leq$1.5 metabolic equivalents of task (METs), while in a sitting or reclining posture during waking hours[29].

We excluded studies restricted to patients with or without cardiovascular diseases, or with no adequate measure of physical activity or sedentary behavior (i.e., no mean time per day engaged in light, moderate or high intensity physical activity, or sedentary behavior).

Search criteria, study selection and critical appraisal

Two independent authors (DV, BS) searched PubMed, PsycARTICLES, Embase and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from database inception to April 1, 2017, without language restrictions.

Key words used were "physical activity" OR "exercise" OR "sedent*" OR "sitting" OR "lying" OR "screen time" AND "severe mental illness" OR "serious mental illness" OR "schizophrenia" OR "psychosis" OR "bipolar disorder" OR "depression" OR "depressive disorder" in the title, abstract or index term fields.

Manual searches were also conducted using the reference lists from recovered articles and recent systematic reviews[21-24]. Clinicaltrials.gov, www.crd.york.ac.uk/prospero and www.who.int/trialsearch were searched to identify any unpublished trials.

After removal of duplicates, the reviewers screened titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. Next, the two reviewers considered the full texts of these articles and the final list of included articles was reached through consensus. A third reviewer (FS) was available for mediation throughout this process. Methodological appraisal included evaluation of bias (confounding, overlapping data, publication bias).

Outcomes

The co-primary outcomes were the mean time (min) per day that people with severe mental illness and healthy controls (in case-control studies) engaged in physical activity, or were sedentary. We collected separate data for light, moderate and vigorous physical activity, in addition to total physical activity, as defined by the original authors, if these data were reported.

We also collected data on those not meeting the physical activity guidelines of 150 min of at least moderate intensity physical activity per week[30], and physical activity behavior among healthy controls where this was reported.

Data extraction

One author (DV) extracted data using a pre-determined data extraction form, which was independently validated by two authors (BS and FS). The data extracted included first author, country, geographical region (Europe, North America, South America, Asia, Africa, Oceania), income status of the country (low or middle versus high according to the World Bank classification), setting (inpatient, outpatient, community, mixed), diagnostic group (schizophrenia spectrum, bipolar disorder, major depressive disorder), type of study (cross-sectional, prospective, retrospective, clinical or randomized controlled trial), age (years),

gender (% males), employment status (% employed), educational level (% with low education: elementary school or none), marital status (% single), psychotropic medication use (% taking antipsychotics, antidepressants, mood stabilizers), smoking (% current smokers), alcohol use (units of alcohol per day), body mass index (kg/m^2), cardiorespiratory fitness status (maximal oxygen uptake, ml/kg/min), physical activity and sedentary behavior assessment method (objective or self-report), and the primary outcomes.

Statistical analyses

Due to anticipated heterogeneity, a random effects meta-analysis was employed. Heterogeneity was measured by the I^2 statistic, with values above 75 considered as a high level of heterogeneity[31].

The meta-analysis was undertaken in the following steps. First, we pooled data on each physical activity category and sedentary behavior for people with severe mental illness. Next, we compared physical activity and sedentary behavior levels between people with schizophrenia, bipolar disorder or major depressive disorder and general population control groups that were matched on age and gender, using data from studies in which they were directly compared. In both analyses, only comparisons of specific severe mental illness groups or a severe mental illness group with a matched general population group were included that had been performed within the same study, in order to minimize variability due to different sampling and assessment procedures. We also conducted subgroup analyses to investigate differences between the three main diagnostic subgroups, between settings and geographical regions, and between physical activity assessment methods (i.e., self-reported vs. objective measures).

Further, we conducted meta-regression analyses (if the number of studies was at least 4) to investigate potential moderators: age (years), % males, % unemployed, % single, % with low education, illness duration (years), % antipsychotic medication use, % antidepressant medication use, smoking prevalence, number of alcohol drinks per day, body mass index (kg/m^2), and cardiorespiratory fitness levels (ml/kg/min), using the Comprehensive Meta-Analysis software (version 3).

Publication bias was tested using the Egger's regression method[32] and Begg-Mazumdar test[33], with a p value <0.05 suggesting the presence of bias. When we encountered publication bias, we conducted a trim and fill-adjusted analysis to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size iteratively, until the funnel plot was symmetrical around the (new) effect size.

RESULTS

Study selection and included participants

The electronic database searches identified 526 articles (excluding irrelevant papers and duplicates) which were considered at the title and abstract level. Four-hundred seventy full texts were reviewed and 401 were excluded (see Figure 1), with 69 unique studies (including 83 study estimates) meeting the eligibility criteria.

The final sample comprised 35,682 unique persons with severe mental illness (mean age 43.0 years; 39.5% male) and 2,933 controls. The median sample size was 46. At study level, the mean illness duration of people with severe mental illness was 16.6 years (range 1.9-31.6), the mean body mass index was 29.1 kg/m^2 (range 23.5-38.0) and the mean maximum oxygen uptake (measure of cardiorespiratory fitness) was 21.4 ml/kg/min (range 14.8-31.6). Twenty-four studies reported the percentage of current smokers, with a mean prevalence of 42.2% (95% CI: 35.9-48.5%).

In data available from 20 studies, 57.6% (95% CI: 45.9-69.2%) of the participants were single. In data reported in 16 studies, 62.3% (95% CI: 51.6-72.9%) were unemployed. Nine studies reported on the educational level, with a percentage of 31.5% (95% CI: 11.8-51.3%) having a level equal to or lower than elementary school.

In studies reporting on psychotropic medication use, 91.8% (95% CI: 85.4-98.1%) were prescribed antipsychotics, 46.7% (95% CI: 33.7-59.8%) antidepressants, and 17.9% (95% CI: 0.0-36.9%) mood stabilizers. Overall, 23 study estimates of physical activity were based on objective measures, three utilized objective and subjective measures and 57 were based on self-report questionnaires.

Daily amount of sedentary behavior

Across 21 study estimates, people with severe mental illness were sedentary for 476.0 min (95% CI: 407.3-545.4) per day during waking hours. While the Begg-Mazumdar (Kendall's tau $b = 0.0$, $p=0.97$) indicated no publication bias, the Egger test (bias = 7.1; 95% CI: 0.4-13.7, $p=0.04$) did. The trim and fill analysis found, however, the same amount of sedentary behavior per day (476.0 min).

People with severe mental illness were more sedentary than healthy controls (standard mean difference, SMD = 0.1; 95% CI: 0.0-0.2, $p=0.003$, $I^2=37.1$), equating to a mean difference of 10.1 minutes per day (95% CI: 1.9-22.2).

There were geographical differences in sedentary behavior ($p<0.001$, $I^2=99.2$). People in Europe were significantly less sedentary (413 min per day, 95% CI: 335-491) than those in North America (586 min per day, 95% CI: 461-712), South America (555 min per day, 95% CI: 266-844) or Asia (579 min per day, 95% CI: 369-789).

People with bipolar disorder (615 min per day, 95% CI: 456-774) were significantly more sedentary ($p<0.001$, $I^2=99.2$) than those with schizophrenia (493 min per day, 95% CI: 400-586) or major depressive disorder (414 min per day, 95% CI: 323-505). There were no significant differences according to the setting in which patients were living.

Greater amounts of sedentary behavior were found when assessed using objective (574 min per day, 95% CI: 479-668)

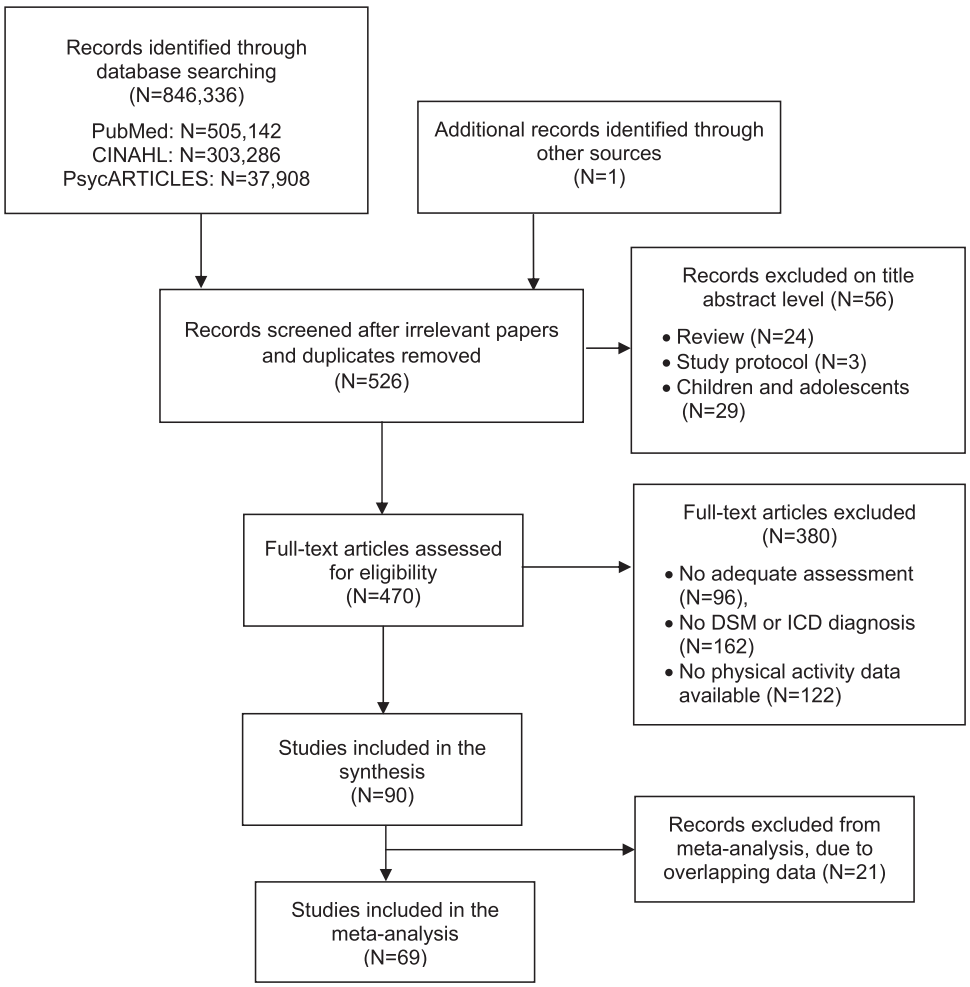

Figure 1 Flow diagram for the search results

versus self-reported measures (403 min per day, 95% CI: 322-485) ($p<0.001$).

None of the variables examined significantly moderated levels of sedentary behavior (see Table 1).

Daily amount of moderate or vigorous physical activity

The mean amount of moderate or vigorous physical activity in people with severe mental illness was 38.4 min per day (95% CI: 32.0-44.8). The Begg-Mazumdar (Kendall's tau $b = 0.5$, $p<0.001$) and the Egger test (bias = 7.2; 95% CI: 4.0-10.4, $p<0.001$) indicated there was publication bias. The trim and fill analysis confirmed, however, the same mean amount of moderate or vigorous physical activity per day (38.4 min).

People with severe mental illness engaged in less moderate physical activity (mean difference = 10.2 min, 95% CI: 17.2-3.2; SMD=0.35; 95% CI: 0.6-0.1, $p=0.002$, $I^2=76.8$) and vigorous physical activity (mean difference = 3.2 min, 95% CI: 6.4-1.1, SMD=0.2, 95% CI: 0.3-0.1, $p<0.001$, $I^2=53.0$) than healthy controls.

Significantly higher levels of moderate or vigorous physical activity were reported in Europe (47.6 min per day, 95% CI: 39.3-55.9), compared to North America (26.0 min per day, 95% CI: 17.9-34.0) and Oceania (13.1 min per day, 95% CI: 0.0-34.2) ($p<0.001$, $I^2=97.9$).

People with bipolar disorder (84.2 min per day, 95% CI: 60.3-108.1) engaged in significantly more ($p<0.001$, $I^2=97.9$) moderate or vigorous physical activity than those with schizophrenia (37.5 min per day, 95% CI: 29.1-46.0) and major depressive disorder (28.8 min per day, 95% CI: 17.8-41.8).

Significant differences in moderate or vigorous physical activity levels were observed according to the treatment setting where patients were assessed ($p=0.001$, $I^2=97.9$). Inpatients (90.1 min per day, 95% CI: 72.7-107.5) were more physically active than outpatients (32.5 min per day, 95% CI: 25.6-39.5), whilst community patients were the least active (16.0 min per day, 95% CI: 9.5-22.5).

There were no significant differences between objective and subjective measures of moderate or vigorous physical activity, but significantly lower levels of vigorous physical activity ($p=0.04$, $I^2=95.8$) were reported with objective measures (2.4

Table 1 Meta-regressions of moderators for physical activity behavior in people with severe mental illness

	N studies	β	95% CI	p	R^2
Sedentary behavior					
Age (years)	22	1.7	−4.6 to 8.1	0.58	0.00
Illness duration (years)	9	10.5	−1.2 to 22.4	0.08	0.36
% male	20	−0.2	−3.4 to 3.0	0.90	0.00
Body mass index (kg/m^2)	15	14.3	−1.8 to 30.5	0.08	0.05
% smoking	6	−9.0	−18.8 to 0.7	0.07	0.62
% antipsychotics	5	14.4	−11.4 to 40.3	0.27	0.04
Moderate or vigorous PA					
Age (years)	34	0.7	−0.0 to 1.5	0.05	0.00
Illness duration (years)	12	−0.3	−2.0 to 1.4	0.72	0.11
% male	34	0.3	0.1 to 0.6	0.03	0.05
% single	4	−1.3	−2.2 to −0.4	0.003	0.60
% unemployed	6	−0.3	−0.4 to −0.2	<0.001	1.00
Body mass index (kg/m^2)	28	−3.2	−4.9 to −1.4	<0.001	0.07
% smoking	9	0.6	0.3 to 0.9	<0.001	0.67
% antipsychotics	14	0.5	−6.1 to 7.1	0.88	0.00
% antidepressants	10	−0.6	−1.2 to −0.1	0.02	0.00
Maximum oxygen uptake (ml/kg/min)	8	9.9	−6.7 to 13.0	<0.001	0.01
Not meeting PA guidelines					
Age (years)	27	0.0	−0.0 to 0.0	0.17	0.00
Illness duration (years)	9	0.0	−0.0 to 0.1	0.04	0.71
% male	27	−0.0	−0.0 to −0.0	0.11	0.00
% single	9	−0.0	−0.0 to 0.0	0.80	0.00
% low educational level	5	0.0	0.0 to 0.1	0.005	0.82
Body mass index (kg/m^2)	18	−0.0	−0.2 to 0.1	0.59	0.00
% antipsychotics	11	−0.0	−0.0 to −0.0	0.01	0.61

PA – physical activity

min per day, 95% CI: 0.0-4.8) vs. subjective reports (7.2 min per day, 95% CI: 5.7-8.7).

Meta-regression analysis (Table 1) illustrated that a higher percentage of people taking antidepressants, a lower percentage of male and single participants, a higher percentage of unemployment, a lower percentage of smokers, a higher body mass index and a lower cardiorespiratory fitness were associated with lower moderate or vigorous physical activity levels.

Across 28 study estimates and 29,523 people with severe mental illness, 54.7% (95% CI: 48.8-60.6%; $p<0.001$, $I^2=95.8$) did not meet the recommended 150 min of moderate physical activity per week. While the Begg-Mazumdar (Kendall's tau $b = 0.1$, $p=0.58$) indicated there was no publication bias, the Egger test (bias = 3.1; 95% CI: 1.3-4.9; $p=0.002$) did. The trim and fill analysis found a lower rate (N adjustments = 7): 44.9% (95% CI: 38.2-49.7%).

People with severe mental illness were more likely not to meet the physical activity guidelines than healthy controls (odds ratio = 1.5; 95% CI: 1.1-2.0, $p<0.001$, $I^2=95.8$).

People with bipolar disorder (31.4%, 95% CI: 12.8-58.9) were less likely not to meet the guidelines than those with schizophrenia (54.8%, 95% CI: 43.4-65.6%) and major depressive disorder (60.2%, 95% CI: 49.5-69.9%). There were no significant differences between settings. The proportion meeting the target was similar when assessed via objective measures (57.0%, 95% CI: 37.7-74.4%) or subjective questionnaires (54.5%, 95% CI: 48.2-60.6%). Meta-regression analysis demonstrated that longer illness duration, lower educational level, and antipsychotic medication prescription were associated with a greater likelihood of not meeting the physical activity target (see Table 1).

DISCUSSION

The present meta-analysis is the first to examine sedentary behavior and physical activity levels and relevant predictors in

people with severe mental illness using all of the data available around the world. Data indicated that these people are more sedentary than age- and gender-matched controls from the general population, spending a mean of 476 min per day (or almost 8 hours) during waking hours in sedentary behavior. In addition, people with severe mental illness are significantly less physically active and spend only an average of 38.4 min per day in moderate or vigorous physical activity. Meta-regression analysis revealed that a higher body mass index is associated with lower moderate or vigorous physical activity. Antidepressant prescription, male gender, unemployment, non-tobacco use, and being single are associated with lower moderate or vigorous physical activity levels.

In addition, our analyses revealed that approximately half of people with severe mental illness do not meet the recommendation of at least 150 min of moderate physical activity per week, and that these people are 50% more likely not to meet this physical activity target compared to matched healthy controls. Not meeting physical activity guidelines is associated with longer illness duration, less years of education and antipsychotic medication prescription. Overall, not meeting physical activity guidelines is estimated to occur in around 30% of the world population[34]. Moreover, in the general population, it is estimated that a decrease of 10% in the number of people not meeting these guidelines could result in averting 533,000 premature deaths each year[35]. Reducing sedentary behavior and increasing physical activity levels of people with severe mental illness should therefore be a global public health priority. Our findings support recent calls to expand individual-focused and community-level interventions at a global level in order to reduce excess mortality in people with severe mental illness[36,37].

We found significant geographical differences. People with severe mental illness in Europe tend to have the highest moderate or vigorous physical activity levels. One possible explanation is that in many European mental health care settings, in contrast with elsewhere in the world[38-40], physical activity is an integral part of the multidisciplinary treatment of people with severe mental illness[41]. These findings indicate that, although interest in physical activity in the treatment of these people is increasing, the potential utility of physical activity interventions as an integrated component of standard care is yet to be fully embraced in most parts of the world.

The higher levels of moderate or vigorous physical activity in inpatients suggest that there is increasing interest in aerobic exercise as a valuable treatment modality in psychiatric centres[42], especially when delivered by specialized health care professionals[43,44]. In regions with limited resources, where such specialists are not readily available, the existing workforce should be trained in assisting patients to reduce sedentary habits and adopt a more active lifestyle[45-48]. In these low-resource contexts, in particular in outpatient and community settings, a stepped-care approach, where patients start with self-management, may be a feasible strategy. Then, if patients do not achieve guideline-specific levels of physical activity, they could continue with a manualized approach under the supervision of a non-specialist (e.g., a nurse). Patients would only be referred to a specialist clinician (e.g., an exercise physiologist or physiotherapist) if no significant increase in physical activity levels occurs.

Our data documented that higher body mass index, lower cardiorespiratory fitness, and antidepressant or antipsychotic prescription might constitute barriers for engaging in physical activity. The association between antidepressant or antipsychotic prescription and less physical activity may be due to fatigue as a medication side effect. On the other hand, a psychotropic medication prescription might as well be a measure-of-proxy for illness severity. Due to the limited data available, we were not able to assess the role of individual psychiatric symptoms and illness severity in sedentary behavior and physical activity levels.

Our analyses also demonstrated that socio-demographic factors should be considered. Those who are single or unemployed, those with a low educational level and men are less physically active. Novel strategies targeting outpatient and community programs are warranted, as we consistently found that inpatients engaged in higher levels of physical activity.

In our study, people with schizophrenia were the least physically active. While people with bipolar disorder were the most physically active, they were also the most sedentary diagnostic subgroup, indicating that both physical activity and sedentary behavior should be considered. In people with severe mental illness, sedentary behavior should be considered independent from physical activity and has been associated with poorer cognition[49] and a worse metabolic profile[50]. Therefore, interventions to reduce sedentary behavior should be a major treatment focus. Pragmatic and feasible interventions to reduce sedentary behavior may include encouraging patients to rise from a chair and move around during television commercial breaks, or adding brief (e.g., less than or equal to 5 min) walks throughout the day, for example walking short distances rather than using motorized transport[51].

Although many people with severe mental illness are unemployed, those who continue working in more sedentary environments, such as office workers, should be supported in the use of sit-to-stand desks as an effective way to reduce sedentary time[52]. In addition, there is provisional evidence that, as in the general population[53], higher levels of physical activity may ameliorate the relationship between sedentary behavior and metabolic risk[54], which adds to the pressing need to promote physical activity in this population.

Another interesting finding in our subgroup analyses was that objective measurement of physical activity resulted in higher estimates of sedentary behavior and lower estimates of vigorous physical activity compared to self-report questionnaires. In contrast with general population studies, this result suggests that people with severe mental illness may underestimate the amount of sedentary behavior they engage in and overestimate their vigorous physical activity levels. There have been concerns that reliance on self-report may lead to inaccu-

rate estimates of physical activity in people with severe mental illness[55], which may be exacerbated by cognitive impairment which is frequently present among people with schizophrenia and bipolar disorder[56] as well as major depression[57]. Clearly, this calls for the development of more accurate and clinically useful measures for clinical practice, if we are to monitor and record physical activity in routine care[58].

Finally, a somewhat counter-intuitive finding was the association between higher moderate or vigorous physical activity levels and higher prevalence of tobacco smoking. It may be that individuals with severe mental illness who smoke at low levels have an increased affinity for physical activity, perhaps because of its reward-related reinforcing effects. However, more research is needed to understand this relationship.

Whilst the results of this meta-analysis are novel, several limitations should be noted. First, the vast majority of the studies included relied on data drawn from self-report questionnaires. Second, we encountered high heterogeneity in the meta-analyses we undertook, which is expected when pooling observational data[25]. However, our subgroup and meta-regression analyses explained a large part of the between-study heterogeneity. Third, there was inadequate information regarding specific medications prescribed, which precluded meta-analytical or meta-regression analyses. Fourth, the data were cross-sectional and to date there is a paucity of longitudinal physical activity research in people with severe mental illness. Future research is required to understand the impact of specific antipsychotics, antidepressants and mood stabilizers on sedentary and physical activity behavior. Nevertheless, allowing for these caveats, the current meta-analysis provides important information for clinicians and researchers.

In conclusion, our data document that people with severe mental illness engage in significantly more sedentary behavior and significantly less physical activity compared to healthy controls, and are less likely to meet physical activity targets as embodied in international guidelines. Addressing these modifiable risk factors for premature mortality through the implementation of evidence-based sedentary behavior reduction and physical activity promotion interventions is an international imperative. We identified a number of potentially modifiable correlates of sedentary behavior and physical activity in this vulnerable population. Translation of evidence-based interventions into routine care specifically aimed to reducing sedentary behavior and increasing physical activity is urgently required.

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Screening for depression: the global mental health context

Depression is the leading mental health related cause of the Global Burden of Disease. The sequelae of depression contribute further to its immense public health burden, including impact of maternal depression on child growth and development, and increased risk for dementia, suicide, and premature mortality from co-occurring physical disorders. The World Health Organization (WHO)'s Mental Health Gap Action Programme (mhGAP) guidelines recommend antidepressant medication or brief psychological treatments for moderate to severe depression, and there is a mounting body of evidence from trials on how these treatments can be delivered in real-world primary care settings in low resource contexts by relying on lay health workers and primary care practitioners[1].

Despite this evidence on cost-effective and scalable models of depression care, the vast majority of people suffering from this condition – for example up to 90% in India and China – do not receive treatment. A major barrier to receiving treatment is the low detection rate in primary care. To date, virtually all efforts to improve detection have focused on training of general practitioners, and this is also the approach adopted by the mhGAP guidelines. Yet, the evidence in support of training is weak. In an early WHO Collaborative Study, following training of primary care workers in four countries (Colombia, India, Sudan and Philippines) to detect mental disorders, detection rates barely increased from 2.4% to 2.6%[2]. In a Kenyan study, detection rates post-training did not significantly differ between the trained and the control group[3]. In a cluster randomized controlled trial conducted in Malawi, while there was a significant difference between the 5-day mental health trained primary care workers and workers in the control condition, the training arm failed to detect 90% of patients with depression[4]. In short, training alone has a negligible or, at best, a small impact on detection rates.

It is in this context that screening should be considered as a cost-effective supplementary strategy to improve the detection of depression in routine care settings and translate the evidence of effective interventions to reduce its global health burden. Many of the trials in low and middle income countries, as well as US-based studies such as IMPACT[5] and PROSPECT[6], have shown that lay workers or general medical ancillary personnel (e.g., nurses and social workers) can be taught to screen for depression and other common mental disorders effectively using brief questionnaires with a high degree of acceptability.

We emphasize that the use of such questionnaires also meets the criteria recommended for screening tests, for example, that the test is valid, feasible at a very low resource cost, and that there are cost-effective interventions to follow. Additionally, screening using symptom measures avoids the complexity of diagnosis, and the same measure can be used for monitoring of clinical progress and outcomes, as in the Improving Access to Psychological Treatments national program in England[7]. Based on these experiences, and the recent recommendations of the US Preventive Services Task Force[8], we propose steps regarding the implementation of screening for depression in routine care.

The first consideration is *what* measure should be used for screening for depression. Experience supports the use of brief, self-report questionnaires, such as the Patient Health Questionnaire (PHQ-9)[9], which has been widely used internationally, takes a few minutes to complete, can be used to generate a diagnostic outcome, and shows sensitivity to treatment response. One caveat, however, is that, because depression and anxiety frequently co-exist, additional brief screening for anxiety may also be appropriate, using such measures as the Generalized Anxiety Disorder 7 (GAD-7)[10].

The second consideration is *how* screening should be done. These questionnaires can be delivered either in self-report or health worker delivered formats and, with the growing use of digital technologies, can also be used on devices to allow for self-screening and remote monitoring of clinical progress. Stepped approaches to screening, for example using the two-item version of the PHQ routinely for all attenders, followed by the remaining seven items for those who screen positive on at least one question, may also be a cost-effective approach.

The third consideration is *who* should be screened. Given the high prevalence of depression and other common mental disorders in primary care populations, one option is to routinely screen all adult attenders. However, this may not be feasible in the very low resource settings, where the possible yield of cases may greatly exceed the feasibility of delivering effective interventions. This challenge may be partly addressed by calibrating the screening questionnaire cut-point to a higher level, so that only more severe presentations are identified. An alternative approach is to screen high-risk or vulnerable groups such as mothers with newborn children, people with chronic diseases, people with chronic sleep disturbances or medically unexplained somatic complaints or severe social stressors.

The fourth consideration is *when* screening should take place. Since depression is frequently a recurring condition, annual screening, in particular for individuals with a prior history, would seem sensible.

In conclusion, now that we have strong evidence on how we can effectively treat patients with depression in a cost-effective way using locally available resources, it is time to scale up this evidence through addressing the barrier of low detection rates by instituting routine screening. This recommendation to improve detection needs to be accompanied by a research agenda addressing many of the considerations outlined above regarding the implementation of screening, such as the measure to be used, the frequency, the method of delivery and the target group.

Routine screening for depression in adult primary care attenders is a vital milestone in the journey towards reducing the very large treatment gaps globally and scaling up the robust evidence on cost-effective interventions for this common mental disorder.

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Antidepressants and suicide risk in depression

The last years have witnessed a controversy about antidepressant use that is still in the balance. On one side, treating depression with antidepressants seems to reduce the risk of suicide at an epidemiological level[1]. This is in accord with the high population attributable risk for a first occurrence of suicidal ideation and suicide attempts in people with mood disorders, which has been estimated at 51% and 44% respectively[2], and with the finding of a history of depressive episodes in most completed suicides (approximately 60%). On the other, the possible emergence or worsening of suicide risk at the beginning of treatment, at least among the young, has led regulatory bodies to issue specific warnings. Antidepressant prescriptions fell as an effect of these warnings, also in adult populations, and research about the *suicidal effect* of antidepressants was fostered. Doubts about the usefulness of antidepressants in the treatment of depressed patients who are or become suicidal need an urgent response.

The controversy began in 2003, when re-analyses of data from randomized controlled trials (RCTs) found that the risk of suicidal ideation or suicidal attempts among youth treated with antidepressants was doubled compared with those treated with placebo (4% vs. 2%), independently of the indication (see Brent[3] for a review). Later, a meta-analysis of RCTs across the life span reported an increased risk of "suicidality" with antidepressants under the age of 25 years. Of note, this risk was found only in patients with psychiatric indications other than depression, while antidepressants showed a protective effect in depressed elderly subjects[4]. Reporting about suicidal events in RCTs, most of which are not aimed at examining suicidality, is limited by important shortcomings. Anyway, the warnings – amplified by the alarming media coverage – led many physicians to decrease antidepressant prescriptions, even when no alternative was available[5].

The use of antidepressants to prevent suicidal behaviour is supported by several facts. First, most pharmacoepidemiologic studies, which are more representative of patient populations than RCTs, show a protective effect of antidepressant use with respect to suicide[1]. Second, although observational studies suggest an increased risk of suicidal ideation or suicide among young people receiving antidepressants, antidepressants actually seem to reduce the risk when confounding by indication is accounted for[3]. Third, post-mortem studies with toxicological detection of antidepressants indicate that suicides in depressed patients occur more often among those who are not taking an antidepressant[1].

Furthermore, treatment-related suicidal events can be minimized. The guidelines produced by the US Food and Drug Administration and the UK National Institute for Health and Care Excellence recommend a closer monitoring of antidepressant treatment in suicidal patients or those younger than 30 years, with a follow-up visit one week after the start of a new antidepressant. Web-based tools and smartphone apps may help in the near future to improve the monitoring of patients at risk. On the other hand, depressed patients are frequently non-adherent to treatment, which has made some authors wonder if antidepressants have actually any effect, positive or negative, on suicide rates at the level of the general population[6].

This controversial context has also fostered research, but only some observational studies have investigated the predictors of *de novo* suicidal behaviour in depressed patients starting an antidepressant[5,7]. In general terms, treatment-emergent suicidal ideation is infrequent in adults and tends to disappear progressively in the first 4-6 weeks of treatment. The lack of response to treatment, a history of previous suicide attempts and a history of substance use disorders are the best predictors of the emergence of new suicidal ideation or attempts. Of note, starting treatment with high doses of antidepressants (beyond the recommendations) seem to increase the risk of suicidal ideation or attempts[5].

Suicidal events at the onset of antidepressant treatment may also be associated with an undiagnosed bipolar disorder, whose presence may be suggested by early onset of depression and atypical depressive episodes. Moreover, the age effect in treatment-emergent suicidal ideation or attempts is probably influenced by the more frequent association of substance abuse and impulsive aggression with depression in the youth.

All these findings sum up to the general need of a paradigm shift in the treatment of suicidal patients. The clinical response to antidepressant treatment is poorer in subjects presenting suicidal ideation or a history of suicide attempts, independently of clinical confounders or the type of antidepressant[7]. Those who are most in need of an efficient treatment respond less well. The

current development of RCTs designed for depressed patients at risk for suicide will help to refine short-term treatment strategies for these patients.

Some potential treatments for suicidal patients deserve to be investigated in depth: first, the combination of lithium or antipsychotics with antidepressants; second, the nearly immediate and dramatic anti-suicidal effect of low doses of ketamine. This latter effect is particularly intriguing and might be explained by an impact on glutamatergic neurotransmission, particularly in the anterior cingulate cortex[5]. There is also mounting evidence on the role of social, psychological and physical pain in suicidal behaviour. The μ-opioid receptor system is involved not only in physical pain but also in the modulation of social pain, and represents a relevant target for suicide prevention. A four-week study in patients with elevated suicidal ideation showed that an ultra-low dose of sublingual buprenorphine was more effective than placebo in the reduction of that ideation[8].

A call for caution is finally needed regarding the current risk of psychiatric patients to undergo physician-assisted suicide. Legalized physician-assisted suicide should not be a manifestation of therapeutic nihilism[9]. It is ethically mandatory that evidence-based treatments and available anti-suicidal strategies be implemented whenever a psychiatric condition is present.

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The clinical relevance of qualitatively distinct subtypes of depression

Depression is a heterogeneous disorder, with great variation in symptoms and behavior, severity, onset and course. Given its broad nature, it is likely that diverse aetiologic and pathogenetic factors are involved in different subtypes of the disorder. Despite encouraging research findings, including genetics, epigenetics, gene expression, combinations of biomarkers in peripheral blood, neurocognition, and neuroimaging, biomarker candidates for depression remain still not useful in clinical practice. Furthermore, aetiologic and pathogenetic factors are rarely studied in subtypes of depression.

Clinically, subtypes of depression are to some degree qualitatively distinct and of some relevance in predicting prognosis and treatment outcome. Different subtypes of depression can be identified according to polarity (unipolar vs. bipolar), symptoms (melancholic, atypical, psychotic, or anxious), onset (specific events, seasons, or age), recurrence, and severity[1]. These diagnostic specifiers and subgroups may guide treatment decisions to some extent.

Most clearly, the distinction between unipolar and bipolar depression, the latter being characterized by decreased psychomotor activity[2], implies different treatment options. Antidepressants are used as first-line monotherapy in unipolar but not in bipolar depression[1], as in the latter they may induce switch into mania or mixed episodes, destabilize mood and potentially increase the risk of developing rapid cycling. Further, the distinction between mild, moderate and severe depression predicts the long-term risk of relapse and suicide[3] and guides to some extent the choice of treatment (e.g., mild depression should not be treated with antidepressants, as long as the depressive episode does not get a chronic course). There is some evidence that tricyclics (TCAs) and electroconvulsive therapy are more effective in melancholic depression than selective serotonin reuptake inhibitors (SSRIs) and psychotherapy, and that monoamine oxidase inhibitors are more effective in atypical depression, although this evidence is still controversial. Psychotic depression often requires treatment with a combination of antidepressants and antipsychotics, and light therapy has effect in seasonal depression. Finally, compared with late-onset depression (31-70 years), early-onset depression (18-30 years) may present with more comorbid personality disorders and neuroticism, and fewer stressful life events prior to onset, but treatment response has not been found to differ between these groups[4].

Beyond these partly controversial clinical and treatment implications, subtyping of depression remains to be investigated in much more detail. A so far widely overlooked complication in the above studies is that the pathophysiology and psychopathology of depressive episodes may change during the course of illness, due to the progressive nature of unipolar disorder, with increasing risk of recurrence, duration and severity of episodes[5]. Consequently, a staging model has been suggested in unipolar depression, with a prodromal stage with vague symptoms and subthreshold mood symptoms progressing to a single depressive episode, recurrent depression and ultimately treatment resistance[6]. Nevertheless, there is at present no clear evidence that treatment response decreases with the number of episodes[6].

A more psychopathological and poorly studied approach is to characterize subtypes according to the presence of the core features of depression, i.e., symptoms that are required to fulfill

DSM and ICD operational criteria. According to the DSM-5, the core features of depression are depressed mood and anhedonia. ICD-10 adds a third core item, "decreased energy or increased fatigue". These core features have been identified clinically to be central to depression and are included in the six-item version of the Hamilton Depression Rating Scale, along with guilt feelings, psychic anxiety and psychomotor retardation[7]. This scale is clinically and psychometrically valid, but does not characterize phenomenologically the three core features. These features may also identify three subtypes of depression, marked predominantly by depressed mood, anhedonia or decreased energy/increased fatigue, respectively.

However, such potential subtypes of depression have been studied rarely, partly due to the fact that the core items of depression have not been clearly operationalized. The ICD-10 Diagnostic Criteria for Research state that depressed mood should be "to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances (non-reactivity), and sustained for at least 2 weeks". This wording is partly replicated in the ICD-10 itself: "The lowered mood varies little from day to day, and is often unresponsive to circumstances, yet may show a characteristic diurnal variation". The DSM-5 requires depressed mood to be present "most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others". Anhedonia has also been seldom studied, partly due to its inconsistent conceptualization in depression[8]. Aspects of anhedonia (e.g., low interest-activity), have been found to predict poor antidepressant outcome and prolonged time to remission[8]. Analogously, although psychomotor disturbances may have prognostic implications, explicit definitions of psychomotor phenomena remain elusive[9].

We are currently developing and testing the applicability of a new diagnostic assessment of depression, which focuses on the phenomenology of the core features of the syndrome according to ICD-10 and DSM-5 (depressed mood, anhedonia, and decreased energy), the CORE Interview. We propose that an increased emphasis on the phenomenology of the core items will improve the validity of the diagnosis of depression and help to identify clinically meaningful subtypes. A more specific diagnosis can help clinicians identify the patients who are more likely to benefit from certain types of antidepressant treatment and improve the search for genes and biomarkers for mood disorders.

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Who are excellent lithium responders and why do they matter?

After more than six decades of use in modern psychiatry, lithium remains one of the first-line treatments for prevention of manic and depressive recurrences of bipolar disorder. A number of longitudinal observations report remarkably similar response rates of about 30%, although this estimate is probably influenced by non-compliance in some patients[1]. Some of those people who stabilize on lithium particularly well have been called excellent, full or complete responders[2]. These patients not only cease experiencing further mood episodes, but also return to their pre-illness level of functioning.

This raises a question as to where these patients fit in the current diagnostic classification. Robins and Guze proposed five criteria to delineate a diagnostically valid disorder in psychiatry, including clinical description, laboratory studies (biological markers), delimitation from other disorders, stability of diagnosis at follow-up, and family studies (familial nature of the condition)[3]. Lithium responders have distinct clinical features that largely fit these criteria and thus might constitute a distinct diagnostic category[4].

Their treatment response is stable in the long term[5], they present with a typical recurrent episodic illness and relatively fewer comorbidities[6], and their affected relatives often respond to lithium as well[7]. The episodic pattern of the clinical course, which is among the strongest correlates of lithium response, is also familial[8]. There are also accumulating data on biological markers specific to these patients and differentiating them from lithium non-responders, including most recently data from studies of neurons derived from induced pluripotent stem cells[9]. Hence, compared to other psychiatric conditions, lithium responsive bipolar disorder appears to be a narrower, more homogeneous and highly heritable phenotype. Distinguishing this phenotype from the rest of mood disorders has both clinical and heuristic value.

Clinically, many lithium responders do not stabilize on other treatments; when they are unable to stay on lithium, for instance because of poor tolerability, finding an effective replacement often becomes difficult[10]. The search for clinical predictors of lithium response is still going on, but several factors are emerging repeatedly out of different studies. The key features are the episodic recurrent clinical course and the family history of bipolar disorder, especially lithium responsive bipolar disorder[7]. However, more accurate clinical and biological predictors of lith-

ium response still need to be introduced into clinical practice; as more options for long-term treatment of bipolar disorder are available, it is crucial to help clinicians select the right treatment for individual patients.

At the same time, there are many open questions that deserve further study. Among them are uncertainties about the time to response. Clinically some people improve after few days, while others need several months to stabilize. This has led some to suggest that the morbidity in the first year of treatment may not be completely predictive of long-term outcome. Robust predictors of excellent response will help deciding in specific cases for how long a lithium trial needs to extend.

Recognition of lithium responders as a specific form of bipolar disorder has also implications for planning of clinical services. For instance, clinical programs that provide primarily one-time consultations or only short-term follow-up are at a higher risk of missing these patients. Additionally, the tendency to use unnecessary drug combinations can be damaging, obscure the clinical presentation and lead to treatment refractoriness. As a result, a number of potential responders may receive suboptimal treatment, paradoxically sometimes even in specialty programs.

From the research point of view, it is valuable to study a medication that works fully in a proportion of patients rather than drugs that are partially effective in almost everybody. The specificity and the quality of the response suggest that the pharmacodynamic effects of lithium may provide important clues about the neurobiology of bipolar disorder. However, it is not easy to determine which of the multitude of lithium's actions is responsible for its episode preventing effect. A number of mechanisms have been postulated, from changes in electrolyte balance, membrane transport, interaction with various elements of second messenger system, calcium signaling, to chronobiological changes and neuroprotective effects[4].

Clinical research findings in lithium responders also challenge certain concepts of bipolar disorder. For instance, contrary to the now popular staging model, the excellent response in this group does not seem to diminish with treatment delay or with the duration of the illness[5]. The narrow phenotypic spectrum in these patients (and their families) is at odds with the notion of the common comorbidity of bipolar disorder with many other psychiatric disorders and their shared genetic underpinnings.

At the same time, the higher genetic risk and familial nature of the treatment response make this group a promising target for molecular genetic investigations. These started with linkage analyses and association studies of candidate genes; then the field turned towards genome-wide association analyses. Once replicated, genome-wide analyses may provide clinically applicable tools such as polygenic risk scores to guide selection of long-term treatment.

Most recently, several studies confirmed the specificity of lithium response in a novel cellular model of bipolar disorder. Neurons derived from induced pluripotent stem cells of people with bipolar disorder were hyperexcitable in comparison with neurons from healthy controls. This hyperexcitability could be attenuated by *in vitro* lithium treatment, but only in cells from people who responded to lithium clinically, not in cells from non-responders[9].

Over the last 20 years, lithium has become a less commonly used option in the long-term treatment of bipolar disorder. Many physicians now consider it a difficult medication to use. Yet, the excellent responders are a reminder that there is a group of patients for whom lithium is not only the best, but perhaps the only treatment option. For this reason alone, they deserve our clinical and research attention.

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When illness severity and research dollars do not align: are we overlooking eating disorders?

When determining funding allocated for psychiatric research, several important factors warrant consideration, including scientific opportunity, the status of existing evidence, public health need, disease severity, economic-related burden of illness, and the scope for high impact research[1]. Eating disorders are among the most pernicious and complex psychiatric disorders, for which the precise etiology remains elusive, but relatively little funding has historically been allocated to their research.

Approximately 20 million women and 10 million men in the US can be diagnosed with a DSM-5 eating disorder (i.e., anorexia nervosa, bulimia nervosa or binge eating disorder) at some point during their lifetime, many of whom are not treated by specialist providers. Lifetime prevalence estimates range from 0.9% for anorexia nervosa to 3.5% for binge eating disorder, and while some evidence points towards a gradual increase in the rate of new cases, empirical studies have struggled to discern what represents changing trends of incidence or an increased demand for treatment.

Anorexia nervosa yields the highest mortality rate of any psychiatric illness, demonstrating a six-fold increase compared to the general population and a crude mortality rate of 5-7%[2]. Even in non-lethal presentations, eating disorders frequently run a chronic and relapsing course, which impart multi-systemic organ damage, including cardiac abnormalities, structural and functional brain impairment, and bone disease. As such, up to 97% of those with eating disorders report significant functional impairment, which is comparable to autism and schizophrenia. Moreover, elevated psychiatric comorbidity is common, alongside a four-fold increase in substance abuse, and a 57-fold increase in suicidality relative to the general population[3].

Despite the grave health-related implications of eating disorders, treatment outcomes to date are modest. In adult presentations of anorexia nervosa, for instance, no gold standard psychological interventions or pharmacological treatments approved by the US Food and Drug Administration (FDA) have emerged. In adolescent presentations, the leading empirically supported intervention, family-based treatment, typically yields long-term remission rates of approximately 35-40%[4]. Treatment outcomes for bulimia nervosa are similar, demonstrating remission rates of approximately 40% by end of treatment, in both adolescents[5] and adults[6].

Treatment costs are burdensome, with the cost of adequate treatment totalling approximately US$119,200 per patient, and an incremental cost-effectiveness ratio of US$30,180 per year of life saved[7]. This is exponentially higher than per-person treatment costs for schizophrenia and obsessive-compulsive disorder[8], and comparable to depression[9].

However, funding for eating disorder research remains relatively low. A recent funding report by the US National Institute of Mental Health revealed that, across all psychiatric conditions, funding for eating disorder research was the most discrepant from the burden of illness they represent[1]. In 2015, the volume of federal support for eating disorder research equated to approximately US$0.73 per affected individual. In contrast, autism research was supported at a rate of US$58.65 per affected individual, and schizophrenia research at a rate of US$86.97 per affected individual.

In analyzing trends in funding for eating disorder research in other countries, similar patterns are evident. In Australia, government funding for this research equates to approximately AUD$1.10 per affected individual, which stands in marked contrast to research funding for autism (AUD$32.62 per affected individual) and schizophrenia (AUD$67.36 per affected individual). Similarly, government funding for eating disorder research in Canada equates to approximately CAD$2.41 per affected individual, relative to CAD$462.14 per individual with autism, and CAD$103.31 per individual with schizophrenia. Cumulatively, these data point towards a global trend in the underfunding of eating disorder research.

As psychiatry research moves toward the target of precision medicine, the subject of inquiry has shifted from a behavioral focus to a pathophysiological and neurobiological emphasis, and consequently research costs have increased. With the urgent need for improved treatment outcomes for eating disorders, coupled with the high risk for those afflicted, and elevated costs of care, the underfunding of research on these disorders is cause for concern.

Recent technological advances in neuroimaging and gene mapping offer much translational promise in developing precision treatments, although the preliminary insights gleaned from existing studies have not yet advanced treatment outcomes. Without recalibrating the volume of funding support directed to eating disorder research, targeted attempts to treat the most lethal of psychiatric presentations may likely be thwarted.

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People meeting ultra high risk for psychosis criteria in the community

The last two decades have seen an exponential growth in research on people at ultra high risk (UHR) for psychosis, generating valuable new information on the factors that contribute to the onset of the disorder[1]. However, most of these findings were obtained from individuals who presented to mental health services specialized for the UHR group. Because they have been selected through a clinical referral process, these subjects may differ from individuals who also meet UHR criteria but do not contact such services[2]. To date, research in this field has not included the latter group, which remains largely uncharacterized.

We sought to address this issue by identifying young adults in the general population (aged 18-35 years) who met UHR criteria. We assessed their need for care and whether they had sought help, then compared their demographic and psychopathological features with those of UHR individuals who had presented to a clinical UHR service.

Cross-sectional data from a general population sample (N=208) were collected via face-to-face clinical interviews between 2011 and 2013. Participants were recruited within the London boroughs of Southwark and Lambeth, using two sampling methods, which provided 100 and 108 individuals, respectively. One set of participants was enrolled from a random sample of local households identified using the Post Office's Small User Postal Address File[3]. The other set was contacted through local general practitioners, who sent out invitations to join the study. Inclusion required that individuals had never been diagnosed with a psychotic disorder or prescribed antipsychotic medication. Individuals from the community sample who met criteria for the UHR state were compared with UHR individuals (N=36) from the same geographical area who had presented to a clinical UHR service[4] in the same time period.

Psychopathology was assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS)[5] and the Schizophrenia Proneness Instrument, Adult Version (SPI-A)[6] by a researcher trained in their use. Participants were categorized as being in an UHR state if they met either the Personal Assessment and Crisis Evaluation (PACE)[5] or the Cognitive Disturbances (COGDIS) criteria[7]. The level of functioning was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS), while need for care was evaluated using the Camberwell Assessment of Need Short Appraisal Scale[8]. Information on help seeking was collected using questions from the US National Comorbidity Survey.

Inverse sampling probability weights were calculated by comparing the age, gender and ethnicity of the study sample with census data (2011) for Southwark and Lambeth. Consequently, all percentages that follow are weighted. Binary logistic regression was used to quantify associations between age, gender, ethnicity, migrant status, childhood trauma, regular cannabis use and UHR status. Multinomial logistic regression was used to assess relationships with need for care and patterns of help seeking. Comparisons between clinical and community groups were made using χ^2 and t tests. Analyses were adjusted for age, gender and ethnicity where appropriate. Finally, p values were adjusted for multiple testing using Hochberg's step-up procedure.

Of the 208 participants, 100 were male. Mean age was 27.0 ± 4.9 years. Eighteen participants (8.7%) met the PACE criteria for the UHR state[5], 16 (7.7%) met the basic symptom criteria[7], and four met both, yielding a total of 30 (14.4%; estimated weighted prevalence: 12.6%, 95% CI: 8.8-17.7) who met criteria for the UHR state. Those who met UHR criteria were much more likely to have reported an unmet need for care than those who did not (OR=12.85, 95% CI: 3.94-41.96). They were also more likely to have sought help from any (professional or non-professional) source (OR=5.28, 95% CI: 1.71-16.33) and from professional agencies specifically (OR=4.99, 95% CI: 1.39-17.87). Approximately half of those meeting UHR criteria had sought help for a psychological or an emotional problem in the preceding 12 months, usually from a health professional (general practitioner, counsellor or psychologist). Only 35% of those who met UHR criteria had not felt they needed professional help.

The community UHR individuals were similar to UHR individuals who had presented to a UHR service in age, gender, ethnicity, employment status, years in education, history of childhood trauma, and current cannabis use, but were more likely to be first generation migrants (40% vs. 11%, $\chi^2=7.44$, $p=0.036$). They had less severe positive symptoms ($z=-4.21$, $p<0.001$, $r=0.515$), negative symptoms ($z=-2.63$, $p=0.017$, $r=0.321$) and general psychopathology (an index of depression/anxiety) ($z=-2.74$, $p=0.019$, $r=0.334$), and higher levels of social and occupational functioning (mean SOFAS score: 70.47 ± 12.39 vs. 60.9 ± 11.11; $t=-3.34$, $p=0.001$, $r=0.212$). However, they had poorer functioning than non-UHR subjects (mean SOFAS score: 80.79 ± 9.71; $t=4.45$, $p<0.001$, $r=0.277$).

These findings suggest that there may be a substantial number of young adults in the general population who meet UHR criteria but are not seen by specialized early detection services, even when these are relatively well developed[4]. These individuals appear to have less severe symptoms and functional impairment than those presenting to clinical services, consistent with the notion that the risk of psychosis in UHR samples depends on how they were recruited[9]. Nevertheless, the community UHR individuals were not, as has sometimes been suggested, "non-help-seeking"; half of them had already sought help, albeit from other non-specialized agencies.

Clinical early detection teams may need to further extend their services into the community so that these individuals have better access to specialized mental health care. This might also increase the representation of this subgroup in research studies of the UHR state.

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Khat use and occurrence of psychotic symptoms in the general male population in Southwestern Ethiopia: evidence for sensitization by traumatic experiences

Khat trees are native to East Africa and the Arabian peninsula. Their leaves contain amphetamine-like alkaloids such as cathinone, cathine and norephedrine, and are chewed for their stimulating and euphorigenic effects[1]. Khat use varies by season: in the dry season, there is limited availability and market prices are high; in the rainy season, the opposite is true. Excessive use is associated with dependence and khat-induced psychosis[2].

In collaboration with the Gilgel Gibe Field Research Center of Jimma University, in Southwestern Ethiopia, we studied khat use and khat-induced psychotic symptoms in 1,100 men aged 18 to 40 years (mean 28.4 ± 6.6), randomly selected from the center's population registry.

Trained raters interviewed participants at two subsequent time points, i.e. during the dry season (T1; N=853) and during the rainy season, nine months later (T2; N=695). They explored khat use during the past 7 days using the Timeline Followback Method Assessment. Psychotic symptoms experienced during the past 6 months were assessed by four items from the Composite International Diagnostic Interview (CIDI) selected on the basis of previous studies[3]. Khat-induced psychotic symptoms were defined as being present during or up to 6 hours after consumption and assessed with supplementary questions[3]. Potentially traumatic experiences (e.g., assault or life-threatening injury) during the period up to T1 or since T1 were explored by an adapted version of the Life Events Checklist for DSM-5 (LEC-5)[4]. A cut-off of four experiences was fixed by median split. Urine samples were collected to analyze khat alkaloids through immunoassay tests for amphetamine.

Khat use in the past 7 days was reported by 599 individuals (70.2%) at T1, and 565 (81.3%) at T2. The 6-month prevalence of khat-induced psychotic symptoms was 7.9% at T1 and 12.8% at T2.

At T2, we found 225 individuals with a positive immunoassay test. In these subjects, the rate of khat-induced psychotic symptoms was 26.6% among those with a history of four or more past traumatic experiences (N=124) and 14.0% among those with a history of less than four of those experiences (N=121) (p=0.015). This result could not be explained by higher khat use among the high trauma group (p>0.081 for all use indicators in the last 7 days among people with high vs. low trauma load).

We also observed that recent trauma exposure was associated with elevated presence of khat-induced psychotic symptoms in individuals with low trauma exposure during the period up to T1 (with recent trauma: 28%; without recent trauma: 12%; p=0.009). Among individuals with high trauma exposure during that period, additional recent trauma did not have this effect (with recent trauma: 25%; without recent trauma: 26%; p=0.933).

Our findings suggest that, in the general male population of an African country, traumatic experiences can sensitize to the effects of a psychomimetic substance. This is in line with the behavioral sensitization paradigm, which suggests that repeated administration of amphetamines or exposure to stress can cause sensitization of dopamine neurons and consequently a higher dopamine release in response to subsequent stress or amphetamine, which facilitates the development of psychotic symptoms[5-7].

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Malaria and mental disorder: a population study in an area endemic for malaria in Kenya

Malaria, a disease transmitted by blood borne plasmodium parasites from mosquito bites, is still a key contributor to morbidity and mortality in parts of sub-Saharan Africa. However, to our knowledge, there have been no previous epidemiological or clinical studies of the relationship between this disease and mental disorders[1].

The potential links between malaria and mental disorders are complex. Malaria, as a debilitating physical illness, may predispose to depression, while depression may predispose to malaria by affecting immunity and by altering behaviour. Depression may hinder treatment and recovery from malaria, and vice versa. African clinicians are known to often misdiagnose complaints of fatigue and general malaise as malaria when in fact the person has no parasitaemia but suffers from depression. Such misdiagnosis may lead to erroneous prescriptions of antimalarials, which may clear protective low-grade parasitaemia. Meanwhile the individual remains with undiagnosed and untreated depression, which may predispose to malaria and also discourage personal preventive action on malaria.

We conducted a household survey in an area of Kenya endemic for malaria in order to examine the associations between malaria and mental disorders. The detailed methods of the survey have been reported elsewhere[2-8]. To summarize, we drew a random sample of households from a rural health and demographic surveillance site[9] of over 70,000 population near Kisumu, Lake Victoria, Kenya, and selected one adult aged 16 or over at random from each household. Research nurses undertook standardized clinical interviews and blood tests for malaria parasites, which were analyzed at the Kenya Medical Research Institute.

The clinical interviews included a systematic assessment of socio-demographic variables. Moreover, we administered the Clinical Interview Schedule-Revised, which appraises the presence of depression, obsessive-compulsive disorder, panic disorder, phobic disorder, generalized anxiety disorder and mixed anxiety-depressive disorder by measuring the presence of 14 symptoms in the preceding month and the frequency, duration and severity of each symptom in the past week, and combining the symptom scores with diagnostic algorithms based on ICD-10. Alternatively, a score of 12 or more across the 14 sections of the interview is considered an indication of the presence of "any common mental disorder (CMD)".

Further assessment instruments included the Psychosis Screening Questionnaire, which measures psychotic symptoms; the WHO Adult ADHD Self-Report Scale Screener, which appraises symptoms of attention-deficit/hyperactivity disorder (ADHD); the Trauma Screening Questionnaire, which appraises symptoms of post-traumatic stress disorder (PTSD); and the Alcohol Use Disorders Identification Test for Consumption (AUDIT), which assesses hazardous drinking. We also asked questions about suicidal thoughts and attempts (last week, last year, and lifetime), and the quantity and frequency of alcohol use.

Ethical approval was granted by the King's College London and Kenya Medical Research Institute Boards of Research Ethics. Informed written and witnessed consent was asked of heads of sampled households, and then of sampled participants, to take part in the study.

1,158 subjects consented to the study, while 32 refused to participate and 149 refused to give a blood sample, thus giving an overall response rate of 91.4%. Malaria parasites were present in 28% of participants, CMD in 10.3%, one or more psychotic symptoms in 13.9%, PTSD in 10.6%, lifetime suicidal thoughts in 7.9%, suicidal attempts in 1.9%, and hazardous drinking in 6.4%.

We conducted bivariate and multivariate analyses on the association of malaria with the various mental disorders identified by the assessment instruments, and found that the presence of malaria parasitaemia was associated at the bivariate level with increased rates of CMD (OR 1.7, $p=0.014$), but not with increased rates of psychotic symptoms, ADHD, PTSD, alcohol use, hazardous drinking, or suicidal ideation or attempts. When adjusted for other variables including gender, the association between malaria and CMD remained significant (OR 1.6, $p=0.05$), indicating that the risk of malaria was 60% higher in those with any CMD.

This association did not arise from shared method variance due to measurement of symptoms of malaise and fatigue, because – although CMD caseness was identified by the occurrence of 14 different psychological symptoms including fatigue and excessive concern about bodily symptoms – malaria parasitaemia was ascertained by the presence of actual malaria parasites rather than of symptoms *per se*.

The fact that we did not find an association between malaria and psychotic symptoms is interesting but not surprising, as cerebral malaria, which may present with visual hallucinations, necessitates urgent hospital admission, while our sample included all ambulant adults living at home.

The key strength of this study is the use of a large representative sample of adults in a health and demographic surveillance site, with a high response rate. Limitations included practical difficulties of collecting blood samples in the field, and getting them safely to the laboratory.

The relatively high prevalence rates of both malaria and mental disorders, and the association of malaria parasitaemia with common mental disorder, indicate the importance of strengthening the competence of front line health workers and the ability of health management information systems to record the presence of specific mental disorders as well as of comorbidity between physical and mental disorders. A biopsychosocial approach to training, supervision and health man-

agement information systems is required to address the burden of mental as well as physical disorders and their co-occurrence in sub-Saharan Africa.

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Can reduced drinking be a viable goal for alcohol dependent patients?

Abstinence from any alcohol remains the safest treatment option for individuals with alcohol dependence, and the one associated with the best long-term outcomes.

However, many individuals with alcohol use disorders, including severe alcohol dependence, do not wish to seek treatment because they are unwilling or feel unable to engage in abstinence[1]. Thus, allowing for alternative treatment options that offer drinking reduction goals is an important step to decrease the treatment gap associated with alcohol use disorder.

People in treatment are likely to change their drinking goals a number of times. Acceptance of a patient's drinking goal in a client-centered approach usually helps create a stronger therapeutic alliance, and patients who initially select a moderation goal might ultimately transition to abstinence[2].

Controlled studies testing this alternative approach have shown sustained drinking reductions for many patients following behavioral treatments and pharmacotherapy[3,4]. With reduced drinking, long-term improvements have been reported regarding mortality rates, incidence of alcohol-associated injuries and accidents, levels of mood symptoms, quality of life, social functioning, along with significant weight reduction, a normalization of systolic and diastolic blood pressure, slowed progression of alcohol-attributable liver fibrosis, and recovery of ventricular heart function[5].

Treatment guidelines and the guidance papers of European and US authorities have taken note of these research findings and accept "intermediate harm reduction" (European Medicines Agency, EMA) or "low-risk drinking limits" (US Food and Drug Administration, FDA) as indicators of treatment success.

The FDA recommends a low risk drinking outcome of no heavy drinking days (where a heavy drinking day is defined as more than 70 g of alcohol for men and more than 56 g of alcohol for women). The EMA allows several harm reduction goals, including change from baseline in mean daily consumption of alcohol and reduction in number of heavy drinking days (where a heavy drinking day is defined as more than 60 g of alcohol for men and 40 g of alcohol for women).

The EMA also provides examples of the levels of reduction that could indicate a positive treatment response, including a 50%, 70% or 90% decrease in mean daily alcohol consumption or a significant categorical shift in World Health Organization (WHO)'s risk levels of drinking.

Recently, the clinical value of a shift in WHO risk levels of drinking with respect to improvement in functional outcomes has been validated in a clinical sample[6] and a population-based sample[7] of drinkers. Specifically, results indicated that even a one level shift in WHO risk levels – e.g., reduction from very high risk (61+/101+ g per day for women/men) to high risk (41 to 60/61 to 100 g of alcohol per day for women/men) – resulted in clinically meaningful decreases in drinking consequences and improvements in mental health.

Based on this compelling scientific evidence[4-7], there is growing recognition that harm reduction outcomes including reduced alcohol consumption need to be considered in addition to abstinence for defining treatment success, even among alcohol dependent patients.

However, at the level of individual patients, potential limitations need to be acknowledged. The harm reduction approach may deter severely affected individuals from the difficult path towards abstinence. Even among those who accept reduced drinking as a viable treatment option, there is consensus that non-abstinence goals are less appropriate for some patients, particularly those at the severe end of the alcohol dependence continuum and pregnant/nursing women.

In conclusion, a wider acceptance of reduced alcohol consumption as a goal for dependent patients holds the potential to increase the appeal of seeking help for many of these underdiagnosed and undertreated individuals. Consequently, treatment demands could increase considerably and require additional professional involvement. This calls for a more active role of psychiatrists in counseling, monitoring and treating patients in this sensitive area of mental health care.

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Factors protecting against the development of suicidal ideation in military veterans

The growing rate of suicide among military veterans is a critical public health concern[1,2]. Accordingly, there is an urgent need to better identify at-risk veterans and provide early targeted interventions[3]. Numerous studies have examined risk factors for suicide in veterans, which have generally focused on mental and physical health problems[4,5]. Surprisingly scarce research has sought to identify modifiable protective factors, despite emerging theoretical frameworks of suicide risk emphasizing such factors, including psychological resilience (i.e., psychological qualities that allow one to better manage adversity, such as self-efficacy and cognitive flexibility), acceptance-based coping (i.e., acceptance that a traumatic or stressful life event is real and must be addressed), social support, optimism, and curiosity[6-8].

Characterization of risk and protective factors linked to early indicators of suicide risk, such as suicidal ideation, is critical to informing targeted suicide prevention efforts[3]. Prospective cohort studies that follow population-based, non-psychiatric samples *prior to* the development of suicidal ideation are an ideal context within which to identify such factors. We explored the risk and protective factors associated with the development of suicidal ideation over a 4-year period in a nationally representative sample of military veterans.

We analyzed data from the National Health and Resilience in Veterans Study, a nationally representative, prospective cohort study of US veterans. The sample was drawn from a survey panel of 50,000 US adults maintained by GfK Knowledge Networks Inc. The baseline survey was conducted in September-October 2011, and follow-up surveys were carried out in September-October 2013 and 2015. In the current study, we analyzed data from 2,093 veterans who did not endorse suicidal ideation at baseline and who completed at least one follow-up assessment over the 4-year follow-up period. The study was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System.

Suicidal ideation was assessed using a two-part question from the Patient Health Questionnaire-9: "Over the last 2 weeks, how often have you been bothered by the following problems: thoughts you might be better off dead, and thoughts of hurting yourself in some way?". Items were coded 0 ("not at all"), 1 ("several days"), 2 ("more than half the days"), or 3 ("nearly every day"). Incident suicidal ideation was operationalized as endorsement of "1" or higher on either question over the 4-year follow-up period. A comprehensive range of socio-demographic, military, health and psychosocial (perceived resilience, optimism, purpose in life, social support, coping strategies, and religiosity/spirituality) characteristics were assessed[9].

A hierarchical multivariate binary logistic regression analysis was conducted to evaluate baseline predictors of incident suicidal ideation over the 4-year period. Socio-demographic (e.g., age) and military (e.g., combat veteran status) variables were entered in step 1; potential risk factors (e.g., depression, post-traumatic stress disorder (PTSD), somatic problems) in step 2; and potential protective factors (e.g., scores on measures of psychosocial characteristics and social connectedness) in step 3. Incident suicidal ideation (no/yes) was the dependent variable. The analysis was weighted post-stratification based on the demographic distribution from the most contemporaneous current population survey of the US Census Bureau, to permit generalizability to the US veteran population.

The mean age of the sample was 62.4 ± 13.8 years (range 22-93) and included predominantly male (92.0%), white (78.5%) and non-combat-exposed (68.4%) veterans. One hundred forty-three (weighted 7.5%) veterans developed suicidal ideation over the 4-year follow-up period.

Increased risk of incident suicidal ideation was associated with loneliness (i.e., score on Short Loneliness Scale; relative risk ratio, RRR=1.22, p=0.002; relative variance explained, RVE=16.5%); disability in instrumental activities of daily living (i.e., endorsement of needing help with activities such as doing housework and taking medication properly; RRR=3.46, p<0.001; RVE=14.8%); PTSD symptoms (score on PTSD Checklist; RRR=1.05, p<0.001; RVE=7.9%); somatic problems (i.e., score on somatization subscale of Brief Symptom Inventory-18; RRR=1.09, p<0.001; RVE=7.0%); alcohol use problems (i.e., score on Alcohol Use Disorders Identification Test-Consumption; RRR=1.10, p=0.001; RVE=5.7%); denial-based coping (i.e., endorsing use of denial to cope with trauma on the Brief COPE; RRR=3.36, p=0.002; RVE=4.3%); and higher age (RRR=1.02, p=0.015; RVE= 2.0%).

Decreased risk of incident suicidal ideation was independently associated with greater social support (score on Medical Outcomes Study Social Support Scale-5; RRR=0.94, p=0.002; RVE=20.3%); curiosity (score on "I frequently find myself looking for new opportunities to grow as a person (e.g., information, people, resources)" item from the Curiosity and Exploration Inventory; RRR=0.85, p<0.001; RVE=9.3%); resilience (score on Connor-Davidson Resilience Scale-10; RRR=0.96, p=0.009; RVE=8.0%); and acceptance-based coping (endorsement of use of

acceptance-based coping on the Brief COPE; RRR=0.60, p=0.014; RVE=4.2%).

This study provides one of the most comprehensive assessments to date of risk and protective factors for developing suicidal ideation in a nationally representative sample of military veterans. They replicate prior work implicating mental and physical health problems as risk factors for suicidality in veterans[4,5] and extend these findings to suggest that loneliness, disability in instrumental activities of daily living, and denial-based coping may additionally contribute to suicidal ideation risk in this population.

Greater perceived social support, curiosity, resilience, and acceptance-based coping accounted for more than 40% of the total variance in predicting suicidal ideation risk. These protective factors are modifiable and addressed in contemporary cognitive-behavioral psychotherapies[6-8], and thus may be promising targets in prevention efforts designed to mitigate suicide risk in veterans.

Taken together, the results of this study underscore the importance of comprehensive and multi-modal assessment, monitoring, prevention, and treatment approaches that target a broad range of risk and protective factors for suicidal ideation[10].

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Protecting youth mental health, protecting our future

Youth mental health disorders cause immense disease burden and high mortality. Finding an effective response to this challenge is now more pressing than ever, because "the largest generation of young people in human history is coming of age"[1]. The urgency and importance of the issue has alerted many political leaders, researchers and others[2,3].

However, despite these calls for action, very little has happened. Yet, to many of us working in this area, the barriers to the implementation of an effective strategy do not seem insurmountable. The key barriers to early identification and prevention are known[4], and include low rates of help seeking, the limited capacity of existing services to respond, and the fact that health systems are not suited to young people's needs.

These barriers have been overcome for other illnesses, such as cancer and HIV. Yet, not so for depression in youth. So, the question is: why this lack of action? We suggest two explanations. The first is that the misconceptions and falsehoods around the nature of youth depression accumulate to form the idea that mental health disorders are "too hard" or that we know too little. The second is the lack of an actionable, prioritized, *implementable* blueprint supported by governments around the world.

Depression is wrongly conceptualized by many as a "first world problem", that is more prevalent in more affluent countries, and is secondary to more important physical or communicable diseases that are higher contributors to mortality. In reality, however, depression is the third leading cause of disability for 15-24 year olds globally after skin and subcutaneous diseases, and low back and neck pain[5], and in many high-income countries, suicide is the leading cause of death for 15-29 year olds[6]. It is true that in less affluent countries depression can be seen as a proportionally less significant problem, because death from other causes, such as infectious diseases, is higher. However, death from these causes is decreasing, and non-communicable diseases are on a rising trajectory. Moreover, depression is pervasive in its effects on all aspects of the person's life: work productivity as well as other means of contributing to and benefiting from the social, political and other aspects of community. This is particularly true for young people who are the world's future.

A second misconception is that depression is not a "real" medical disorder. This is demonstrated by the fact that many people believe that treatment of depression is via "social support", connectivity, or the use of vitamins. When depression is not seen as a "real" disorder, stigma and discrimination will thrive.

As to intervention, many believe wrongly that there are no effective treatments for depression, so seeking help will be of limited value, and that prevention of depression is not possible, even though a meta-analysis found that the number needed to treat to prevent one case of depression, using currently available interventions, was 22[7]. This is staggeringly high compared to statins, that have to be taken by 60 people for one cardiac incident to be averted, or aspirin, that has to be taken by 1,667.

A number of significant plans have been put forward to address youth depression, but these rarely get "air play". Most existing blueprints consistently recommend three actions.

School programs should be implemented for all school aged children, including digital prevention programs for depression as well as drug and alcohol abuse, the re-introduction of physical activity, mental health literacy, and stigma reduction pro-

grams, and screening programs for severe depression and suicide ideation. Currently, countries rarely implement evidence based programs in schools; there is no central regulation or guidance, leading to one-off, fragmented approaches.

The second is to improve treatment, through *better service models*, which will vary as a function of country. In the US, integration of mental health services into primary/paediatric care may be preferred by patients, because of stigma and convenience, and there is a clear need for realistic payment models for mental health services. Cost effective e-health services are underutilized in most countries.

The third action is to develop an *agenda to bridge knowledge gaps* through targeted and large scale research. The key topics for this agenda include the risk and protective factors for mental disorders, developing better and more cost-effective treatments and prevention, and building precision medicine by investing in better prediction tools and by exploiting technology. The racial and ethnic diversity of youth engenders the need to develop models of depression from other than perspectives of white people, in order to engage youth and their families. Despite the need, current funding for mental health research is woefully disproportionate to disease burden worldwide.

Youth don't vote. They often don't have a voice and depend upon others to champion their right to health justice. The growing prevalence of youth mental health problems is a tsunami, and parents, the community and governments float in a small boat, named "denial", on the quiet sea.

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Correction

It was brought to our attention that in Table 1 of the paper "Has the rising placebo response impacted antidepressant clinical trial outcome? Data from US Food and Drug Administration 1987-2013", by Khan et al, published in the June 2017 issue of *World Psychiatry*, the primary efficacy measure used in the trial 62-A was reported incorrectly. It should be CGI instead of HAM-D.

The WPA Action Plan 2017-2020

The WPA Action Plan 2017-2020 sets out a strategy for expanding the contribution of psychiatry to improved mental health for people across the globe. It is based on consultation within the WPA and with potential partner organizations as well as on the work that has preceded it. It builds on the strong capacity of the WPA to promote mental health and improve equitable access and quality of mental health care. In doing so, the plan provides a targeted strategy for reaching people, particularly young people, who face adversity and disadvantage.

Three characteristics frame the *strategic intent* of the Action Plan: continuation of WPA's contribution to developing the profession of psychiatry; development of operational work that focuses on critical mental health topics; attraction of new investment to support this work.

This intent is translated into action through a *strategic framework* based on three dimensions:

- Impact on population groups – strengthening the contribution of psychiatrists to reducing distress, illness and suicidal behaviour among vulnerable populations. Three specific populations include women and girls facing adversity[1]; people under extreme stress, including those affected by conflict and emergencies; and people living with long-standing mental illnesses and their caregivers.
- Enabling activities – supporting psychiatrists to promote mental health and improve care capacity. These activities include: service development; awareness raising and advocacy; education, publications and research. All are conceived as gender- and culturally-sensitive.
- Partnerships and collaboration – expanding the reach and effectiveness of partnerships with service providers, service beneficiaries and policy makers.

In focusing on *specific population groups*, the plan calls attention to the needs and strengths of children and young people, who are prominent in each of the groups identified. Mental health promotion as well as prevention and treatment of mental illness are all incorporated into the plan. Three types of actions are anticipated. The first is support for sharing of best practice. The second is building capacity for the profession to work effectively in specific settings of disadvantage. The third is encouraging psychiatrists and other health professionals to use their expertise in facilitating the mental health work of non-specialists across a range of community settings.

The *enabling activities* find expression in a series of projects. The projects include:

- Strengthening the contribution of psychiatrists to improving mental health capacity in health systems. This entails training and support for psychiatrists to work effectively with other health and community cadres in primary care and community-based mental health systems.
- Facilitating a working group of organizations and people to develop initiatives on suicide prevention. The work will take into account the key World Health Organization (WHO) initiative Preventing Suicide: A Community Engagement Toolkit. The purpose will be to focus on the sharing of knowledge and practice, especially as it relates to the needs of young women and men in low-income countries.
- Developing publications, resources and educational programs on the subject of human rights and psychiatry. The Association will seek to inform debate especially in the context of ratification of the United Nations Convention on the Rights of Persons with Disabilities. It will foster professional advancement in topical areas such as intimate partner violence, through education and advocacy for policy and practice changes. With the help of Member Societies, it aims to monitor and assist the use of the new online WPA Competency-Based Curriculum for Mental Health Providers on Intimate Partner Violence and Sexual Violence Against Women, including the development and delivery of undergraduate, post-graduate and continuing education curricula.
- Seeking partners to establish a multi-disciplinary group, including psychiatrists and journalists, to foster good practice in the reporting of mental health and related topics in conflict and disaster situations.
- Working with journals and other publications in low- and middle-income countries. The WPA proposes re-establishing a task force on peer support for editors of psychiatric journals in low- and middle-income countries[2-6]. This initiative will enable editors who work in low resource and isolated situations to draw on support for their activities and to contribute to the work of others.
- Collecting information on psychiatrists' demographic characteristics, training and practice, which is crucial for WPA to achieve its aims, for access to psychiatrists to be improved and for the profession to identify opportunities to collaborate. We propose to conduct a survey of psychiatrists globally through our Member Societies to create a report on these topics.

The third dimension of the strategy, *partnerships and collaboration*, addresses service beneficiaries including service users, their families, and their communities; primary health care professionals; and a range of governmental, inter-governmental and non-governmental organizations. All of the above projects encourage and support collaborations of this type, as better collaboration underlies all effective activities. In particular:

- The plan proposes advancing and sharing knowledge about best practice in working with service users and their carers. It proposes operational activities to implement the recommendations of the WPA Task Force on Best Practice in Working with Service Users and Family

Carers[7] at a local level, and monitoring and evaluation to draw out the significant lessons and support dissemination of the findings.

- The plan supports increased collaboration with primary health care professionals, and partnerships with relevant organizations.
- The plan proposes building on the strength of the formal relationship of the WPA with the WHO by a Collaborative Action Plan to advance the goals common to the two organizations.
- The plan will initiate a program to strengthen the contribution and availability of psychiatrists in national and international responses to conflict and humanitarian emergencies. The program will train and support psychiatrists to perform their roles in emergency responses alongside other humanitarian actors. It will draw on the past experiences of joint WPA-WHO training for disaster response[8] as well as of leading international non-governmental organizations.

In order to achieve its aims, the WPA will mobilize the professionals, knowledge and resources available to the Association. We will encourage the participation of Member Societies and individual psychiatrists in the themes and activities described. Many organizations have been working for extended periods of time to address the global mental health needs that also concern us. Working together in a clear and strategic manner will allow us to serve vulnerable populations globally in a better way.

The activities set forward by this Action Plan are designed to be attractive to new funders and investors. They provide opportunities to have an impact on needs that are priorities for human and social development globally.

Helen Herrman
President Elect, World Psychiatric Association

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WPA Secretariat: playing a dynamic role

The WPA was established in 1950 as a non-profit organization. It functions in compliance with the Swiss Civil Law and its registered office is in Geneva, Switzerland. The WPA Secretariat started functioning at the Geneva University Psychiatric Hospital "Belle Idée" since 2005, when J. Cox was the Secretary General. This followed an "accord of collaboration" which was signed in September 2004 by the then WPA President A. Okasha on behalf of WPA and the Dean of the Geneva University Hospital[1].

English is the working language of the Association. WPA statutes provide that other languages (including Arabic, Chinese, French, German, Japanese, Portuguese, Russian and Spanish) may be used in official matters depending on specific needs and circumstances. The English text of the Association's statutes, by-laws and manual of procedures is used for WPA administration. The WPA logo consists of a representation of the Greek letter *psi* and the earth globe in crimson red. The logo may be supplemented by the name of the Association in English or any other language.

The WPA Secretary General is in charge of the WPA Secretariat and is responsible for the administrative tasks of the Association. The basic goal of the Secretariat is to facilitate the administrative functioning of the WPA to achieve the purposes prescribed by the statutes as well as the policies and guidelines approved by the General Assembly, the Executive Committee and the Board. The Secretary General works closely with the interim chief executive officer and deputy administrator, in consultation with the President and the Executive Committee, whenever required.

The Secretariat ensures good communication and collaboration with all WPA components and provides administrative and institutional services to the various categories of WPA membership, including Member Societies, Affiliated Associations and Individual Members. Services encompass admission procedures, distribution of institutional information, facilitation of access to and interaction with WPA governing bodies and of participation in various institutional activities.

The WPA Secretary General coordinates the work of WPA Zonal Representatives and serves as liaison between them and the WPA governing bodies, and through the Secretariat coordinates and supports their work through various modes of communication. They in turn collaborate with the Secretariat in stimulating the activities of Member Societies in their respective Zones. The Secretariat also supports the work of members of the Executive Committee, Standing and Operational Committees, Task Forces, Scientific Sections, the Board and the Council. The organizational work related to the General Assembly, being held every three years, is a further major responsibility of the Secretary General and the Secretariat.

Liaison with the Geneva University Psychiatric Hospital, the World Health Organization and other international organizations is also one of the functions of the Secretariat. It also coordinates the provision of legal services to the WPA, including yearly reports to authorities in Switzerland. Furthermore, it holds the archives of the Association.

The WPA Executive Committee, chaired by President D. Bhugra, met at the Secretariat on July 17, 2016 and discussed various Association matters[2-11]. The Planning

Committee met a day earlier at the Secretariat, chaired by President Elect H. Herrman, to discuss draft changes in the statutes and bylaws.

V. Cameron, Chief Executive Officer of the Royal College of Psychiatrists, UK, and S. Levin, Chief Executive Officer of the American Psychiatric Association, visited the Secretariat in August 2015 and gave valuable inputs. WPA Past President N. Sartorius too has visited the WPA Secretariat on a number of occasions and given useful suggestions. We have also received constant support from B. Levrat, J.-M. Aubry and F. Ferrero of the Geneva University Psychiatric Hospital.

The performance of the WPA website www.wpanet.org has been most encouraging. Its popularity is growing day by day, and in less than three months from February 1, 2017 we had 28,132 contacts. Of the 21,826 users, 72.3% were new ones. We also keep publishing the bulletin *WPA News* every three months. Unfortunately, we had to stop production of the printed version due to financial constraints.

The WPA Secretariat has collaborated with the Secretary for Meetings M. Takeda in the organization of various events. The recent WPA International Congress in Cape Town (November 18-22, 2016) had more than 2,000 delegates. The organizers worked hard to ensure a comprehensive program which was aimed at setting the agenda on a number of issues, including psychiatry's and psychiatrists' social contract, as well as forming continental alliances for integrated mental health in Africa.

The WPA International Conference on Education in Latin America entitled "Perspectives in Education and Research" was held on February 7-11, 2017 in Cuenca, Ecuador as a joint initiative of the WPA and the Ecuadorian Association of Psychiatry. The exchange of ideas among the attendees allowed to explore the opportunities for education and research in the Latin American region.

The WPA Interzonal Congress on "Changing Society, Changing Psychiatry and Changing Self" was held in Vilnius, Lithuania on May 3-6, 2017. A part of the Congress took place at the Lithuanian Parliament. More than 500 psychiatrists and other mental health professionals from over 40 countries attended.

The Secretariat plays a dynamic role in fulfilling the goals and mission of WPA!

Roy Abraham Kallivayalil
WPA Secretary General

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The ICD-11 clinic-based field studies are about to be concluded

The clinic-based (or ecological implementation) field studies, which will contribute to guide the construction of the chapter on mental and behavioural disorders of the 11th revision of the International Classification of Diseases and Related Health Problems, are about to be concluded.

The participating field studies coordinating centres have included the Department of Psychiatry of the Federal University of São Paulo, Brazil; the Royal Ottawa Mental Health Centre in Ottawa, Canada; the Shanghai Mental Health Centre in Shanghai, China; the Department of Psychiatry and Psychotherapy of the Heinrich-Heine University in Düsseldorf, Germany; the Department of Psychiatry of the University of Naples SUN in Naples, Italy; the Department of Psychiatry of the All India Institute of Medical Sciences in Delhi, India; the Japanese Society of Psychiatry and Neurology in Tokyo, Japan; the Department of Psychiatry of the American University of Beirut, Lebanon; the National Institute of Psychiatry Ramón de la Fuente in Mexico City, Mexico; the Department of Psychiatry of the University of Ibadan, Nigeria; the Moscow Research Institute of Psychiatry in Moscow, Russian Federation; the Department of Psychiatry of the Universidad Autónoma de Madrid in Madrid, Spain; the Department of Psychiatry of the University of Cape Town, South Africa; and the Department of Psychiatry of the Columbia University in New York, USA.

The clinic-based field studies have included two components: clinical consistency studies and clinical utility studies[1,2].

The clinical consistency studies have covered the mental disorders accounting for the highest disease burden and utilization of mental health services worldwide[3,4]. One protocol has covered psychotic and mood disorders in patients presenting with any psychotic symptom; a second protocol has focused on mood disorders, anxiety disorders and disorders specifically associated with stress in patients presenting with relevant symptoms but no psychotic feature; a third protocol has dealt with common childhood and adolescence mental disorders (attention deficit, disruptive behaviour, mood and anxiety disorders) in children and adolescents presenting with relevant symptoms. The studies have aimed to explore whether independent clinicians, based on the same information, arrive at the same diagnostic conclusion using the field study version of the ICD-11 diagnostic guidelines. The studies are allowing to identify the aspects of that version of the guidelines which are more likely to be interpreted differently by independent clinicians.

The clinical utility studies have covered the mental disorders considered in the clinical consistency studies plus additional disorders of interest to study sites. Clinical utility has been repeatedly identified as a major objective of classifications of mental disorders[5-7], but this is the first time that the clinical utility of a

diagnostic system has been tested widely and systematically. The specific elements assessed have been: conceptualization (do the proposed diagnostic guidelines help in understanding and communicating the patient's condition?); goodness of fit (do the guidelines accurately capture patients' symptom presentation?); ease of use (are the guidelines clear and easy to use in ordinary practice?); and adequacy (how adequate are the guidelines for the assessment of patients and for making clinical management decisions?). These studies have been conducted in patients seeking routine health care in specialty mental health care settings. Clinicians have applied the clinical guidelines and made ratings of their clinical utility with regards to each patient.

The field study version of the ICD-11 diagnostic guidelines for the various groups of mental disorders is being published on the Internet platform called GCP.Network (http://gcp.network) and is open for comments by registered members of the Global Clinical Practice Network. A reflection of the ongoing debate on the ICD-11 characterization of some groups of mental disorders – such as disorders related to sexuality and gender identity, bodily distress disorder, pathological gambling, Internet-related disorders, childhood disruptive behaviour and grief-related disorders – can be found in previous issues of this journal[8-12].

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