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## The World Psychiatric Association (WPA)

The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 135, spanning 118 different countries and representing more than 200,000 psychiatrists.

The WPA organizes the World Congress of Psychiatry every three years. It also organizes international and regional congresses and meetings, and thematic conferences. It has 69 scientific sections, aimed to disseminate information and promote collaborative work in specific domains of psychiatry. It has produced several educational programmes and series of books. It has developed ethical guidelines for psychiatric practice, including the Madrid Declaration (1996).

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## World Psychiatry

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## The need for a conceptual framework in psychiatry acknowledging complexity while avoiding defeatism

The notion – often put forward nowadays – that what we call mental disorders are just convenient constructs that may or not appropriately reflect what exists in the real world is very likely to be misinterpreted by several psychiatrists (contributing to their current frustration about the status of our profession), by many colleagues within the medical community (reinforcing their skepticism towards our discipline), by the general public (already sensitized by the recent debates following the publication of the DSM-5), and by people with mental health problems and their carers (further discouraging them from seeking our help and listening to what we say). The primary (but not the only) problem is that the difference between this notion (which acknowledges both the existence of mental illness and the limitations of current diagnostic categories) and the radically “constructivist” position of Szasz and others (stating that current diagnostic categories are just a theoretical fiction or a myth, i.e., that there is no such thing as mental illness except by metaphor) is not easy to grasp for someone who does not have a philosophical background.

Much easier to understand and less destructive is the notion that many of what we call mental disorders, although not qualifying at the moment as proper “disease entities”, are indeed patterns of observed signs and reported symptoms that trained clinicians have been able to recognize for decades in a variety of clinical contexts and in the community (although also noticing their frequent co-occurrence as well as the existence of intermediate and subthreshold forms) and have been managing with a degree of success that, although less than optimal, is actually comparable to that achieved by many other branches of medicine for the conditions they deal with.

It is certainly true that several diagnostic concepts in psychiatry have changed to some extent through the years and that some of them have disappeared along this way. Also, several diagnostic categories have been split or lumped in a way that is questionable. There is surely much room for improvement in our diagnostic practices. However, it would be difficult for me to identify a substantial difference between the history and the current characterization of, say, the mental disorder called depression versus the non-mental disorder called migraine. Both of them are defined syndromally, and mainly on the basis of what the person reports; both of them have an unclear and certainly heterogeneous etiopathogenesis; both of them have been classified and subtyped differently along the decades; and both of them have various clinical presentations, including *formes frustes*, and fuzzy diagnostic boundaries. It would also be difficult for me to accept that, imagining to turn the clock back ten thousand years and allow human civilization to develop again – as K. Kendler proposes as a thought experiment in this issue of the journal<sup>1</sup> – the pattern of depression would be less likely to emerge and be identified than that of migraine (unless,

of course, the nature itself of human beings were to be totally different).

True, the project launched in the early 1980s to validate DSM-III categories by elucidating their “specific” etiopathogenetic underpinnings<sup>2</sup> seems to have failed, but the picture that has gradually emerged during the past 35 years does represent in itself a prominent scientific advance, that the use of the DSM-III and its successors has not obstructed. We know today that the etiopathogenesis of most or possibly all patterns of mental disorder is very complex, involving the interaction of a multiplicity of biological, intrapsychic, interpersonal and socio-cultural factors. We also know that several of these factors are not specific for individual DSM/ICD categories. This complexity is not only due, as frequently stated, to the fact that the brain is a much more complex organ than the others we have in our body, but more crucially to the fact that mental disorders are not merely “brain diseases”, but actually emerge at the interface between that complex organ which is the brain and the even more complex world of interpersonal relationships in which we are all immersed.

For some patterns of mental disorder, e.g. eating disorders, the role of sociocultural factors in shaping their psychopathological identity is already obvious, but even for patterns such as psychotic disorders there may be some distance between any neurobiological mechanisms that we are likely to elucidate and the level at which their psychopathological identity emerges. So, taking for granted that these patterns can be fully “explained” at the neurobiological level, and feeling defeated or blaming our discipline because we are unable to do so, may be inappropriate, and the elucidation of the “higher-order processes”<sup>3</sup> which are involved may be crucial (see, for instance, Howes and Nour<sup>4</sup> in this issue of the journal). Furthermore, several different neurobiological processes may have a role in each of the limited number of patterns of mental disorder that human beings are able to express, and the same neurobiological process may be involved in several of those patterns.

I am also not very keen of the distinction between “utility” and “validity” of psychiatric diagnoses. There is an extensive overlap between what is called today “utility” and what used to be called “predictive validity”. If the utility of a diagnostic entity resides in its ability to predict further course and response to treatments, then the ascertainment of that utility is an intrinsic component of the “validation” process delineated by Robins and Guze<sup>5</sup>. And it would be appropriate to pay some attention to that component because, if the project of validating our current diagnostic entities by elucidating their specific etiopathogenetic underpinnings may have failed<sup>2</sup>, other components of the above validation process may have been less unsuccessful, although also requiring a refinement.

Otherwise, all the clinical research of the past 35 years may risk to be thrown into wastebasket, which would probably be a mistake.

On the other hand, we have to distinguish between the “utility” of a given diagnostic category and the “utility” of a whole diagnostic system. The DSM and ICD may be not sufficiently “useful” for ordinary clinical practice, in the sense that they may have features which discourage their use by clinicians. We have indeed some evidence<sup>6</sup> that a substantial proportion of psychiatrists worldwide do not use formal diagnostic systems in their ordinary practice, or use them just as “coding systems” (i.e., they use the ICD codes in clinical records and other similar documents, but do not have in mind the ICD descriptions when they use those codes, or have never read those descriptions). Certainly something should be done, and to some extent is being done<sup>7</sup>, in this respect.

I think that psychiatrists worldwide, and the people with whom they interact daily (colleagues of other medical disciplines, other mental health professionals, politicians, administrators, journalists, patients, carers, residents, students), need today a conceptual framework which explicitly acknowledges the above complexity and the oversimplifications which may have occurred, while avoiding to indulge in a pessimism that may be excessive and destructive.

Mental disorders may not be “disease entities” in the proper philosophical sense, but a large proportion of them are certainly not theoretical fictions. They are patterns of observed signs and reported symptoms that trained psychiatrists are able to recognize and manage, often successfully, in clinical settings and in the community. We do not have laboratory tests on which to base our diagnoses, but this means that psychiatrists are expected to be very skilled clinicians, and that high-quality clinical training is even more important in psychiatry than in other medical disciplines.

It is not true that there has been no progress in etiological research in psychiatry in the past 35 years. On the contrary, we have learnt that the etiopathogenesis of most mental disorders is very complex, involving the interaction of a multiplicity of biological, intrapsychic, interpersonal and sociocultural factors, that research is gradually identifying and weighing. No simple explanations are to be expected, though the complex models which may emerge will need to be made understandable by all the above-mentioned stakeholders.

Neurobiological mechanisms are likely to be involved in most or all mental disorders, but the level at which the psychopathological identity of these disorders emerges may be higher than that of the brain machinery, and the elucidation of the higher-order (e.g., psychological, cultural) processes which intervene may be crucial. Therefore, a dialogue should be kept between the neurosciences and other (anthropological, psychological, social) sciences when exploring the etiopathogenesis of what we should probably accustom ourselves to more exactly conceptualize, following the latest Kraepelin<sup>8</sup>, as “patterns of mental disorder”.

**Mario Maj**

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## Dopamine and the aberrant salience hypothesis of schizophrenia

Decades of investigation have established a central role for pre-synaptic mesostriatal dopamine dysfunction, in particular elevated dopamine synthesis and release capacity, in the pathoaetiology of psychosis<sup>1,2</sup>. The question of exactly *how* increased striatal dopamine synthesis and release capacity causes the symptoms and signs of psychosis, however, remains unresolved<sup>2,3</sup>.

Dopamine's role in the basal ganglia was first thought of purely in terms of motor function. Subsequent electrophysiological studies in animals established a role in reward processing and motivation<sup>4</sup>. Recent preclinical studies have demonstrated that mesostriatal dopamine signaling has a much more nuanced role in cognition, and in particular a critical role in processing the salience of stimuli<sup>5</sup>. These insights may bridge the explanatory gap between neurobiology and phenomenology, explaining how dopamine dysfunction might underlie psychotic symptoms.

Several lines of evidence indicate that schizophrenia is a disorder of abnormal dopamine signalling. Drugs which increase striatal dopamine release may cause psychosis, and the potency of an antipsychotic medication is proportional to its ability to antagonize D2/3 receptors<sup>6</sup>. Studies using positron emission tomography (PET) provide robust evidence that dopamine synthesis and release capacity are elevated in patients with schizophrenia compared to control subjects, both in the striatum<sup>1</sup> and in the midbrain origin of the neurons<sup>7</sup>. Furthermore, these elevations are also seen in patients at high risk of developing schizophreniform psychosis<sup>8</sup> and are specifically linked to those who later develop psychosis<sup>9</sup>. Striatal dopaminergic dysfunction has thus been proposed as a final common pathway leading to psychosis in schizophrenia<sup>6</sup>. To answer the question of how this neurochemical abnormality is related to the symptoms and signs of psychosis, it is instructive to consider what is known about the function of mesostriatal dopamine signalling in the healthy brain.

Early electrophysiological studies in animals showed that activity in the dopaminergic mesolimbic pathway increases transiently after the presentation of unexpected rewards or reward-predicting stimuli, but decreases when an expected reward is omitted. This activity has been construed as a marker of incentive salience, underpinning motivated action selection<sup>4</sup>. Midbrain dopamine neurons, however, are not homogeneous: whilst a proportion encode motivational *value* for positive outcomes such as food, engendering seeking behaviour and value learning<sup>4</sup>, others respond to salient but non-rewarding (e.g., aversive) stimuli, encoding a motivational *salience* signal that triggers orienting and exploration behaviour<sup>5</sup>.

Early articulations of the aberrant salience hypothesis of schizophrenia proposed that disordered mesostriatal dopamine release results in an over-attribution of meaning and motivational value (incentive salience) to irrelevant environmental events<sup>2</sup>. Evidence supporting the heterogeneous character of phasic dopamine signalling<sup>5</sup>, however, suggests that dopaminergic dysfunction may contribute to a more multifaceted mis-

attribution of salience involving both rewarding and aversive signalling. This could lead to the world seeming pregnant with significance, generating feelings of apprehension and a sense that the world has changed in some as yet uncertain way. These experiences are characteristic of the prodromal phase of schizophrenia<sup>2,3</sup>. Jaspers<sup>10</sup> referred to this as the *delusional atmosphere*, in which "there is some change which envelops everything with a subtle, pervasive and strangely uncertain light".

Although the aberrant salience account of delusional atmosphere is appealing, it is less intuitive how anomalous experiences lead to positive psychotic symptoms. Cognitive theories of psychosis offer an explanation. Patients experiencing paranoid delusions tend to exhibit a "pessimistic" and "externalizing" thinking style, which may develop after exposure to social adversity and childhood trauma<sup>11</sup> (see also Peters et al<sup>12</sup> in this issue of the journal). Perplexing experiences, when interpreted through this biased appraisal process, may be seen as threatening and uncontrollable, giving rise to persecutory ideas, ideas of reference and delusions of control<sup>11</sup>. By extension, when salience is misattributed to internal representations and self-generated actions, these phenomena may be interpreted as externally generated<sup>3</sup>, giving rise to auditory verbal hallucinations and passivity phenomena. As childhood adversity may also sensitize the dopaminergic system, cognitive theories of psychosis provide an important link between the socio-developmental risk factors, neurobiological substrate and subjective experience of schizophrenia<sup>11</sup>.

More recent formulations of the salience hypothesis of schizophrenia have been informed by computational accounts of brain function, that highlight the role of cortical-subcortical interactions in integrating incoming sensory information with existing internal models of the world. From this perspective, sensory information is salient when it violates the brain's predictive model of the world, represented in cortical regions. Persistent mis-matches between predicted and actual sensory stimuli drive adaptive changes to the brain's world-model<sup>3</sup>. This process is finely modulated by subcortical dopamine transmission, such that even subtle abnormalities in dopamine signalling may result in radical maladaptive changes to brain's world model, which may manifest clinically as false beliefs and perceptions<sup>3</sup>.

Investigation of salience attribution in schizophrenia has mainly focussed on reward-anticipation tasks. In functional magnetic resonance imaging (fMRI) studies, patients with schizophrenia generally show reduced activation in the mesolimbic pathway (ventral tegmental area and ventral striatum) upon presentation of reward-predicting stimuli, and exaggerated neuronal responses to "neutral" stimuli, compared to control subjects<sup>13</sup>. These changes are present in unmedicated and first-episode patients. Furthermore, there is a correlation between mesolimbic signalling abnormalities and both positive and negative symptoms.

In studies that have operationalized salience attribution, medicated patients with schizophrenia demonstrate impaired adaptive salience attribution, and delusional patients exhibit more aberrant salience attribution than non-delusional patients. Moreover, aberrant salience attribution is higher in individuals at ultra-high risk of psychosis compared with healthy volunteers, and both aberrant salience attribution and ventral striatal fMRI responses to irrelevant stimuli are correlated with severity of delusion-like symptoms<sup>14</sup>.

Despite the intuitive appeal of the aberrant salience model, a number of issues remain. To date there has been no direct demonstration of aberrant phasic dopaminergic activity in patients with schizophrenia, because of inherent methodological challenges. Different experimental approaches measure different aspects of neuronal function. The relationship between electrophysiological activity (measured by single-unit recordings) and transmitter release (in voltammetry, microdialysis and PET studies) is incompletely understood, and confounded by modulatory neurotransmitters and autoreceptor feedback. These experimental approaches also have vastly different spatial and temporal resolution.

In humans, the most commonly used tool for investigating the neuronal correlates of aberrant salience attribution is fMRI, which neither directly measures neuronal activity nor dopamine release, but rather regional changes in the blood oxygen level on a time-scale of seconds. PET, which does allow non-invasive measurement of dopaminergic activity, has a temporal resolution that is several orders of magnitude larger than the animal electrophysiological studies on which the aberrant salience hypothesis is based.

Finally, it remains an open question whether aberrant salience attribution is sufficient to explain the full spectrum of symptoms in psychosis, and whether this abnormality is specific to schizophrenia. The hypothesis may account for delusional atmosphere and delusion formation, but it is less clear how it extends to thought alienation and hallucinations. Moreover, recent evidence suggests that ventral striatal fMRI responses to anticipatory reward are also reduced in alcohol dependence and major depressive disorder<sup>15</sup>, and further comparative studies are needed to understand the specific nature of aberrant salience processing in schizophrenia.

The aberrant salience hypothesis has the potential to bridge the explanatory gap between biological, psychological and behavioural features of schizophrenia<sup>2,3</sup>. In order for the hypothesis to be rigorously tested, however, the gap between animal and human studies must be bridged. Preclinical studies that employ electrophysiological recordings and neuroimaging in the same animals, undertaking clinically relevant

behavioural tasks, will be critical to this endeavour. Human studies that combine multiple imaging modalities (e.g., fMRI, PET) with behavioural and physiological markers of salience attribution are needed to explore how inter-individual differences in dopamine synthesis and salience-related neuronal activity are related<sup>14</sup>. Finally, longitudinal studies investigating patients at multiple stages of the disease process, from the prodrome to established psychosis and relapse, will test whether aberrant salience attribution is causally implicated in psychosis.

If it can be shown that aberrant salience attribution, caused by dopaminergic dysfunction, is the final component in the causal pathway leading to psychosis, then the most effective therapeutic approach is likely to involve medication targeting the presynaptic dopaminergic dysfunction to dampen aberrant salience attribution, followed by a programme of psychotherapy to help the patient reappraise his/her model of the world, and reinterpret his/her place within it. Ultimately, studies directly modulating the dopamine system and measuring associated changes in psychological appraisal will provide the final proof that the aberrant salience hypothesis bridges the explanatory gap from neurobiology to symptoms of psychosis.

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# The nature of psychiatric disorders

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*A foundational question for the discipline of psychiatry is the nature of psychiatric disorders. What kinds of things are they? In this paper, I review and critique three major relevant theories: realism, pragmatism and constructivism. Realism assumes that the content of science is real and independent of human activities. I distinguish two “flavors” of realism: chemistry-based, for which the paradigmatic example is elements of the periodic table, and biology-based, for which the paradigm is species. The latter is a much better fit for psychiatry. Pragmatism articulates a sensible approach to psychiatric disorders just seeking categories that perform well in the world. But it makes no claim about the reality of those disorders. This is problematic, because we have a duty to advocate for our profession and our patients against other physicians who never doubt the reality of the disorders they treat. Constructivism has been associated with anti-psychiatry activists, but we should admit that social forces play a role in the creation of our diagnoses, as they do in many sciences. However, truly socially constructed psychiatric disorders are rare. I then describe powerful arguments against a realist theory of psychiatric disorders. Because so many prior psychiatric diagnoses have been proposed and then abandoned, can we really claim that our current nosologies have it right? Much of our current nosology arose from a series of historical figures and events which could have gone differently. If we re-run the tape of history over and over again, the DSM and ICD would not likely have the same categories on every iteration. Therefore, we should argue more confidently for the reality of broader constructs of psychiatric illness rather than our current diagnostic categories, which remain tentative. Finally, instead of thinking that our disorders are true because they correspond to clear entities in the world, we should consider a coherence theory of truth by which disorders become more true when they fit better into what else we know about the world. In our ongoing project to study and justify the nature of psychiatric disorders, we ought to be broadly pragmatic but not lose sight of an underlying commitment, despite the associated difficulties, to the reality of psychiatric illness.*

**Key words:** Psychiatric disorders, realism, pragmatism, constructivism, homeostatic property clusters, DSM-5, ICD-10

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A foundational question for the discipline of psychiatry is the nature of what we treat and study: psychiatric disorders. What kinds of things are they? This question can be fruitfully addressed from several perspectives. We could, for example, ask about their etiology and contribute to the long running argument about whether they are better understood from a psychological versus a biological perspective. We could explore their historical development and the differentiation of psychiatric from neurologic conditions. But I will not be taking such approaches here. Rather, my questions are more philosophical (or, to be more precise, metaphysical) in nature.

I will review and critique three major theories about the nature of psychiatric disorders: realism, pragmatism and constructivism. This is not an exhaustive list of the theories applied to this question. But together they do cover most of the major issues. I will at times adopt a descriptive voice, trying to outline and contextualize these three positions. However, I will also sometimes be more autobiographical and proscriptive, exploring both how I have considered these theories over my career and how I view them now.

I posit that these three theories of psychiatric disorders can be placed on a single dimension, best conceived as a scale of “realness” (which might be defined, in philosophy talk, as “existence in mind-independent space”). I will complicate this typology by four further refinements, in an effort to find an optimal approach to understanding the nature of psychiatric disorders. I do not seek to provide a definitive resolution to this very difficult question, but rather hope to illuminate the range of relevant issues.

## REALISM

Realism is a major position in the philosophy of science which assumes that the content of science is real in a way that is independent of human conceptions and activities. It is the common sense position accepted by most working biomedical scientists, who, if asked about the nature of the subject of their studies (be it genes, the clotting cascade, or types of autoimmune disease), would reply: “Of course, the things I work on are real. What a silly question!”. This was a position I would have endorsed whole-heartedly when I was a resident and young assistant professor working on biological theories of schizophrenia. “Of course, schizophrenia is a real thing”.

I want to discriminate between two flavors of this realist position. The first is based in the hard science of chemistry, and the second in biology. For the first, the paradigmatic scientific construct or “kind” is elements in the periodic table like carbon, nitrogen and oxygen. They are wonderful in the clarity of their “mind-independence”. We can be confident at any time and place in our universe, if a civilization of sentient beings develops far enough, that they will discover something structurally isomorphic to our periodic table. That is, our periodic table and the elements in it are a deep truth about our world entirely independent of humans. We could all disappear tomorrow and their reality would be unperturbed.

Elements in the periodic table illustrate another important feature of realistic kinds: they can possess an essence. Elements of the periodic table have essences. That is, once you know the atomic number (not, as some first thought, the

atomic weight), you can predict most of what you need to know about an element: its melting point, its density, its ability to combine with other elements, etc.. A helpful metaphor for an essence is a “level” of scientific knowledge which you can grab, knowing that it tells you most of what you want to know about your particular object of study. For atomic elements, that level is the atomic number.

For the second flavor of realism, the paradigmatic kind is the biological species. Species differ from elements in four important ways. First, they have fuzzy boundaries. The features of a species typically vary over its range, and at its limits the dividing line between sister species can become indistinct. The borders between elements, instead, are sharp. Second, the existence of a species is much more conditional than that of an element. The species we know about only exist in our biosphere and are temporally limited, existing only between their emergence and extinction. An element such as hydrogen is universal and practically timeless. Third, unlike elements, species have no essence. There is no one thing that defines a species that makes a walrus, robin or drosophila. Fourth, not all members of a species are identical to one another, as are atoms of any element.

Clearly, the biological flavor of realism is more appropriate for psychiatric disorders than chemistry-flavored realism. Psychiatric disorders are much more like species than elements. However, both flavors of realism share a critical feature: they postulate that scientific kinds exist independent of our efforts to study them. That is, we could “discover” a new psychiatric disorder in the same way a hitherto unobserved species of bird is found in a rain-forest. We do not “create” our disorders; rather we find them in nature.

## PRAGMATISM

A common-sense summary of pragmatism in psychiatry would be as follows:

As a working scientist or clinician, I just want to predict and control features of the world. I want a psychiatric diagnosis that tells me what treatment to use, is good at predicting course of illness, and correlates well with important biomarkers. What the hell do I care about metaphysics and vague philosophical phrases such as “mind-independent reality”!

Pragmatism eschews metaphysical speculation and is a close cousin to a view in philosophy of science called instrumentalism, which sees key concepts in science as “instruments” or tools with which to understand the world. In common sense terms, instrumentalism judges scientific categories by whether they work or not, not on whether they are real or not.

Pragmatism is a coherent, sensible, moderate position that has been well articulated by Zachar<sup>1-3</sup>. As will be clear later, I continue to struggle to find a comfortable space for psychiat-

ric disorders somewhere between realism and pragmatism. But for now, I want to focus on one important limitation. Pragmatism, in its classic form, is unambitious and is reluctant to make claims about the underlying reality of psychiatric disorders. This for me is problematic.

To explain why, I have to admit to two problems with the pragmatic approach to psychiatric disorders that are not entirely philosophical in nature. First, I have spent many years of my life caring for the psychiatrically ill and speaking with their families. Taking a “pragmatic” approach to psychiatric illness (and to all the tremendous pain it causes to the patients and their relatives) to this day feels disrespectful, as if I am not fully acknowledging the reality of their illness. This position is, at its essence, an ethical one. Over history, many cultures have done a poor job of properly seeing the other in those who are psychiatrically ill. It has been too easy to deny their humanity, to say they are not really sick. I continue to feel an obligation to counter this position and argue for the reality of mental illness.

Second, I am deeply committed to the status of psychiatry as a legitimate biomedical discipline deserving of respect, and more funding for our clinical and scholarly activities. Surgeons do not spend time or energy worrying about the reality of gall stones, infected appendices or subdural hematomas. Does taking a pragmatic approach to psychiatric illness help us in our debates about respect and resources with our medical and surgical colleagues, some of whom are disinclined to see anything psychiatry does as “real”? In my scientific worldview, the mind is part of the body and its disorders are just as real. It would be inconsistent, or an admission of defeat, to regard psychiatric disorders as being of a different status than classical physical-medical disorders. As public advocates for our field and our patients, defending the reality of psychiatric illness is important.

## CONSTRUCTIVISM

For most working psychiatric researchers and clinicians, claims for the constructivist nature of psychiatric disorders are “fighting words”, because this perspective, best articulated in the anti-psychiatry writings of T. Szasz<sup>4</sup>, is associated with attempts to delegitimize our field. To consider constructivism objectively, we need to back away from this initial emotional and defensive reaction.

What are socially constructed things? They are the sorts of ideas and things that humans make like euros, passports, narrow ties, and hip-hop music. To say something is socially constructed is *not* to say that it is not “real” in a practical sense. That is, having euros in my wallet allows me to buy things, and having a U.S. passport allows me to travel to Norway. Nevertheless, to say that something is socially constructed is to say that it would not exist without the activities and social conventions of human beings.

Before we tackle the difficult question of whether psychiatric disorders could be socially constructed, let me make a



weaker and hopefully less controversial claim about the role of social processes in the construction of psychiatric disorders. Consider the history of post-traumatic stress disorder (PTSD) in DSM-III<sup>5</sup>. Traumatic reactions to the barbarity of warfare had long been recognized. But the decision to add PTSD to DSM-III arose out of a complex, historical context involving the Vietnam Veterans Against the War and politically involved prominent U.S. psychiatrists who believed that suffering Veterans were not being recognized or adequately treated by the country they served. The historical record suggests that the decision to include PTSD, with its specific criteria, was substantially influenced by the social and political environment in the U.S. in the late 1970s associated with the Vietnam War.

Consider a more recent example. Zachar and I have recounted the story of the intense debates from DSM-III-R through DSM-5 about the inclusion of a menstruation-related mood disorder<sup>6</sup>. After forceful and often public debate, the relevant DSM committees for DSM-III-R and DSM-IV decided to exclude such a diagnosis from the main manual, including it instead in an appendix. In DSM-5, by contrast, with little fanfare, it was included in the main document. After interviewing most of the main contributors to this debate, we concluded that the accumulating scientific evidence in favor of the validity of what has become premenstrual dysphoric disorder (PMDD) played some role, but at least as important were two external “social” factors. First, in 2000, the U.S. Food and Drug Administration approved the popular antidepressant fluoxetine under a new trade name for the treatment of PMDD. This provided a very important external validation of the diagnostic entity. Second, to paraphrase one of our interviewees:

Feminism had changed. The new generation of feminists was not nearly so threatened by this diagnosis. Mainline women’s magazines carried stories about PMDD. If diet and relaxation did not work, it was fine to visit your doctor and ask for treatment.

I could multiply examples. My experiences over many years and hundreds of hours of DSM deliberations (from DSM-III-R through to DSM-5) have disabused me of the notion that we can revise our nosology in a “purely” scientific process. Although I am no anti-psychiatrist, to argue that social factors do not impinge in a substantial way on our nosology is not a sustainable position. Critically, I am not saying that social forces created PTSD or PMDD. Rather, I assert that social forces influenced the debate about the recognition of these disorders in our official nosology.

Before we feel too much embarrassment about this, it would be salutary to note that the “harder” sciences are not devoid of such influences. Hull<sup>7</sup> documents the long, acrimonious and highly politicized debates among competing schools about the optimal approach to biological taxonomy. More recently, a drama unfolded about the struggle about the definition of a planet in the International Astronomical Union. This debate, which concluded with the down-grading of Pluto

to a “dwarf-planet”, eerily resembled certain modern nosologic debates in psychiatry<sup>8</sup>.

Let us turn to the harder question of true “social construction” for psychiatric disorders. Consider the epidemic in the U.S. in the 1990s of multiple personality disorder (MPD), which was often accompanied by repressed memories of bizarre ritual sexual abuse<sup>9</sup>. While I cannot possibly do justice to this complex story here, there is good reason to think that a proportion of these individuals had iatrogenic disorders – ones that were actually “constructed” from the expectations of their therapists<sup>9,10</sup>. I do not mean to imply that such individuals were not in some ways “disordered” when they sought treatment. Rather, I argue that in most if not all such cases the specific syndrome of MPD and associated “recovered” memories was constructed by patient-therapist interactions. A similar story has been told about the grand hysteria constructed under Charcot’s care in Paris in the late 19th century<sup>11</sup>. To please the professor, his patients became actresses displaying the expected sequence of symptoms and signs before his public audience.

Socially constructed psychiatric disorders have existed in our history. I would however argue that such situations, in which the social processes that created the disorder did not track anything true about the world, are rare. By contrast, socially influenced disorders are common, as our nosologic processes typically involve important social and cultural elements. We do not ever want our disorders to be theoretical fictions like (at least most cases of) MPD. For disorders like PTSD and PMDD, which we learned to see at one point in our history, we should routinely assure ourselves that they were “out there” before we learned to see them and included them in our nosology.

## TWO ARGUMENTS AGAINST REALISM FOR PSYCHIATRIC DISORDERS

We have completed a brief review of our three traditional positions on the metaphysical nature of psychiatric diagnoses: realism, pragmatism and constructivism. I now want to complicate this picture further. At first blush, realism is very attractive. Pride in our specialty should want us to declare that our disorders are real. We experience the suffering they bring to our patients and their families. What could be better proof of their reality?

However, I want to counter this enthusiasm by reviewing two strong arguments *against* realism as a plausible model for psychiatric disorders: pessimistic induction and historical contingency.

### Pessimistic induction

The philosopher Kuhn articulated the essence of the pessimistic induction argument as follows: “All past beliefs about nature have sooner or later turned out to be false”<sup>12</sup>. To be

more specific, all scientific theories postulate the existence of entities. Consistently, over the history of science, as older theories have been replaced by newer theories, the entities of the older theories, often long regarded as real, are frequently discarded and judged to not exist at all. We no longer teach about ether in physics, phlogiston in chemistry, or the humoral theory in medicine or psychiatry. Sitting in the present, we look back at earlier theories, now falsified, and conclude that the entities referred to by these theories do not in fact exist, and therefore are not, in any sense, real.

If the pessimistic induction argument is true – that past scientific theories have typically been disproven and their key constituents shown to not exist – common sense suggests that it will also be true in the future. That is, looking back from the future, won't the scientific constructs that we now regard as real likely be replaced and viewed as false?

One could construct a counterargument against this position. It would go something like this:

All those prior scientists were mistaken about the value of their theories. But we finally have things right. The entities referred to by our current best theories are real. The truth is now in our hands.

This counterargument, however, is implausible and boastful.

The pessimistic induction argument is relevant for our realist models of psychiatric illness because we have, in the history of psychiatry, many diagnostic categories that were once used and accepted, and have now been abandoned. With little difficulty, anyone knowledgeable about the history of psychiatry could come up with many such categories. From Esquirol<sup>13</sup>, we could find lypemania, demonomania and monomania. From Wernicke, we could note somatopsychosis and anxiety psychosis<sup>14</sup>. Late in life, Kraepelin proposed a category of paraphrenia that was used by his students for a few decades and then abandoned<sup>15</sup>. In his lovely book on personality disorders<sup>16</sup>, Schneider has several categories, such as the “fanatic psychopath”, which are no longer used. In the 20th century, Leonhard – a follower of Wernicke – proposed a novel classification for the endogenous psychoses used by a number of his followers that included such ornate titles as “parakinetic catatonia”, “phonemic paraphrenia” and “insipid hebephrenia”<sup>17</sup>. Hysteria was a major psychiatric category for many decades of the 19th and early 20th centuries, which has now been abandoned. I could go on.

Here is the bite. Given the dozens of psychiatric diagnostic systems that have come and gone over the history of our discipline, can we really argue that with DSM-5 or ICD-10 we have finally got it right and that the truth is now in our hands? Like the above counterargument against pessimistic induction, this sounds implausible. If history is any guide, isn't it highly likely that our current DSM and ICD categories will, in the future, eventually be seen as false (or more politely as “sub-optimal”)? If so, what does this do to our current claims for the realism of psychiatric disorders? Indeed, such issues are quite current. During the development of DSM-5, one major proposal, not

ultimately accepted, called for the deletion of five of the ten DSM-IV personality disorders and another, eventually accepted, eliminated the classical subtypes of schizophrenia.

## Historical contingency

I can make two different arguments for the historically contingent nature of our current psychiatric categories. The first is a thought experiment. Imagine turning the clock back ten thousand years and allowing human civilization to again develop agriculture, writing, science, medicine, and, finally, something resembling psychiatry. Then we wait till this psychiatry-like discipline decides to write a diagnostic manual and we get a copy of this manual. We then repeat this experiment 100 times and classify the resulting categories alongside our current DSM-5 and ICD-10. What will we find? My intuition (and those of many with whom I have shared this thought experiment) is that a substantial proportion of our current categories will not be represented reliably in these manuals. Unlike the elements in the periodic table, our current menu of psychiatric disorders would not likely be consistently rediscovered.

The second argument is that our current diagnostic system is highly dependent on some particular historical events. What would have happened if Kraepelin stayed in Wundt's laboratory, as he wanted, and never went on to his psychiatric career? What if Wernicke, the one genuine competitor with Kraepelin for prominence in Germany psychiatry at the turn of the 20th century, had not died from a bicycle accident at the age of 52 in 1905? What if Spitzer really liked psychoanalysis and never got involved in psychiatric nosology? One can plausibly argue that, if any of these events had occurred, DSM-5 and/or ICD-10 would be meaningfully different from what they are now.

These two arguments are inter-related. If there are many steps between the overt manifestations of psychiatric illness on the one hand and the creation of an official psychiatric nosology on the other, and some of these steps involved historical contingencies, then we would expect that re-running the “tape of time” over and over would not always produce the same DSM or ICD categories.

## FOUR POSSIBLE MODIFICATIONS OF THE REALISTIC POSITION FOR PSYCHIATRIC DISORDERS

In this section, I explore four ways in which the realism position for psychiatric disorders can be modified and made more credible.

### Homeostatic property clusters

I want to expand our prior discussion about the preference for biological over chemical models of realism for psychiatry by considering the concept of a “homeostatic property cluster”, as originally proposed by the philosopher R. Boyd<sup>18-20</sup>. Consider

what makes up a stable biological species, from the ecosystem to physiology, from mating processes to predator-prey relationships, from dietary adaptations to DNA sequence. As noted above, the properties of a species do not arise from a single essence like the properties of carbon can be derived from its number of protons. Rather, the nature of a lion or starling arises from a cluster of properties that inter-relate with one another in a stable manner over time. While we have sought for the key to humanness by comparing the genomes of humans with those of chimps and gorillas, it is clear that there are hundreds of meaningful genetic differences between us and our nearest primate relative, no one of which is definitional<sup>21,22</sup>.

In our views about psychiatric disorders, we still often utilize essentialist thinking. Think about how we teach residents about the diagnostic criteria for major depression. What we typically say is: "There is this entity we call major depression. It can be diagnosed using these specific set of symptoms and signs which are manifestations of the underlying state of depression". Is this an optimal way to think about the underlying nature of psychiatric disorders? Where in the mind-brain system might these "essential factors" exist? Is there a mind-brain depression center with an "on-off" switch in it? Is it not more likely that our psychiatric syndromes arise from inter-connected networks that can profitably be understood at the level of mind (e.g., symptoms of guilt leading to ideas of suicide) or at the level of brain (e.g., disturbed reward systems produce anhedonia which then impacts on appetitive systems producing decreased appetite)? Psychiatric disorders can then be understood as emergent syndromes arising from disturbances in mind- and brain-based networks rather than concrete "things/essences" that exist in some definable place in the mind or brain.

Homeostatic property clusters can allow us to "soften" the unsustainable demand for true "essences" in realistic models for psychiatric disorders. They give us a tractable kind of "emergent" pattern. What makes each psychiatric disorder unique are sets of causal interactions amongst a web of symptoms, signs and underlying pathophysiology across mind and brain systems.

Homeostatic property clusters also have implications for how we should understand the inter-relationship between the symptoms and signs of psychiatric disorders. As advocated by Borsboom and colleagues in a series of influential papers<sup>23-26</sup>, it may be more sensible to assume direct causal relationships between symptoms (insomnia causes difficulties in attention, guilt causes suicidal ideation) than to assume that each symptom is only the reflection of some essence of the disease – in this case depression. While beyond my charge, it is clear that this approach has produced novel insights into the nature of psychiatric disorders.

### **A more limited view of realism for psychiatric disorders**

We can also take a more philosophical approach to trying to develop a better realism-based model for psychiatric disorders. My approach goes back to fundamentals – the nature of

truth. Philosophy has two prominent theories of what it means for something to be true: a correspondence theory and a coherence theory. The correspondence theory is what most of us think about naively when we say something is true. The statement "It is raining outside now" is true if and only if it is indeed raining outside. So that statement "corresponds" to something in the world that we can easily verify, in this case by looking outside the window.

This seems to be a high standard. While it is easy to know if it is raining, how would we apply this approach to the statement "Schizophrenia as defined in DSM-5 is a valid disease"? What would *correspond* to this statement? Would it be enough to show changes in a magnetic resonance imaging scan, genetic risk factors, or a response to medication?

What if we wanted to be less demanding of ourselves in calling something true? A humbler approach can be found in the coherence theory of truth. This theory considers something to be "true" when it fits well with the other things we know confidently about the world. This is well expressed in the following metaphor:

Consider a table with a puzzle on it all assembled but missing one piece. Think about the satisfaction you feel when you find that piece and fit it neatly into the missing space with a pleasing "snap".

That "snap" would reflect the coherence theory of truth. So what then do we mean, using this approach to say a diagnosis is true (or real)? We might say it is "pretty well" connected with the other pieces – that it is "pretty well" integrated into our accumulating scientific data base. In other words, a diagnosis is real to the degree that it "coheres" well with what we already know empirically and feel confident about.

Another way to apply this theory to psychiatry is to consider the question: "What do we mean when we want to say that one diagnostic concept (e.g., our modern concept of *schizophrenia*) is more real than another (e.g., the concept of *frenzy* in the early 19th century)?" Using a coherence theory of truth, the answer is simple. To be more real means to be connected to more already existing things we know.

The coherence theory of truth has one more important benefit to offer us. The other pieces in our puzzle metaphor for the coherence theory are what we have called validators since the days of Robins and Guze<sup>27</sup>. The best diagnoses we have are the ones that are strongly connected with other things we know about – that is, are "well validated".

For individuals assigned to that diagnostic class, we follow the connecting pieces and see all the other things that we learn about them – genetic risk factors, premorbid susceptibilities, imaging findings, neurochemistry, course, prognosis, treatment, etc.. As a disorder becomes more valid, it becomes more connected with our knowledge-base and, from a coherence perspective, more real.

The coherence theory, therefore, provides a framework for what it might mean to make our constructs refer to something

“more” real. We should require that, for each iteration of our diagnostic manual, changes be made in our diagnostic categories only when they result in the diagnosis becoming “more” real, which by the coherence theory means more interwoven into the fabric of our scientific findings.

I do not want to underestimate the potential importance of adopting a coherence theory for psychiatric illness, because it departs in some important ways from our conventional ideas about truth. Indeed, it moves our ideas about “truth” in a distinctly pragmatic direction. Right now we can do a much better job of applying this more modest and practical view of truth to psychiatric illness than we can with the more ambitious correspondence theory.

### Types of psychiatric disorders versus tokens

Our discussion up until now has had one glaring deficiency. In discussing the question of “what sort of thing is a psychiatric disorder”, we have treated psychiatric disorders as if they formed a homogeneous entity. This assumes that autism, schizophrenia, nicotine dependence, narcissistic personality disorder, nightmare disorder, and factitious disorder are the same kind of thing. Is this a plausible assumption?

Philosophy has a distinction that can help us here: between types and tokens. Tokens are specific manifestations of a broader general class, while types are the broad class, which can have several levels. So we would have a super-ordinate type of “automobiles”, subtypes of Ford, GM, Volvo and BMW sedans, and then tokens would be the individual cars themselves – my beat up 16 year old Volvo station wagon.

To parse this in psychiatric terms, we could say that psychiatric disorders would be the superordinate type, subtypes would include “mood disorders” and “psychotic disorders”, and the tokens would be the individual disorders: schizophrenia, panic disorder and pathological gambling.

I want to argue that we should be more committed to the reality of psychiatric types than of psychiatric tokens. Think of the historical contingency argument. The probability that our current diagnostic category of histrionic personality disorder would show up every time we re-ran the tape of time, over and over again, strikes me as low. If I were to defend the realism of psychiatric illness, I would not choose to make histrionic personality disorder my *cause celebre*. What about the stability over multiple “replications” of human history of the broad concept of personality disorder? That sounds like a better bet to me.

Consider the pessimistic induction argument. This is the argument that since things we have taken to be true in the past have been shown to be false, the same could happen to those things we accept as true and valid today. However, while specific diagnostic categories will come and go over time, is it more probable that certain broad constructs – like neurodevelopmental, internalizing or psychotic disorders – will stand the test of time?

The logical extreme of this would be to stake our claim for reality on the broadest possible type – all psychiatric illness.

This argument has important strengths. This broad category is much less vulnerable to the pessimistic induction or historical contingency arguments. Specific psychiatric disorders may come and go, but the phenomena that we now describe as psychiatric disorders are likely part of the human condition, and will exist and be described in some way by any human culture during any historical time period. However, this argument is not a panacea and risks descent into the woolly “unitary theories of psychiatric illness”. With respect to impact on human suffering, in arguments for the need for clinical care or the viability of our profession as a sub-discipline of medicine, this argument has force. Nonetheless, in the halls of research institutions and most care clinics, we want to continue to subdivide our patients, however imperfectly, into our diagnostic categories.

### An historical perspective applied to psychiatric disorders

Up until now, we have been viewing the problem of psychiatric kinds from a largely static cross-sectional perspective. In this section, I want to briefly explore what we might learn by adopting an historical perspective. I will here borrow from the philosopher of science I. Lakatos<sup>28</sup>. As he suggested, research programs can be progressive or degenerative. I suggest that diagnostic concepts in medicine, in general, and psychiatry, particularly, can also be progressive or degenerative. I will define “progressive” for our purposes as roughly “continuing to yield new insights into etiology, course and treatment”. For our discussion here, I want to suggest that, as disorders continue to provide us new insights, they become more “real”. This relates directly to our discussion above about the coherence theory of truth.

Take, as an example of a highly generative diagnostic position, the splitting of the syndrome of diabetes mellitus into type 1 or insulin-dependent, and type 2 or insulin-resistant forms<sup>29</sup>. This diagnostic distinction has proven very fertile, as these two forms of diabetes mellitus now have well understood entirely different etiologies, different treatments and prognoses. Recent molecular genetic studies have shown non-overlapping sets of risk genes for the two types<sup>30</sup>. Clearly, this has been a “progressive” diagnostic program.

I do not think that in psychiatry we have any story of successful diagnostic “splitting” that can compete with the diabetes mellitus story. However, we have two that come close.

Kraepelin’s concept of manic-depressive insanity included what we now call major depression and bipolar illness. For a range of reasons, some having to do with writings of Leonhard<sup>17</sup>, bipolar illness was separated out from major depression in the middle of the 20th century. We now know that this too has been a “progressive” diagnostic splitting, leading to clear differences in treatment and etiology, including molecular genetic findings.

Our other success story might be separating the broad category of anxiety neurosis into panic disorder and generalized

anxiety disorder (GAD). This was a direct result of studies by D. Klein<sup>31</sup> using a method he called “pharmacologic dissection”. What differentiated panic disorder patients from those with other forms of anxiety was a rapid response to relatively low dose imipramine. We now know that panic disorder and GAD differ meaningfully in etiology and, somewhat, in their pharmacologic and psychotherapeutic treatment.

So, this tentative line of thought would suggest another way to think about how our disorders become more “real”. In an historical extension of the coherence theory of truth, those disorders become real if over time they “keep on giving”, providing us with continued fresh insights into etiology and treatment.

## CONCLUSIONS

In this final section, I want to describe the evolution in my own thinking about the kind of things that psychiatric disorders are. As I noted above, in my early years, as an avid young biological psychiatrist on the trail of verifying the dopamine hypothesis of schizophrenia, I would have been an unreflective, hard-nosed realist. It would never have occurred to me that schizophrenia was not a real thing, and as real as elements in the periodic table.

I do not believe that any more. I have read too much psychiatric history. I have sat through too many DSM meetings. While I remain committed for both scientific and personal reasons to the reality of psychiatric disorders, I have struggled to find a more acceptable way to frame those beliefs. Chemistry-based models of scientific realism do not work for psychiatry. Our disorders are not real in the same way that oxygen and carbon are – not in our historical era and, probably, not ever. They are by nature much messier, which is not surprising when you compare the complexity of the human mind-brain system and atoms.

The biology flavor of scientific realism provides a much more comfortable fit for psychiatry. So, that is a clear improvement. But then we have to confront this question about essences. The debate about whether realistic kinds in science had to have essences is a long one. I do not think this is likely a sustainable position for psychiatry. I have to admit an autobiographical influence here. It was only shortly after my brash days as a biological psychiatrist seeking to find “*the*” neurochemical cause for schizophrenia that I set out to find “*the*” gene for schizophrenia by studying large high-density pedigrees in Ireland<sup>32</sup>. Both efforts were driven by a naïve view of schizophrenia that it had a single essence – one biological secret which if understood would explain all we wanted or needed to know about the disorder. Linkage studies had worked for Huntington’s disease and for cystic fibrosis. Why not for schizophrenia? Even though I knew better (the pattern of schizophrenia in families was nothing like that found for classic Mendelian genetic diseases), the passion was there to find the cause for schizophrenia. If not one neurotransmitter, why not one gene? Thirty years later, we have now identified

well over 100 risk genes for schizophrenia<sup>33</sup> and the number is likely to grow rapidly. So much for essences!

Our disorders are probably inherently multifactorial. In this sense, they do not differ from the most important of our non-infectious common medical disorders, such as hypertension, type 2 diabetes, coronary artery disease, or osteoporosis. So if we give up on essences as being the bed-rock of psychiatric kinds, with what might we be left? The best framework that I have found for this is networks of interacting causes and symptoms like Boyd’s homeostatic property clusters. The stability of our disorders over space and time is an emergent property of the human mind-brain system – not the result of one essence from which all the symptoms and signs develop.

The pragmatic position toward psychiatric disorders is a perfectly respectable one. It can be well defended and has a strong common-sense appeal. Ultimately, the practice of psychiatry is a pragmatic one. However, for a range of reasons, some well-grounded and others probably less so, this position is insufficiently ambitious for me. But, I am clearly willing to use pragmatic tools to reach realist goals.

We should not get backed into a corner claiming that social processes play no role in the construction of our categories. That is not a defensible position. There is no shame here. All scientific enterprises have social components. To suggest that we could keep psychiatry immune from social processes is unrealistic. However, we can vigorously defend the difference between social processes in our science and nosology, and socially created disorders. It is this latter category that we must assiduously guard against.

If I were to have a public debate with an arch anti-psychiatrist, I would not want to put myself in the position of defending the reality of every category in the DSM-5 or ICD-10. The pessimistic induction and historical contingency arguments are too powerful for me to be able to confidently defend our current system as “true”, as many of our diagnostic categories are tentative working models that are likely to change. We have many more reasons to defend the reality of the broad classes of psychiatric illness than the specific categories in our current diagnostic manuals.

One of the key compromises I am willing to make with pragmatism is the adoption of the coherence theory of truth as our working model. It is a less ambitious (philosophers would call it “deflated”) view of truth than the more standard correspondence theory. Nonetheless, it is a helpful move. If we do not and cannot expect essences for our disorders, how exactly can we define their “real-ness” in a correspondence theory? The coherence theory of truth seems to fit so well into our ongoing efforts as a young science. Our disorders become more real as they fit better and better into our emerging empirical knowledge of the causes and consequences of psychiatric illness. As I have long argued, in the end, it is in the grounding of our disorders in our empirical science (via validators) that we have the greatest probability of producing lasting, valid and “true” categories.

Instead of thinking about the truth of our disorders as a static concept, we might wish to consider them in an historical

framework. Viewed from this perspective, a true disorder is one that over time grows more and more valid, explains things about the world for us and increasingly fits in our world view. This approach, which has a clear pragmatic “flavor”, can be seen as taking the coherence theory of truth and putting it into an historical framework.

In conclusion, I would advocate for a “soft” realist position for psychiatric disorder – one that is much closer to biology- than chemistry-based realism and has elements of the pragmatic position. Our disorders are unlikely to have essences in a classic sense, with their natures probably arising from “networks” of causes, symptoms and signs, as postulated within homeostatic property clusters. We need to soften the realist position through the use of coherence theories of truth. The best available antidote against the power of the pessimistic induction and historical contingency arguments is to place more trust in our psychiatric types than the specific tokens of psychiatric illness which now populate our diagnostic manuals. In our project to study and justify the nature of psychiatric disorders, we ought to be broadly pragmatic but not lose sight of our underlying commitment to the reality of psychiatric illness.

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# Treatment engagement of individuals experiencing mental illness: review and update

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*Individuals living with serious mental illness are often difficult to engage in ongoing treatment, with high dropout rates. Poor engagement may lead to worse clinical outcomes, with symptom relapse and rehospitalization. Numerous variables may affect level of treatment engagement, including therapeutic alliance, accessibility of care, and a client's trust that the treatment will address his/her own unique goals. As such, we have found that the concept of recovery-oriented care, which prioritizes autonomy, empowerment and respect for the person receiving services, is a helpful framework in which to view tools and techniques to enhance treatment engagement. Specifically, person-centered care, including shared decision making, is a treatment approach that focuses on an individual's unique goals and life circumstances. Use of person-centered care in mental health treatment models has promising outcomes for engagement. Particular populations of people have historically been difficult to engage, such as young adults experiencing a first episode of psychosis, individuals with coexisting psychotic and substance use disorders, and those who are homeless. We review these populations and outline how various evidence-based, recovery-oriented treatment techniques have been shown to enhance engagement. Our review then turns to emerging treatment strategies that may improve engagement. We focus on use of electronics and Internet, involvement of peer providers in mental health treatment, and incorporation of the Cultural Formulation Interview to provide culturally competent, person-centered care. Treatment engagement is complex and multifaceted, but optimizing recovery-oriented skills and attitudes is essential in delivery of services to those with serious mental illness.*

**Key words:** Engagement, recovery, schizophrenia, shared decision making, person-centered care, first episode psychosis, alliance

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Individuals living with serious mental illness are often difficult to engage in ongoing treatment, and dropout from treatment is all too common. According to data from both the U.S. National Comorbidity Survey and the Epidemiologic Catchment Area survey, up to half of individuals with a serious mental illness had not received mental health treatment in the prior year<sup>1</sup>. Poor engagement may lead to exacerbation of symptoms, rehospitalization, and not fully realizing the potential benefits of treatment.

Because numerous factors contribute to maintaining someone's commitment to and willingness to engage in treatment or causing someone to leave, it is a challenge to outline key components to enhance engagement<sup>2</sup>. Disengagement may be related to issues of utility (people feel the treatment is not working), attitude (people feel mistrustful, or coerced), or practical reasons (treatment may be difficult to get to, difficult to schedule). There is not a one-size-fits-all approach, as engagement occurs in the context of an individual's unique personality, social and life circumstances, and symptom burden. In order to most effectively improve treatment engagement, approaches that target any and all of these presumed roadblocks may be used. In this review we highlight various innovations in mental health treatment, both practical and conceptual, which have been shown to improve engagement in this treatment.

We have found it helpful to view techniques and tools for increasing engagement within the framework of "recovery-oriented care". Recovery, as defined by the Substance Abuse and Mental Health and Services Administration (SAMHSA) in the U.S., is "a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential"<sup>3</sup>. The recovery movement embodies a shift in attitude and clinical approach that has been emerging over the past few decades, with the President's

New Freedom Commission report recommending that mental health care be recovery-oriented, consumer- and family-driven<sup>4</sup>. Four dimensions of recovery-oriented practice are promoting citizenship, organizational commitment, supporting personally defined goals, and a strong working relationship<sup>5</sup>. The approaches we review below are all promising ways for service providers to increase engagement in those with serious mental illness, assuming a recovery-oriented stance.

One very important feature of recovery-oriented care is its explicit prioritization of autonomy, empowerment and respect for the person receiving services<sup>6,7</sup>. As such, we outline factors that may enhance a client's experience of mental health treatment and hope for recovery. We discuss critical factors for the therapeutic alliance, shared decision making, and person-centered care, as related to treatment engagement. Next, we discuss how these have been applied within a few populations that are thought to be "difficult to engage", and show how various recovery-oriented practices have helped improve engagement. We then more closely focus on some specific practices, and describe how incorporating these into a treatment model may enhance engagement. We conclude by outlining the difficulties of engagement from the provider's standpoint, and ways that this can be addressed as the field of mental health services evolves.

## ATTITUDES AND INTERPERSONAL FOCUS

### The therapeutic alliance

In her qualitative analysis of young adults engaged in treatment for first episode psychosis, Stewart<sup>8</sup> theorizes that the quality of relationships developed in the treatment process

between providers and recipients may serve an important role in determining success of engagement.

Alliance is one component of treatment relationships that has been examined empirically, and has been described as the dynamic ability to work together in the interest of problem solving, with three elements: goals, task and bond. It has been consistently shown to be a chief predictor of successful outcomes in psychotherapy<sup>9</sup>.

Alliance has also been found to be important in work with individuals who have serious mental illness. Frank and Gunderson<sup>10</sup> measured working alliance among patients receiving treatment for schizophrenia and found that individuals who were able to form a good alliance with their therapists within the first 6 months were more likely to stay in treatment and adhere to medications, and had a better outcome at 2 years. Within the first episode psychosis population, Melau et al<sup>11</sup> examined the association between working alliance and clinical and functional outcomes, and concluded that an initial strong working alliance may serve as a prerequisite for adherence to services specialized for first episode psychosis, laying a foundation for positive treatment outcome.

Because of the importance that working alliance seems to have for clinical outcome and engagement, it is essential to identify which modifiable components predict good therapeutic alliance with patients who may be difficult to engage. In a study of patients with schizophrenia and schizoaffective disorder, independent predictors of therapeutic alliance included clinician's recovery orientation, lower reported self-stigma, and greater levels of insight. Interestingly, severity of clinical symptoms, attachment style, age and duration of treatment were not related to quality of alliance<sup>12</sup>. This study shows that, at least at some levels, the alliance can be enhanced by recovery-oriented efforts made by the clinician.

Given the importance of the therapeutic alliance in influencing engagement in care and the relationship between clinicians' recovery orientation and alliance, it is critical for providers to adopt a recovery orientation to facilitate engagement in care.

## Person-centered care

The concept of person-centered care is becoming increasingly common in the changing health care landscape<sup>13</sup>. Person-centered care has no single, operationalized definition or standard of measurement. We find the following description of person-centered care in the setting of mental health services to be particularly compelling and a good framework for the following discussion: "a comprehensive approach to understanding and responding to each individual and their family in the context of their history, needs, strengths, recovery hopes and dreams, culture and spirituality... assessments, recovery plans, services and supports, and quality of life outcomes are all tailored to respect the unique preferences, strengths, vulnerabilities (including trauma history) and dignity of each whole person"<sup>13</sup>. It is the concerted effort to incorporate an individu-

al's own culture, background and immediate goals into treatment planning.

Mental health services that integrate elements addressing an individual's immediate needs may enhance engagement<sup>14-16</sup>. For example, housing and finances are two potential sources of significant stress that may impinge on someone's wellbeing. Addressing these barriers as specific components of clinical care can help enhance engagement, both directly and indirectly. If someone is financially secure and housed, he/she may have fewer concrete barriers to coming to treatment appointments. A more indirect, broader outcome of addressing these components in health care may be that the treatment recipient will feel helped, enhancing faith within the system, building alliance, and serving as a foundation for future treatment work.

Shared decision making can be seen as one approach to providing person-centered care. In contrast to more authoritative models of health care delivery, shared decision making is a collaborative, dynamic, interactive process between two equally involved parties. In this model, physician and patient both take part in an exchange of information that leads to an agreed decision for treatment<sup>17</sup>. Over the past decade, this approach to clinical care has gained a following, though many of the studies examining its efficacy have been done in non-psychiatric populations. Though multiple studies have suggested that shared decision making is effective for those with serious mental illness, providers may be concerned that patients' decisional making capacity is impaired, and thus, may be less likely to use shared decision making with this group<sup>18</sup>.

Given that one common theme that has emerged in analyses of successful engagement is the participant's feeling that his/her goals, desires and life situation are being considered, it stands to reason that a more shared decision making stance can improve engagement in care. In a cross-sectional study of nearly 900 outpatients with mental illness, patient self-reported shared decision making revealed significant deficits. A majority of the study participants reported that their doctors did not want to know their level of involvement desired in decision making, and that their doctors did not ask them about their preferences<sup>17</sup>. Those who reported higher levels of shared decision making tended to have a more positive attitude towards medications and higher self-efficacy. Though causality cannot be determined, we can hypothesize that, if a person feels involved in the decision making process, he/she may be more likely to feel positive about potential treatment options. Further, self-efficacy itself has been associated with improved clinical outcome. The most important outcome of shared decision making may not be the actual decision point, but rather, the process that takes place between the patient and provider. An open, exploratory and non-judgmental space allows for trust to build and ideally enhances treatment engagement.

Not all patients, both in psychiatric and non-psychiatric care, want high levels of involvement in decisions regarding their treatment. Understanding this can guide treatment and creation of decision making aids. In patients with schizophrenia, a clear association has been found between treatment



satisfaction and degree to which patients wanted to be involved in medical decision making. Those who felt coerced into treatment or had higher levels of treatment dissatisfaction (lower perceived fairness and worse pharmacological experiences) reported wanting more involvement in their treatment choice. In contrast, those who were convinced that they needed medications and expressed high satisfaction saw less necessity to participate in medical decision making<sup>19</sup>.

In a study of veterans with serious mental illness, greater preferences for participation in shared decision making were found among those who were African American, working for pay, had college or higher education, had diagnoses other than schizophrenia, and had a poor therapeutic relationship with provider<sup>20</sup>. The study noted that decision making preferences change over time and a constant evaluation of where the patient stands is one important aspect of good clinical care.

Web-based and electronic decision making tools can be helpful for implementation of shared decision making in treatment settings. One study examined the utility of incorporating a computer-based tool for shared decision making in a waiting area of a community mental health clinic, where individuals with serious mental illness received treatment. Participants used this tool prior to doctor's appointments, which generated a written sheet outlining any decisional conflicts they had to bring up with the physician. Participants found this useful in clarifying their own dilemmas, in allowing them to bring up difficult topics, and in organizing their thoughts<sup>21</sup>. Other web-based and electronic decision making tools have been developed, and are generally accepted by both patients and clinicians<sup>22</sup>.

## “DIFFICULT TO ENGAGE” POPULATIONS

We now review the literature on engagement in individuals experiencing first episode psychosis, homeless individuals, and people with co-occurring serious mental illness and substance use disorder (dual diagnosis). Various recovery-oriented strategies have been used to enhance engagement in these populations. Identification of these strategies can help inform the design of mental health services that maximize treatment engagement.

### First episode psychosis

Research suggests that approximately one third of young adults experiencing a first psychotic episode delay treatment for 1-3 years. Further, 80% drop out within the first year of care<sup>8</sup>. This high attrition rate highlights the inherent difficulties in engaging young people in care.

Multiple causes for early dropout from treatment or disengagement have been offered, including poor alliance, mistrust of the system, and poor insight into the need for treatment. Additionally, young adulthood is a time of separation from authority figures and self-discovery towards individuation and

autonomy. Early termination of treatment in first episode psychosis programs has been linked to a more chronic course of illness, increased need for hospitalization, a slowed recovery process, and increased levels of functional disability<sup>8</sup>.

First episode psychosis programs, with multidisciplinary teams comprised of therapists and supported education and employment specialists, have gained momentum internationally<sup>23,24</sup>. These programs provide early access to care and intensive psychosocial services, in efforts to decrease duration of untreated psychosis, improve symptom burden, and enhance recovery<sup>25</sup>. Specialized first episode psychosis programs may have greater success in engaging young people in care than routine mental health services<sup>26</sup>, keeping people in treatment longer than standard community clinics<sup>27</sup>.

Some research has been done to identify particular components of these unique treatment programs that either enhance or diminish engagement. Many first episode psychosis programs are purposefully placed outside of traditional adult mental health clinics, as it has been shown that these settings are identified with alienation and treatment dropout<sup>28,29</sup>. Strong engagement may be related to enhancing a young person's wish to be respected, supported and understood<sup>7</sup>.

A qualitative analysis of young adults who were successfully engaged in treatment highlighted shared themes that seemed to promote engagement<sup>8</sup>. For example, in the acute hospitalization phase, two factors were crucial in enhancing engagement: timely introduction of the early psychosis program staff and development of positive relationships with peers on the unit. Other themes that emerged as enhancing engagement were those of collaboration, rational understanding of problems, and a commitment to finding solutions. Multiple participants also commented on the negative experience of acute adult hospitalization. If this negative, frightening experience is the entrée of a young adult into the world of mental health services, it stands to reason that improving the experience and countering it with supportive outpatient services may enhance engagement.

In an analysis of patients who had participated in the RAISE Connection early intervention program, four domains seemed to influence engagement: individualized care, program attributes, family member engagement and personal attributes<sup>30</sup>. For many participants, one key factor of the program was the focus on their own goals: engagement was correlated with receiving non-traditional services that supported such goals, such as supported employment and education.

These studies focused on aspects of the early intervention programs that the participants identified as enhancing engagement. Other studies have examined what participant-level attributes may either enhance or interfere with treatment engagement. Low service engagement has been linked to childhood trauma, high agreeableness, more severe symptoms and poor alliance<sup>31</sup>. Poorer engagement, as rated by clinicians, has also been found to be associated with greater positive and negative symptoms, greater general psychopathology and poorer premorbid social adjustment<sup>2</sup>.

Specialized first episode psychosis programs, designed to engage young people through their design, approach and services offered, may be a strategy for enhancing engagement in care in this group that has often delayed treatment and traditionally drops out of treatment in large numbers.

## Homelessness

Homeless individuals face many barriers to engaging in mental health treatment in traditional settings, including complex social service, medical and mental health needs; high rates of substance use disorders; other priorities that may supersede mental health treatment; and, particularly among street homeless individuals, a mistrust of helping professionals<sup>32</sup>. Homeless individuals may also have strengths that can be harnessed in treatment, including well-developed street skills and knowledge of the service system<sup>33</sup>.

Assertive outreach to homeless individuals involves making contact with them on their terms – where they live – rather than at an agency setting<sup>33</sup>. Assertive community treatment is an evidence-based practice that has been adapted for homeless individuals. It uses a multidisciplinary team-based approach to provide case management, mental health and substance use treatment, crisis intervention, employment support, and family services to individuals in the community. Homeless assertive community treatment teams have been found to decrease psychiatric hospitalization and emergency room use, increase housing stability, reduce symptom severity and, particularly relevant for engagement, increase outpatient visits<sup>34,35</sup>.

Despite the focus of the assertive community treatment model on treatment engagement, little is known about which specific elements promote engagement, particularly among homeless individuals. A recent qualitative study with assertive community treatment staff, not focused on those who are homeless, identified the following as primary elements for engaging clients<sup>36</sup>: therapeutic alliance between staff and clients, persistence and consistency, the provision of practical assistance and support rather than a sole focus on medications, the team decision making process, acceptance of clients as they are, and flexibility. A British study of engagement in assertive community treatment compared to community mental health teams, again not specific to homeless individuals, found that the small caseloads and team approach of assertive community treatment facilitated treatment engagement<sup>37</sup>.

Critical time intervention is another evidence-based practice focused on helping homeless individuals engage in treatment, with a particular focus on periods of transition, such as the transition from the hospital or shelter to housing. Critical time intervention workers provide time-limited intensive case management using a phase-based approach with decreasing intensity over time. The model includes practical assistance, linkage, advocacy, and motivational enhancement to strengthen individual's long-term ties to services and supports. Outcomes include decreased risk of homelessness following hospital dis-

charge<sup>38</sup> and decreased symptom severity<sup>39</sup>. Like assertive community treatment, critical time intervention has an explicit focus on engagement.

A qualitative study of critical time intervention aimed to understand the role of the relationship between practitioners and clients in the model, identifying a “non-authoritative” and “humanistic” working relationship, in which workers respected client autonomy and maintained flexibility with regard to client contact and service activities. Workers followed clients’ leads and used informal approaches to connecting in order to facilitate the development of client trust<sup>40</sup>.

So, in the evidence-based treatment models that have found to be successful for individuals with serious mental illness who are homeless, it seems that an explicit focus on the development of a positive working relationship, meeting clients where they are, persistence, provision of practical assistance, and flexibility in approach are common elements which may serve to promote engagement.

## Comorbid substance use and serious mental illness

Individuals with serious mental illness are more likely than those without such illnesses to use substances, with some studies suggesting that 50-60% of people with schizophrenia have a comorbid substance use disorder<sup>41-43</sup>. It is well-known that those with serious mental illness and substance use are more difficult to engage than those without, and traditional treatments have failed to effectively engage this population<sup>43-46</sup>.

In fact, comorbid substance abuse is one of the strongest factors associated with non-initiation and non-engagement in mental health treatment<sup>1</sup>. This difficulty in initiating and maintaining treatment engagement has multiple downstream effects, including frequent rehospitalization, high symptom severity, impaired psychosocial functioning, as well as trans-institutionalization in jails and other non-mental-health settings<sup>47</sup>.

One reason why individuals with dual diagnosis may be less engaged in treatment is the fragmentation of the care system. Historically, substance use treatment services and psychiatric treatment programs were entirely disconnected, with different funding streams, training and philosophical approaches to treatment. Because of this, people dually diagnosed seeking out treatment were often excluded from either program. A person seeking out substance use treatment was told to first treat “psychiatric” symptoms and vice versa. In addition to introducing yet another hurdle to provision of care, this “sequential treatment” approach did not take into account the interactive and cyclical nature of these disorders<sup>48</sup>.

Integrated dual diagnosis treatment programs (IDDT) began to develop in the 1990s<sup>41</sup>, attempting to address the fragmented treatment that dually diagnosed individuals were receiving. These programs emphasized outreach, comprehensiveness, long-term perspective, and a consistent approach and philosophy<sup>41,49</sup>. Clinicians were trained in motivational techniques, collaboration, social support interventions, and

many such programs also included a community-based component. IDDT is now an evidence-based treatment for people with dual diagnosis, with studies indicating that this approach improves various clinical outcomes, including treatment participation, possible reductions in substance use, more days in stable housing, and greater reductions in psychiatric hospitalization and arrest<sup>50</sup>. Some studies have shown that integrated treatment programs, as well as assertive community treatment, enhance initial and ongoing engagement in the dually diagnosed<sup>43,44,47</sup>.

Within various treatment programs that treat comorbid substance and mental health conditions, factors identified to enhance engagement include shared goals, optimistic outlook that does not focus on medications, ongoing psychoeducation, collaborative team-based care, and community outreach. One study found that treatment engagement in a dual diagnosis program was higher when individuals were referred from inpatient units rather than from the community<sup>51</sup>. It is not clear what component of the inpatient stay served to strengthen later engagement, but this finding is interesting and may suggest that, for certain subsets of the dually diagnosed, inpatient stabilization may be helpful.

One recent study explored the use of peer support in initial engagement in mental health services among veterans with substance use disorders and/or high recidivism. Peers specifically targeted early engagement, providing psychoeducation and bringing participants to their first appointments. This study found that peer support significantly increased treatment engagement, in both treatment-as-usual and experimental integrated treatment conditions<sup>52</sup>. This highlights peer support as an emerging tool to enhance engagement in those with dual diagnosis.

## **RECOVERY-ORIENTED TECHNIQUES FOR ENGAGEMENT**

Below we outline emerging treatment innovations that can optimize engagement in creative, novel ways. We chose them as they all attempt to improve the experience of treatment for the participant. The three strategies outlined below each aim to make treatment more accessible, more focused on the client's needs, and less stigmatizing, in various different ways. To that end, we believe that they embody the spirit of recovery-oriented care, and may help to improve treatment engagement.

### **Electronics/technology**

In a time when the Internet, smartphone apps, and social media serve to connect more and more people to each other, it seems appropriate to consider how to use these technologies in the treatment of those with serious mental illness to promote engagement. There are many theoretical ways that information and communication technologies can improve engagement

and enhance treatment, with multiple different tools to deliver: open messaging boards, closed therapeutic websites, mobile phones, and even smart medication bottles that may improve medication adherence<sup>53</sup>.

One justification for incorporating these technologies into mental health treatment is that they may serve as a natural way to expand the reach of services and reduce barriers to care. This can be important in situations where there are limited providers<sup>54</sup>. It has been proposed that various online and smartphone platforms can serve as a "gateway" to mental health services, removing some hurdles to initial engagement and allowing people an introduction to services in a low-risk, comfortable scenario. This can also be useful for people who have dropped out of treatment and are considering re-engaging, but may have some impediments, either personal (self-stigma, limited insight) or practical (difficult to get to or coordinate).

People experiencing symptoms or questions and seeking out more information may turn to the Internet and social media for answers and support. In a recent study of young adults at an early intervention program, an overwhelming majority endorsed using social media (97.5%), with an average of >2 hours per day. Thirty percent of participants reported discussing their symptoms in social media settings, and searching for information about their symptoms. The majority of this population was amenable to clinicians approaching them during crisis via social media<sup>55</sup>.

Disengagement during times of symptom resurgence may lead to particular distress, and potentially result in visits to the emergency room or inpatient unit. If providers and treatment programs use social media or Internet-based technologies to connect with clients during times of disengagement, perhaps symptom escalation or rehospitalization may be decreased. One way to think of this is as assertive outreach of the 21st century: instead of providers meeting clients in the community, they can meet them online.

Internet-based treatments have also been developed, with promising results<sup>56,57</sup>. One randomized controlled trial of a therapist-moderated website showed that participation led to a decrease in positive symptoms and an improvement in knowledge about schizophrenia<sup>58</sup>. Tablets and other information and computer technologies have been shown to help promote initial engagement in supported employment<sup>59</sup>. Populations who currently do not have access to cutting edge information and communication technologies, such as those who are homeless, may be even more likely to benefit. For marginalized people with few resources, use of technology may add to their sense of belonging and help build social connections. These platforms can be used for psychoeducation, initial engagement or even treatment<sup>60</sup>.

Cloud-based electronic medical records are currently being developed. These systems are secure and compliant to the U.S. Health Insurance Portability and Accountability Act. With a patient's consent, they can allow for information exchange across various organizations and health care providers. Recently, the concept of personalized health records has emerged within these cloud-based systems. They allow for secure

messaging and integration of medical records between patient and provider. Implementation of such personalized health records can enhance patient engagement<sup>61</sup>. By incorporating the patient into his/her own treatment decision making process, and providing easy access and communication with providers, they may remove some practical and perceived barriers to care.

Mental health programs can consider the use of all aforementioned technology-based interventions as part of their treatment approaches to increase engagement. Future studies should focus on how to best incorporate burgeoning technologically-based treatments and connections to care into existing services, taking into consideration the risks associated with Internet and technology, such as need to maintain privacy and mitigate discrimination<sup>62</sup>.

### Peer support

Some studies have suggested that those who have difficulties adhering to or engaging in treatment may have trouble trusting perceived authority figures<sup>31</sup>. Further, many individuals with serious mental illness may feel alienated, marginalized and stigmatized. For this reason, and several others, the use of peer services may enhance engagement in those with serious mental illness.

Over the past decade, peer provider networks have blossomed throughout the U.S., and peer providers now exist in multiple different treatment settings, as well as free-standing peer-run agencies. Peer support has been defined as “a system of giving and receiving help founded on key principles of respect, shared responsibility, and mutual agreement on what is helpful”<sup>63</sup>. The President’s New Freedom Commission on Mental Health Care called for a broader distribution of peer-based services<sup>4</sup>. Additionally, peer support is now a Medicaid reimbursable service<sup>64</sup>.

A review of a peer-led Wellness Recovery Action Plan program highlighted the benefits that participants experienced, including increased sense of self-determination, self-awareness, and positive effects on engagement with traditional providers and self-advocacy<sup>65</sup>. In a study of adults with serious mental illness in community care, traditional case management was compared with peer-delivered case management<sup>66</sup>. The aim was to investigate whether participants receiving peer-delivered services at the beginning of their treatment would be more engaged in services at follow-up (6 and 12 months). This study found that patients receiving peer-delivered services were more engaged at the 6-month point than those with traditional case management services. This between-group difference disappeared at 12 months, which may point to the importance of incorporating peer supports at the initial stages of treatment, in order to rapidly build a working alliance and enhance engagement when the risk of dropout, symptom relapse and rehospitalization is particularly high. Of note, in both groups, the participants who endorsed feeling understood and well-liked at 6 months had higher self-reported motivation for treatment.

Army and combat veterans are a group that has been traditionally difficult to engage in mental health treatment. A recent qualitative study of army veterans found that the major barrier to engaging in initial treatment is self-perceived stigma, and soldiers having trouble knowing or accepting that they need help. Participants in this study were generally positive about the idea of incorporating formal peer networks into initial treatment, noting that it might decrease both internal and external stigma. Soldiers suggested that peer networks could serve as role models, for example if a soldier who is perceived as strong and respected by others discloses his own battle with mental illness<sup>67</sup>. Peer supports have been shown to lower recidivism rates in veterans with substance abuse problems<sup>52</sup>. Though the veteran population is a unique one, self-stigma and need for role modeling may be universal for people struggling with mental illness.

### Cultural Formulation Interview

Individuals with serious mental illness from racial and ethnic minority groups are less likely than non-Hispanic whites to engage in mental health treatment<sup>68,69</sup>. The reasons for this are varied and numerous, and include system as well as social and cultural barriers<sup>70-74</sup>. Providing culturally competent care may be one way to enhance engagement.

One concrete tool for providing culturally sensitive care, and assessing an individual’s cultural background to help guide diagnosis and treatment, is the Cultural Formulation Interview (CFI). Introduced in DSM-5, this is a 16-item questionnaire, supplemented by 12 modules. It also includes an informant version in order to obtain material from caregivers such as family members<sup>75</sup>. The conceptual idea behind the CFI is that a person’s culture and contextual background will shape the way he/she perceives mental illness, treatment, and engagement with the treatment team.

Cultural information includes the social structures in which the individual resides, local environmental resources (financial, time), and individual circumstances. The cultural context is seen as dynamic and unique to each individual. And thus, though there may be trends among different minority groups in regards to how they view their symptoms and treatment, this cannot be assumed and has to be assessed individually. To that end, using the CFI in treatment is a way of explicitly acknowledging the unique individual and focusing on his/her goals and needs.

Though a relatively new tool, the CFI may enhance cross-cultural communication<sup>76</sup>, which may improve treatment engagement.

### CONCLUSIONS

Many innovative strategies are emerging to improve treatment engagement. As demonstrated in this review, engagement strategies focus on practical methods and tools, as

well as on helping to change attitudes and overall approaches to treatment of people with mental illness. In order to implement these strategies to improve engagement, mental health providers, too, must feel engaged with the work they are doing. The new approaches call for open-mindedness and flexibility about a shifting structure and delivery of mental health care.

Though, presumably, all mental health providers are in this field because they are dedicated to improving the well-being and health of those who suffer from mental illness, individual and systemic barriers may prevent providers from delivering treatment that optimally enhances participant engagement. The realities of working within the current mental health system include limited resources, limited time, and increasing oversight by managed care companies. Clinicians commonly cite these concerns as reasons why they are reluctant to change treatment services or take on a more recovery-oriented approach. In tandem, there are myriad attitudinal concerns about recovery-oriented treatment, including fear of increased risk, concern that only certain types of participants can be engaged in treatment, and an assumption that recovery-oriented services devalue professional skills<sup>77</sup>.

It is clear that, in order to affect global change, these concerns must be addressed. Services can be streamlined to more efficiently utilize resources, relieving some of the existing pressures that psychiatrists face, and thus allowing them more time to engage in face-to-face, meaningful clinical interactions<sup>78</sup>. Making concerted efforts to address fears, stigma, misconceptions and practical constraints will help to transform our mental health system to improve initial and ongoing engagement.

This review is not exhaustive, and other areas to consider as ways to enhance treatment engagement include wellness and exercise, role of families – including siblings – in treatment engagement, and use of trauma-informed care to engage individuals with traumatic pasts. Future areas of research may explore issues related to training and implementation of engagement strategies in the context of a rapidly evolving mental health care landscape.

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## Tech giants enter mental health

In September 2015, the Director of the National Institute of Mental Health (NIMH), T. Insel, announced his departure from the NIMH to lead Google's Life Sciences Mental Health Division. His decision attracted global attention. Interestingly for the field of mental health, Google intends to only back innovations expected to be ten times ("10x") better than competitors. Indeed, mental health care and research are beset with myriad challenges that may be better tackled using the informatic capacity that tech giants can leverage.

The field of mental health captures arguably the largest amount of data of any medical specialty, given that it encompasses behaviour, the brain and the mind. The physical neuroscience of psychiatry is augmented by high-resolution neuroimaging of various modalities, as well as "omic" data including genomics, epigenomics, proteomics, microbiomics and metabolomics. The growth of such big data aggregation in psychiatry provides unprecedented opportunities for exploration, descriptive observation, hypothesis generation, and prediction for clinical, research and business/operational issues. The scale of data outputs, however, means that computer models are required to assist humans to find and comprehend meaning and delineate non-obvious patterns – converting data to information, knowledge and wisdom.

Computerized analysis of complex human behaviours such as speech may present an opportunity to move psychiatry beyond reliance on self-report and clinical observation toward more objective measures of health and illness in the individual patient. A recent pilot study used automated speech analyses to predict later psychosis onset in youths at clinical high-risk for psychosis<sup>1</sup>. The analysis assessed for semantic coherence and two syntactic markers of speech complexity. These speech features predicted psychosis development with 100% accuracy and outperformed classification from structured clinical interviews.

Electronic health records (EHRs) have changed the landscape of clinical data collecting and sharing, facilitating more efficient care delivery. They provide multiple types of data about individual patient encounters, as well as longitudinal data about a patient's medical history over an extended period of time (see Hayes et al<sup>2</sup> in this issue of the journal). An example of the value of EHR data comes from a study which developed a statistical suicide risk stratification model<sup>3</sup>. The model resulted from examining suicide attempts and completed suicide in a large cohort of patients who underwent assessment in a regional health service. Researchers compared EHR-based predictions of suicidal behaviour at 3 months with clinician predictions, which were based on a checklist. The model derived EHR was superior (area under the ROC curves, AUC=0.79 vs. 0.58 using the checklist).

Big biomedical data are currently scattered across databases, and intentionally isolated to protect patient privacy. Linking big data will enable physicians and researchers to test

new hypotheses and identify areas of possible intervention<sup>4</sup>. An example of the value of data linkage between genomics and EHRs comes from a large-scale application of the phenome-wide association study (PheWAS) paradigm<sup>5</sup>. The researchers scanned for associations between 2,476 single-nucleotide polymorphisms (previously implicated by genome-wide association studies as mediators of human traits) and 539 EHR-derived phenotypes in 4,268 individuals of European ancestry. Several new PheWAS findings were identified, including a cluster of association near the NDFIP1 gene for mental retardation, and an association near PLCL1 gene for developmental delays and speech disorder.

With the number of smart devices (i.e., smartphones and tablets) reaching into the billions worldwide, there are increasing opportunities to harness their power and multifunctionality for clinical use. There are now several examples of psychoeducation-based products in use for depression, bipolar disorder, dementia and psychological distress. Smartphones also have capacity to offer telemental health functions. These functions are increasingly viewed as useful opportunities for more rapid patient-clinician engagement and offering services to geographically isolated areas. They are reported to be as good as in-person care for diagnosis and treatment in comparative and non-inferiority studies. However, there are concerns about effects on the therapeutic alliance, and more research is required in specific populations (i.e., geriatric, child and minorities)<sup>6</sup>. With the huge number of "apps" available to patients and clinicians, it is important to use sensible approaches to analyzing clinical value. A Mobile App Rating Scale has been developed<sup>7</sup>, and there are websites available which appraise digital mental health programs.

Recent years have seen the rise and miniaturization of many wearable sensors, for personal health care, fitness and activity awareness, as well as the wireless networking of these devices with EHRs and smartphones. These innovations also coincide with the popularity of patient-owned health records, community-based management of disease aiming to avoid hospitalization, and finally participatory health care, where patients are hypothetically empowered for health behaviour change through accessing their own health data. Smart and connected health care aims to accelerate the development and use of innovative approaches that would support the much needed transformation of health care from reactive and hospital-centered to preventive, proactive, evidence-based, person-centered and focused on well-being rather than disease.

The opportunities afforded by tech giants moving into mental health, with their capital, digital and data analysis tools, and human resource talent pools, provide much hope for mental health sufferers around the world. While the encounter of electronic approaches with health is not without its risks, surrounding data privacy, use and storage, its potential is overt<sup>8</sup>. The engagement of tech giants also raises many questions for

how we train our next generation of researchers and clinicians. Convergence science involves the transdisciplinary integration of fields including computer science, physics, engineering, medicine, chemistry, mathematics, the arts and biology; synergy between government, academia and industry is also critical. Convergence psychiatry involves embedding convergence science into the clinical mental health care setting by closer integration of scientists, clinicians and industry, as well as enhanced education of health professionals.

This approach is critical, given modern psychiatric research problems are characterized by their complexity, multi-systemic nature and broad societal impact, hence making them poorly suited to siloed approaches of thinking and innovation. Care must be taken to ensure researchers and clinicians are exposed to these frontier fields, and potential mechanisms include hackathons (intensive collaborations with coders, designers and managers on projects to meet a specific brief), multidisciplinary research groups, educational

systems involving convergence science concepts, and industry-academic collaborations.

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## Should psychiatry deal only with mental disorders without an identified medical aetiology?

Is psychiatry at risk of “losing” part of the conditions it deals with, once their “organic” or genetic origin is identified? The recent removal of Rett syndrome from the DSM-5 autism spectrum disorders category illustrates this issue.

Rett syndrome is a neurodevelopmental disorder characterized by autistic symptoms, cognitive and motor abnormalities and decreased brain growth during childhood<sup>1</sup>. Most cases of the syndrome are caused by a mutation in the MeCP2 gene, although not everyone who has an MeCP2 mutation develops the syndrome<sup>1</sup>. It was originally included in the DSM-IV as a disorder with autistic features of unknown aetiology. Now that its genetic origin has been identified, the main rationale for removing it from the DSM-5 has been that it is considered a distinct entity with a specific aetiology.

The history of medicine contains several other examples where the discovery of the specific aetiology of a mental disorder (or a clinical condition once thought to fall within the realm of mental illness) led to its removal from the framework of psychiatry. In the 19th century, after the psychiatric symptoms of general paresis were attributed to neurosyphilis, that became the first psychiatric disease with definite organicity. Once this finding was confirmed, general paresis was progressively forced out of the field of psychiatry. Further, in 1943, penicillin was proved to be highly effective against primary syphilis. At that juncture, psychiatry definitively “lost” the treatment of general paresis.

However, if knowing the “organic” or genetic cause of a disorder is a rationale for its exclusion from the DSM, the very future of our specialty is at risk, since in time, as more specific

underpinnings of mental disorders are identified, we may “lose” several of the clinical conditions we deal with. Currently, 10-20% of patients with autism spectrum disorders and 40-60% of those with severe intellectual disability are found to have clinically significant copy number variations or deleterious *de novo* mutations<sup>2,3</sup>, and these rates continue to increase<sup>3</sup>. Removing disorders with a known medical aetiology from psychiatry makes as little sense as suggesting that, because some gastric ulcers can be caused by bacteria, they no longer belong in the field of gastroenterology.

Most of us would agree with the principle that without brain there is no mind. Beyond this frame, the mind-brain debate remains inextricable. In a broad sense, mind or “psyche” may be conceived as a subjective phenomenal-experiential realm<sup>4</sup>. The specificity of the conditions classified as psychiatric disorders lies in the peculiarity of the elements that compose them, i.e. mental symptoms that cannot be simplistically reduced to brain dysfunctions. Mental symptoms are rooted in both the natural and social sciences, caused by a blending of biological, semantic and social components<sup>5</sup>. In point of fact, clinical specialties are not grounded simply in our understanding of human biology. Rather, they emerge in complex ways in response to a variety of conditions and situations. Some specialties involve special skills (cardiac surgery) or disorders of organs (nephrology) or systems (gastroenterology). Other specialties arise in response to a type of disorder (oncology) or to stages of the life cycle (geriatrics). Psychiatry is for diagnosing and treating mental disorders.

During the 19th and 20th centuries, a schism arose between neurology and psychiatry, and the two went their separate



ways<sup>6</sup>. Generally, neurology focused on disorders with cognitive and behavioural abnormalities and identifiable brain lesions – e.g., stroke, multiple sclerosis and Parkinson's disease – while psychiatry focused on disturbances of mood and thought without identifiable brain lesions – e.g., schizophrenia, depression, and anxiety disorders<sup>6</sup>. However, the frontiers between neurology and psychiatry have never been clear-cut, with notable areas of overlap between them. In fact, the historical “appropriation” of certain disorders by neurology or psychiatry – e.g., autism, attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, and dementia – seems to some extent arbitrary and based on extra-clinical criteria<sup>6</sup>. Now, over a century later, the boundaries between neurology and psychiatry are being seriously questioned, and many voices within psychiatry are clamouring for it to become a clinical neuroscience<sup>7</sup>.

Yet, the fact that we will probably never be able to formulate a purely objective concept of most mental disorders does not make the search for possible “underlying” dysfunctions fruitless. On the contrary, the effort to find such dysfunctions is critical for the progress of the discipline. As an example, take two biological abnormalities that can be detected in some cases of schizophrenia: chromosome 22q11.2 deletion and presence of anti-N-methyl-D-aspartate receptor (NMDA-R) antibodies.

Chromosome 22q11.2 deletion syndrome is usually defined as a genomic disorder with markedly variable expressivity, associated with high rates of psychotic disorders (including schizophrenia), mood disorders, anxiety disorders or ADHD. Remarkably, there is not a differential symptomatic expression in subjects with 22q11.2 deletion-related schizophrenia as compared to other individuals with a diagnosis of schizophrenia<sup>8</sup>.

Antibodies against the NMDA-R may be found in around 1-2% of patients with a clinical diagnosis of schizophrenia<sup>9</sup>. Several patients with NMDA-R serum antibodies develop a multi-stage symptomatology that progresses from psychosis, memory deficits, seizures, and language disintegration to a state of unre-

sponsiveness with catatonic features. However, some patients with NMDA-R antibodies fully meet the criteria for schizophrenia<sup>9</sup>. These antibodies may represent an aetiological factor of schizophrenia, potentially treatable with a specific therapy.

The fact that schizophrenia can be linked to specific aetiological factors such as chromosome 22q11.2 deletion, anti-NMDA-R antibodies, more than a hundred genetic loci, or greater proportions of rare copy number variations (i.e., recurrent 16p11.2 duplications, 3q29 deletions, or 17q12 duplications)<sup>10</sup> is no reason for this condition to be removed from the field of psychiatry.

Psychiatrists should be able to deal with mental disorders independent of their aetiology. Finding a specific biological aetiology should be a joyous occasion to vindicate the key role of psychiatry as the medical specialty that deals with mental disorders, regardless of whether their aetiology is known or unknown.

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## What can we learn from the high rates of schizophrenia in people with 22q11.2 deletion syndrome?

22q11.2 deletion syndrome (22q11.2DS) is a copy number variant (CNV) syndrome, resulting from a 1.5-3Mb deletion on the long arm of chromosome 22. It occurs in at least 1 in 4,000 live births, making it one of the most common genetic deletion syndromes<sup>1</sup>. The physical phenotype is highly variable, involving multiple organ systems. The common manifestations include conotruncal cardiac malformations, cleft palate, renal abnormalities and immune dysfunction. Cognitive impairment is also common, with IQ distribution shifted about 30 points to the left of the typically developing population<sup>2</sup>.

In the 1990s, it was observed that a high proportion of adults with 22q11.2DS had schizophrenia<sup>3</sup>. Current estimates for lifetime prevalence of schizophrenia are approximately 25% in 22q11.2DS compared to about 1% in the general population. Furthermore, several studies have reported that the prevalence of the 22q11.2 deletion is 10-20 times higher in patients with schizophrenia than the general population<sup>4</sup>. 22q11.2DS is therefore one of the strongest known risk factors for schizophrenia. One argument sometimes heard is that, since many people with 22q11.2DS have low IQ, and intellec-

tual disability is a risk factor for schizophrenia, the psychosis seen in deleted cases is a consequence of low IQ and different nosologically from cases of schizophrenia in the non-deleted population. However, 22q11.2DS increases risk of psychopathology independently of IQ<sup>2,3</sup>, and the other clinical features of schizophrenia in deleted individuals do not differ from those seen in the wider population<sup>5</sup>.

Since carriers of the deletion are often identified as children, there has been much interest in 22q11.2DS as a high-risk population in which the clinical, cognitive and neurobiological antecedents of schizophrenia can be studied. Interestingly, recent evidence suggests that the reciprocal duplication of chromosome 22 is associated with a lower risk of schizophrenia<sup>4</sup>. This further highlights the importance of studying this genetic locus to better understand resilience as well as risk, and to identify potential novel therapeutic targets.

The discovery of high rates of schizophrenia prompted many studies of psychiatric disorders in 22q11.2DS. The emerging picture is one of extensive pleiotropy. In childhood, neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), are common<sup>2</sup>. In adolescence and early adulthood, the prevalence of mood disorders and psychosis increases, while anxiety disorders are common across the lifespan<sup>6</sup>. However, there is considerable variability between individuals in both the nature and severity of their psychiatric symptoms.

Recently, genomic technology has made it possible to detect CNVs across the genome, revealing that 22q11.2 is one among a number of CNVs associated with increased schizophrenia risk. Individuals with schizophrenia have an increased genome-wide burden of large (>100kb), rare (<1%) CNVs generally<sup>7</sup>. Furthermore, a number of specific loci in addition to 22q11.2 are associated with risk of psychiatric disorders. Eleven such loci have been robustly associated with schizophrenia, with variable frequency and penetrance<sup>4</sup>. As with 22q11.2DS, these CNVs confer risk to a range of psychiatric disorders<sup>8</sup>.

The mechanisms by which 22q11.2 deletion increases risk of psychosis and other psychiatric disorders are still not well understood. Individuals with the deletion have only one copy of the genes within the deleted region (hemizyosity). The most likely mechanism is therefore that reduced dosage of one or more genes in the region leads to the clinical manifestations (haploinsufficiency), though other possibilities such as the unmasking of a recessive allele or position effects are also possible. While there are many interesting candidate genes in the region – including *PRODH*, *COMT*, *DGCR8*, *RTN4R* and *TBX1* – none of these has been convincingly implicated as the single factor underlying the increased risk of schizophrenia or indeed other psychiatric phenotypes. It therefore remains possible that the increased risk of psychiatric disorders is conferred by the impact of the deletion on more than one and possibly several genes. This would not be surprising, since no single-gene form of schizophrenia has been convincingly demonstrated.

Another possibility is that sets of functionally related genes (sometimes known as pathways) are particularly impacted by

22q11.2DS and other pathogenic CNVs. A recent pathway analysis across different CNVs has pointed to the role of synaptic genes influencing the balance of cortical excitation and inhibition in psychiatric risk<sup>9</sup>. This is an attractive model, since alterations in excitatory-inhibitory balance have been reported in schizophrenia, ADHD and ASD, and therefore may help to explain the overlapping symptoms experienced by patients with 22q11.2DS, though whether a gene or genes on 22q11.2 are implicated in these pathways remains unclear.

A second, related, question is what factor or factors influence the very different psychiatric and cognitive outcomes seen in 22q11.2DS. The majority of patients with 22q11.2DS (90%) have a 3Mb deletion, which involves around 60 genes, whilst approximately 10% have a nested 1.5Mb deletion involving about 30 genes. It could be that the size of the deletion influences outcome, although this seems unlikely, since no study has yet identified a significant difference in the psychiatric phenotype between those with a 1.5 or a 3Mb deletion, though this issue will not be definitely resolved until larger studies are completed.

Another possibility is that alleles on the intact chromosome are responsible for the pleiotropic outcomes. If this were the case, these would have to be very common to account for the high prevalence rates and there is no current evidence for such variants of large effect. One more possibility is that “second-hit” CNVs or point mutations contribute to increased risk, but again these would need to be common to explain all the increased risk.

Genomic studies have indicated clearly the polygenic nature of psychiatric disorders. In schizophrenia, at least a third of the genetic variance is captured by the combined effects of many hundreds of common SNPs, and it is now possible to assay this using the polygenic score approach<sup>10</sup>. However, as yet, sample sizes have not been sufficiently large to test whether polygenic background can account for the differences in psychiatric outcomes in 22q11.2DS. The effects of environmental factors have not yet been the focus of much research in 22q11.2DS, but the study of the interaction between genes and environment in this at-risk group will be crucial to our understanding of pleiotropy and also of environmental risk factors for schizophrenia more generally. A large international collaboration<sup>6</sup> is currently underway to investigate these questions in a large sample of patients with 22q11.2DS.

There has been much recent research aimed at identifying those who are most likely to develop psychosis within the 22q11.2 population. Other psychiatric disorders, particularly anxiety disorders, have been found to be associated with the development of schizophrenia in 22q11.2DS and, although cognitive impairment *per se* does not mediate the association between 22q11.2DS and psychopathology, cognitive decline may be associated with the onset of psychosis<sup>11</sup>. Whether these represent independent markers of increased risk or prodromal symptoms is not yet clear. Much more longitudinal data are needed to explore predictors of psychosis, including clinical symptoms and intermediate phenotypes, for example neuroimaging abnormalities.

As one of the strongest known risk factors for schizophrenia, 22q11.2DS offers a relatively homogenous high-risk population for exploring precursors and predictors in longitudinal study designs. Furthermore, given the recent advances in genome engineering, it is increasingly feasible to develop both cellular and animal models of the deletion and to relate findings in these to those from human studies<sup>12</sup>. The genetic and mechanistic overlap between neurodevelopmental disorders is a particularly interesting avenue to explore and is timely given recent drives to improve psychiatric classification systems (e.g., Research Domain Criteria<sup>13</sup>). The variability in the presentation of CNV syndromes suggests that defining phenotypes categorically may not be the most appropriate approach to capture the spectrum of symptoms experienced by patients, and a more dimensional system may be more appropriate.

Comparing data across risk CNVs will be an important area of research and may help to identify final common pathways to psychosis and related disorders. Of additional interest will be advancing understanding of not only how CNVs act to increase risk, but also how CNVs such as the 22q11.2 duplication may exert protective effects. This would have clear implications for developing novel treatment approaches.

Although animal models are likely to yield important mechanistic insights, they have their limitations. For example, while there is synteny between the deleted region in humans and mice, there are differences in genomic organization. Moreover, it is likely that human psychiatric phenotypes reflect additional genetic and environmental factors. Furthermore, there are difficulties in modelling complex psychiatric phenotypes in

animals. Animal work will nevertheless be an important component of a multi-level approach to the study of 22q11.2DS, which should integrate other approaches such as cellular models and human brain imaging.

In conclusion, 22q11.2DS and other pathogenic CNVs offer new approaches to studying schizophrenia risk and the relationships between neurodevelopmental disorders. Longitudinal studies of high-risk populations will be crucial and these will inform, and be informed by, animal and cellular studies of CNVs.

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## Psychiatric classifications: validity and utility

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*Despite historical assumptions to the contrary, there is little evidence that the majority of recognized mental disorders are separated by natural boundaries. Diagnostic categories defined by their clinical syndromes should be regarded as 'valid' only if they have been shown to be truly discrete entities. Most diagnostic concepts in psychiatry have not been demonstrated to be valid in this sense, though many possess 'utility' by virtue of the information they convey about presenting symptoms, outcome, treatment response and, in some instances, aetiology. While researchers in genetics, neurobiology and population epidemiology are increasingly more likely to adopt a continuum/dimensional view of the variation in symptomatology, clinicians prefer to hold on to the categorical approach embodied in current classifications such as ICD-10 and DSM-5. Both points of view have plausible justification in their respective contexts, but the way forward may be in their conceptual reconciliation.*

**Key words:** Psychiatric diagnosis, psychiatric classification, validity, utility, DSM, ICD

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In his *Philosophical Remarks*, L. Wittgenstein commented that “the classifications made by philosophers and psychologists are as if one were to classify clouds by their shape”<sup>1</sup>. The metaphor is apt: clouds have fuzzy boundaries, tend to merge imperceptibly, and drift, being carried by invisible air currents. Observation and measurement of their movement predict, within a margin of error, the weather, yet the inner physical and chemical structure of clouds is hidden to the naked eye.

Wittgenstein's aphoristic remark applies equally well to the classifications developed by psychiatrists: the conceptual outlines of syndromes and putative disease entities tend to change with successive revisions of their classification, relative to their *utility* for predicting course, outcome and likely response to available treatments, even if their inner biological and psychological structure is not fully understood. The latter, the quest for *validity* of our concepts, remains an open agenda.

In anticipation of this, the protagonist of modern psychiatric nosology E. Kraepelin stated in one of his last articles, *Patterns of Mental Disorder*, that “it is necessary to turn away from arranging illnesses in orderly well-defined groups, and to set ourselves the undoubtedly higher and more satisfying goal of understanding their essential structure”<sup>2</sup>. This goal of *validity* is yet to be attained.

### THE NATURE OF PSYCHIATRIC CLASSIFICATIONS

The term *nosology* refers to the theory about the nature of medical conditions and the principles and rules of their classification. In psychiatry, we are still facing the recurrent question about the nosological status of the brain and mind disorders that constitute the core of the discipline. Are we dealing with discrete entities, or with graded continuous phenomena to which we can apply cut-off points to separate “pathology” from “normal variation” and to determine the need for treatment? What is the relationship between the clinical manifestations of a disorder and the underlying brain dysfunction, pathological processes or predisposing genetic aberrations?

Notwithstanding the advances in the neuroscience and genetics of psychiatric disorders, many of the present-day answers to these questions are a replay of debates that took place in the earlier periods of scientific psychiatry. This suggests that there may be inherent shortcomings in the nosological classifications in clinical psychiatry adopted since the beginning of the 20th century and all the way to the present versions of DSM and ICD.

Medical classifications are created with the primary purpose of meeting pragmatic needs related to diagnosing and treating people experiencing illnesses. Their secondary purpose is to assist the generation of new knowledge

relevant to those needs (though progress in medical research usually precedes, rather than follows, improvements in classification). Simply stating that medical classifications classify *diseases* (or that psychiatric classifications classify *disorders*) begs the question, as the status of concepts like “disease” and “disorder” remains obscure<sup>3</sup>.

As pointed out by Scadding<sup>4</sup>, the concept of “disease” has evolved with the advance of medical knowledge, and is at present no more than “a convenient device by which we can refer succinctly to the conclusion of a diagnostic process which starts from recognition of a pattern of symptoms and signs, and proceeds, by investigation of varied extent and complexity, to an attempt to unravel the chain of causation”. “Disease”, therefore, is an explanatory construct integrating information about deviance from the population “norm”; characteristic clinical manifestations; characteristic pathology; underlying causes; and reduced biological fitness.

For a cluster of such attributes to be referred to as “a disease”, these characteristics must be shown to form a “real-world correlational structure”<sup>5</sup>, which must be stable and distinct from other similar structures. The typical progression of knowledge starts with the identification of the clinical manifestations (the *syndrome*) and the deviance from the “norm”; understanding of the pathology and aetiology usually comes much later.

However, there is no fixed point or agreed threshold beyond which a syndrome can be said to be “a disease”. Today, Alzheimer’s disease, with dementia as its syndrome, characteristic brain morphology, tentative pathophysiology, and at least partially understood causes, is one of the few conditions in psychiatric classifications that approximates the disease construct. The majority of the “disorders” in our current classifications are, at best, described as syndromes<sup>6</sup>.

The essential task in the construction of a nosology of discrete disease entities is to identify internally cohesive clinical groupings based on established inter-correlations among symptoms and syndromes (the cross-section) and patterns of course and outcome (the longitudinal aspect). Individual groupings should be separated from one another by demonstrable natural boundaries, or a “zone of rarity”<sup>7</sup>. The test of their *validity* is the degree to which they are found to be associated with explanatory variables of deeper structural significance – potential causal factors, pathogenetic mechanisms, treatment response, as well as stability vis-à-vis demographic and cultural variation. However, nosological entities in psychiatry, constructed according to such idealized desiderata, have met with difficulties.

The first problem is that, on the examples of schizophrenia and affective disorders, the requirement of a close correspondence between the cross-section of the disorder and the patterns of its course and outcome was never fully met. Recent attempts to identify in the early, high-risk or prodromal state, symptoms and signs that reliably predict transition to full-blown psychosis have not been successful<sup>8</sup>. It has been furthermore demonstrated in follow-up studies that a proportion of initially “typical” schizophrenias may recover, while a proportion of “typical” manic-depressive illnesses may run a chronic and disabling course. These observations could not be easily reconciled with the assumptions of the original “dichotomy” model of the two disorders.

The argument that recovering schizophrenias are not “true” cases of the dis-

order, and ought to be re-diagnosed if lasting recovery occurs, contradicts the findings of two important World Health Organization (WHO) studies: the International Pilot Study of Schizophrenia (IPSS)<sup>9</sup> and the subsequent Study on Determinants of Outcome of Severe Mental Disorders<sup>10</sup>. In the IPSS, cases were diagnosed in a restrictive way by applying three sets of criteria: clinician’s diagnosis according to ICD; computer diagnosis using the CATEGO algorithm; and empirical grouping of cases by cluster analysis, on the basis of maximum shared characteristics. Patients who met simultaneously the three sets of criteria were designated as a “core” or “concordant” group of schizophrenia, that was expected to be more homogeneous than the rest of the cases. However, the follow-up data did not reveal any significant differences in course and outcome between the concordant cases and the non-concordant ones.

Such findings do not stand alone: a number of recent follow-up studies confirm the notion that severe deterioration is not the typical outcome of schizophrenia, even if a very long follow-up period is involved. According to the WHO Report on Recovery from Schizophrenia<sup>11</sup>, which integrated findings from several long-term follow-up studies conducted under the aegis of WHO, “the most striking overall finding... is that the current global status of over half of these subjects – 56% of the incidence group and 60% of the prevalence group – is rated as “recovered”. Nearly half have experienced no psychotic episodes in the last 2 years of follow-up... These percentages accord fairly well with ratings of both current symptoms and functioning”<sup>11</sup>. These findings suggest that the prognosis of schizophrenia is an open-ended dynamic process whose direction can, within limits, be modified at any point. The presumed “characteristic” psychopathological phenomena, such as the Schneiderian first-rank symptoms<sup>12</sup>, did not appear to have prognostic significance.

A second shortcoming of the classical nosological system is its failure to separate consistently the two entities of schizophrenia and affective disorders. This

has been known for a long time, but the difficulty was thought to reside in the imprecise definition of the diagnostic criteria, rather than in the existence of a large group of conditions which simply defy the dichotomy and exhibit the features of a clinical “hybrid”. This group has attracted a variety of diagnostic labels, including “schizoaffective disorder”<sup>13</sup> or “unsystematic schizophrenias”<sup>14</sup>, and was classified alternately with the schizophrenias or with the affective disorders, but never found a comfortable place in either category. The existence of such “hybrid” cases poses the problem of defining the borderline between the two disorders. One alternative solution is to treat the poor prognosis schizophrenia and the good prognosis affective disorders as two extremes on a single clinical (and presumably genetic) continuum that could include all kinds of intermediate forms.

A third problem for which the classical nosological theory has failed to find an acceptable solution is the classification of the sub-threshold, practically non-pathological forms of cognitive and affective deviations and the unusual personalities which are encountered among biological relatives of schizophrenia patients. The importance and relative frequency of these variants were clearly recognized by Bleuler<sup>15</sup>, who coined the term “latent schizophrenia”, and they were subsequently reported by a bewildering variety of diagnostic labels: “ambulatory schizophrenia”<sup>16</sup>, “pseudoneurotic schizophrenia”<sup>17</sup>, “borderline schizophrenia” or “schizotypal personality disorder”<sup>18</sup> and, more recently, “attenuated psychotic syndrome”<sup>19</sup>. None of these terms has been universally accepted, nor have their diagnostic criteria been unequivocally defined. Epidemiological and genetic evidence has provided support for a link of those subclinical conditions to “core” schizophrenia, strengthening the concept of a schizophrenia “spectrum”<sup>20</sup>. The spectrum forms related to the affective disorders have so far received less attention than the non-psychotic satellites of schizophrenia, but the recognition of a syndrome of “masked depression”<sup>21</sup> and the notion of an affective or cyclothymic personality disorder

suggest that similar problems also exist on the affective side of the classical diagnostic dichotomy of the major psychiatric disorders. At present, the borderline forms are of limited therapeutic interest, since most cases do not require treatment, and there is little evidence that, if provided, treatment is effective. Their theoretical and research importance, however, is considerable, especially from the point of view of the genetics of the major psychotic disorders.

Although the range of possible aetiological factors that may give rise to psychiatric disorders is practically unlimited, the range of psychopathological syndromes, reflecting the brain's responses to a variety of *noxae*, is limited. Since a variety of aetiological factors may produce the same syndrome (and conversely, an aetiological factor may give rise to a spectrum of syndromes), the relationship between aetiology and clinical syndrome is an indirect one. In contrast, the relationship between the syndrome and its underlying pathophysiology, or specific brain dysfunction, is likely to be much closer. This was recognized long ago in the case of psychiatric illness associated with somatic and brain disorders, where clinical variation is restricted to a limited number of "organic" brain syndromes, or "exogenous reaction types"<sup>22</sup>. This was recently reconfirmed by evidence that many focal neurological diseases, neurodegenerative disorders and autoimmune encephalopathies can present with symptom pictures closely mimicking the symptomatology of "endogenous" disorders, such as schizophrenia<sup>23</sup>. In the complex psychiatric disorders, where aetiology is multifactorial, future research into specific pathophysiological mechanisms could be considerably facilitated by a better delineation of the syndromal status of diagnostic categories, providing a rationale for reinstating the syndrome as the basic unit in future versions of psychiatric classifications.

None of the many attempts to re-shape the nosology of the major psychiatric disorders has been entirely satisfactory. There can be no doubt that the classical nosological hypothesis was a major step forward, introducing order and parsimo-

ny in a field that had previously been chaotic or arbitrarily subdivided. The least that could be said is that the nosological hypothesis helped to bring into focus issues which critics could oppose or endorse, thus contributing to a diversity of viewpoints that was fruitful in a developing discipline such as psychiatry. However, a more fundamental re-thinking of the nosological theory underlying the classification of psychiatric disorders will require the development of a conceptual framework that allows a better integration of clinical, neurobiological, genetic and behavioural data.

### DSM-5 AND ICD-10

Classifying in science involves forming categories or *taxa* for ordering natural objects or entities and assigning names to these categories. Ideally, the categories should be jointly exhaustive to account for all possible entities, and mutually exclusive. In biology, there is agreement that classifications reflect fundamental properties of biological systems and constitute "natural" classifications. This is not so with psychiatric classifications. First, the objects being classified in psychiatry are not "natural" entities but explanatory constructs. Secondly, the taxonomic units of "disorders" in DSM-5 and ICD-10 do not form hierarchies and contain no supraordinate, higher-level organizing concepts. Therefore, DSM-5 and ICD-10 are not systematic classifications in the sense in which that term is applied in biology.

Social anthropologists have claimed that an analogue to current psychiatric classifications could be found in the so-called indigenous or "folk" classifications of animals or plants, which do not consist of mutually exclusive categories, have no hierarchies, but may contain many rules applicable *ad hoc*<sup>24</sup>. They are pragmatic and adapted to the needs of everyday life. In that sense, DSM-5 and ICD-10 are not systematic classifications, but they are useful tools of communication and play an important role in research, clinical management and teaching.

Many clinicians are aware that diagnostic categories are constructs, justified only by whether or not they provide a useful framework for organizing clinical experience and making predictions about outcome and the effects of treatment decisions. However, the generic term "disorder" (first introduced as a name for the unit of classification in DSM-I in 1952) has no correspondence with either the concept of disease or the concept of syndrome in medical classifications. The data on which the majority of the current diagnostic rubrics in psychiatry are based consist primarily of reported subjective experiences and patterns of behaviour. Some of those rubrics correspond to syndromes in the medical sense, but many appear to be isolated symptoms, habitual behaviours, or personality traits. Thus, the ambiguous status of the "disorder" creates conceptual confusion and hinders the advancement of knowledge.

The fragmentation of psychopathology into a large number of "disorders", of which many are merely symptoms, facilitates the proliferation of comorbid diagnoses which blur the distinction between true comorbidity (co-occurrence of aetiologically independent disorders) and the spurious comorbidity that may be a feature of multifaceted but essentially unitary *syndromes*. It is, therefore, not surprising that disorders, as defined in the current versions of DSM and ICD, have a strong tendency to co-occur, which suggests that "fundamental assumptions of the dominant diagnostic schemata may be incorrect"<sup>6</sup>.

### VALIDITY AND UTILITY

While the reliability of psychiatrists' diagnoses can be substantially improved by the use of explicit diagnostic criteria, their *validity* remains uncertain. What is meant by validity of a diagnostic concept in psychiatry is rarely discussed and few studies have addressed this question directly. Because the validity of diagnostic concepts, and of their defining criteria, is a critical issue, it is important to clarify what is implied by the term validity in the context of psychiatric diagnosis.

The word “valid”, derived from the Latin *validus*, means strong, and is defined as “well founded and applicable; sound and to the point; against which no objection can fairly be brought”<sup>25</sup>. In formal logic, validity is the characteristic of an inference that must be true if all its premises are true. However, there is no single agreed meaning of validity in science, although it is generally accepted that the concept addresses “the nature of reality”<sup>26</sup>, and that its definition is an “epistemological and philosophical problem, not simply a question of measurement”<sup>27</sup>.

The attribution of validity to scientific concepts and theories is in fact an unending quest: what was regarded as valid knowledge in the past is quickly superseded by new evidence, and this in the nature of scientific endeavour. In a thoughtful review of the subject, Zachar<sup>28</sup> proposed the term *comparative validity*, to summarize the progression of scientific knowledge, which “emphasises rationally justified criteria we use to say that current theories/models are improvements on past theories/models”. In a similar vein, Aragona<sup>29</sup> examined the “epistemological history” of the successive DSM editions, from DSM-I (1952) to DSM-5 (2013), and concluded that all systems share the same view of validity as a “correspondence to external reality”, with the ultimate ideal of validation by neurobiological data.

In psychology, the American Psychological Association’s distinction between content, criterion-related and construct validity<sup>30</sup> still holds, since it provides criteria for the validity of psychological tests. Borrowing terminology from psychometric theory, psychiatrists have mainly been concerned with concurrent and predictive validity, partly because of their relevance to the issue of the validity of diagnoses. The ability to predict outcome, both in the absence of treatment and in response to specific therapies, has always been a key concern to physicians. In a seminal paper, Goodwin and Guze<sup>31</sup> asserted that “diagnosis is prognosis”, and that the follow-up is to the psychiatrist “what the *postmortem* is to the physician”. The types of validity currently employed in the context of psychi-

atric diagnosis – construct, content, concurrent and predictive – are borrowed off the shelf of psychometric theory in psychology. Few diagnostic concepts in psychiatry meet these criteria at the level of stringency normally required of psychological tests.

Despite such ambiguities, a number of *procedures* have been proposed to enhance the validity of psychiatric diagnoses in the absence of a simple measure. Thus, Robins and Guze<sup>32</sup> outlined a program with five components: clinical description; laboratory studies; delimitation from other disorders; follow-up studies; and family studies. This schema was later elaborated by Kendler<sup>33</sup>, who distinguished between antecedent validators (familial aggregation, premorbid personality, precipitating factors); concurrent validators (e.g., psychological tests); and predictive validators (diagnostic consistency over time, rates of relapse/recovery, response to treatment). Andreasen<sup>34</sup> has proposed additional validators, such as findings of molecular genetics, neurochemistry, neuroanatomy, neurophysiology and cognitive neuroscience, suggesting that “the validation of psychiatric diagnoses establishes them as real entities”.

Such procedural criteria implicitly assume that psychiatric disorders are distinct entities, ignoring the possibility that disorders might merge into one another with no clear boundary in between. However, there is increasing evidence of overlapping genetic predisposition to schizophrenia and bipolar disorder, as well as to seemingly unrelated disorders, such as autistic spectrum, intellectual disability and, possibly, epilepsy. It is equally likely that the same environmental factors may contribute to several different syndromes. Should such findings be systematically replicated, their repercussion on future psychiatric classifications would be considerable. It has been proposed that variations in psychiatric symptomatology might indeed be better represented by “an ordered matrix of symptom-cluster dimensions”<sup>35</sup> than by a set of discrete categories. However, it would be premature at this time to discard the current categorical entities.

In contrast to validity, a diagnostic rubric may be said to possess *utility* if it provides non-trivial information about prognosis and likely treatment outcomes, and/or testable propositions about biological and social correlates<sup>7</sup>. The term *utility* was first used in this sense by Meehl<sup>36</sup>, who wrote that “the fundamental argument for the utility of formal diagnosis... amounts to the same kind of thing one would say in defending formal diagnosis in organic medicine. One holds that there is a sufficient amount of etiological and prognostic homogeneity among patients belonging to a given diagnostic group so that the assignment of a patient to this group has probability implications which it is clinically unsound to ignore”<sup>36</sup>.

Many, though not all, of the diagnostic concepts listed in contemporary classifications such as DSM-5 and ICD-10 are useful to clinicians, whether or not the category in question is valid, as they provide information about the likelihood of recovery, relapse, deterioration, and social handicap; they guide treatment decisions, describe symptom profiles, or guide research into the aetiology of the syndrome. However, there is a critical difference between validity and utility. *Validity* is by definition an invariable attribution to a diagnostic category: there may be uncertainty about its justification because of lack of relevant empirical information, but in principle, a category cannot be “partly” valid<sup>7</sup>. *Utility*, on the other hand, is an incremental, graded characteristic that is partly context specific. Schizophrenia may be an invaluable concept to practicing psychiatrists, but of questionable use to researchers exploring the genetic basis of psychosis. For example, the DSM-5 definition of schizophrenia is useful for predicting outcome, because some degree of chronicity is inbuilt. But a broader definition, covering a heterogeneous “schizophrenia spectrum”, is more useful for defining a syndrome with high heritability for genetic research.

## THE VIEW FROM PSYCHIATRIC GENETICS

Can psychiatric genetics inform the nosology of mental disorders? Not so

long ago, tentative findings of overlapping associations between candidate genes (NRG1, DTNBP1, G72/G30, DISC1, DISC2) in DSM-IV schizophrenia and mood disorders raised the expectation that “over the coming years, molecular genetics will catalyse a reappraisal of psychiatric nosology” by conceptualizing “a spectrum of clinical phenotypes with susceptibility conferred by overlapping sets of genes”<sup>37</sup>.

Such reappraisal has not happened. However, recent whole-genome association studies (GWAS), involving large, consortium-pooled samples from multiple research centres, have indeed identified shared genetic variation of common single nucleotide polymorphisms across schizophrenia, bipolar disorder, major depression, autism spectrum and attention-deficit/hyperactivity disorder<sup>38</sup>. The main contributor to these findings was the variation in calcium-channel activity genes (CACNA1C and CACNB2), which appeared to have pleiotropic effects on a range of psychopathology. These findings reinforced the hope that, similarly to medical disciplines such as oncology and cardiology, psychiatry could move “beyond descriptive syndromes... towards a nosology informed by disease cause”<sup>39</sup>.

Further support for a trans-diagnostic commonality of genomic variants underlying susceptibility risks was provided by the largest to date GWAS of schizophrenia<sup>40</sup>, which revealed multiple common polymorphisms converging upon individual genes and definable molecular pathways in the brain, involving glutamatergic synaptic and calcium channel functions, as well as a highly significant contribution of the immune system. Importantly, there was evidence of overlap between rare copy number variations associated with schizophrenia and rare *de novo* mutations observed in intellectual disability and autism spectrum disorders. However, instead of an imminent reappraisal of psychiatric classification, these novel findings add to the tremendous complexity of the genotype-phenotype problem in common mental disorders.

In a recent review, Kendler<sup>41</sup> outlined “possible scenarios” of biological coherence in the genomic findings, ranging from low coherence (clinical syndromes

do not have specific underlying pathophysiology) to high coherence (risk genes and polymorphisms map to a single biological pathway underpinning a single disease process). Since psychiatric disorders are significantly more heterogeneous than other complex disorders, greater heterogeneity means also greater complexity, and emergent traits in the “mind-brain” system may be “more remote from individual gene effects than those seen in other tissues”. For these reasons, we may be ill-advised to call, under the sway of important novel findings, for a premature overhaul of psychiatric nosology.

### CONCLUSION: THE WAY FORWARD

The present diagnostic manuals, ICD and DSM, are classifications of current diagnostic concepts, and not of “natural kinds”, such as people or diseases. There is little evidence that most recognized mental disorders, including the psychoses, are separated by natural boundaries. There is a growing understanding, supported by recent advances in genetic and neurobiological research, that many of the present diagnostic categories are endpoint phenotypes for heterogeneous gene networks, pathophysiological pathways, and environmental modifiers. Probably we shall see in the future increased experimentation with research-based classifications and diagnostic tools, focusing on improving and refining the clinical *utility* of both categorical and dimensional models of psychopathology, and seeking a consilience between the two, leading to concordance.

Paraphrasing Jaspers’ dictum<sup>42</sup>, *validity* is an “idea in Kant’s sense of the word... an objective which one cannot reach since it is unending, but all the same it indicates the path for fruitful research and supplies a valid point of orientation for particular empirical investigations”. This means that our primary concern should be the progressive refinement of the *utility* of the diagnostic concepts and tools, towards the enhancement of their phenomenological

accuracy, predictive value and capacity to guide person-focused treatment and management decisions.

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## A report card on the utility of psychiatric diagnosis

Controversy about the utility of medical diagnosis and its relation to treatment had its origin 2500 years ago. The two leading centers of medical practice were then located in the Greek colonies at Cnidus and Cos. They had together revolutionized disease theory by substituting a secular biological model of causation for the previous belief in divine punishment. But the two schools differed greatly when it came to diagnosis and treatment approach. At Cnidus, there was great emphasis on specific diagnosis and accompanying specific treatment. At Cos, under the influence of Hippocrates, the contrasting approach was that it is more important to know the patient who has the disease than the disease the patient has. Neither model is appropriate for all times and all patient presentations. The more we understand disease process, the more valuable is specific diagnosis and specific treatment. But too often in the history of medicine, theory and practice have extended a reach that far exceeded their grasp.

Almost all medical theories have turned out to be false and many of the medical treatments they justified have turned out to be dangerous, sometimes deadly. Doctors have confidently bled their patients; purged them with emetics and cathartics; fed them with heavy metal poisons; made them hot and made them cold. That patients keep coming back for more provides proof of the power of the placebo effect and of the (sometimes excessive) trust accorded physicians. The recent miraculous advances in the scientific understanding of genetics, molecular biology, and organ functioning have inspired great hope that we would soon have fundamental understanding of the various disease processes and specific treatments to cure them. This expectation has so far been mostly unfulfilled. There is an enormous, and mostly unbridged, gap between the basic medical sciences and clinical practice. The more we learn about the body, the more we learn how much we don't know and how complicated and heterogeneous is the pathogenesis

of disease. And despite the hype, much of medical research turns out to be simply wrong because the methods used are inadequate; the biases and conflicts of interest profound; and the data over or mis-interpreted<sup>1</sup>.

The appropriate diagnostic thresholds and criteria for defining and diagnosing most diseases remain controversial. There is no bright line separating diabetes, hypertension, osteoporosis, or even many cancer-like cells from normal. As always, scientific medicine has been oversold and overbought – a recurring triumph of hope over experience. In the process, the Hippocratic emphasis on the doctor/patient relationship, natural healing, and doing no harm has been greatly undervalued. Most doctors treat lab tests, not patients; drugs are carelessly dispensed to those more harmed than helped by them; and medical mistakes are the third leading cause of death in the U.S..

All the inherent and pervasive limitations of scientific medicine are exaggerated in psychiatry, because its target organ of interest is the most complicated entity in the known universe. If we haven't yet gotten very far in dealing with cancer in the breast, the simplest organ in the body, how can we expect simple answers to the riddle of psychiatric disorders, arising from remarkably heterogeneous malfunctions in its most complex?

I have known and admired A. Jablensky for almost 30 years and fully endorse his masterful summary of the current state of psychiatric diagnosis<sup>2</sup>. I find nothing to disagree with in his general analysis of the relationship between clinical utility and validity. Our current systems of psychiatric diagnosis are all crude, heterogeneous approximations that will seem silly and invalid as we slowly and painstakingly acquire deeper knowledge. There will probably not be any low hanging fruit when it comes to finding genetic explanations, characteristic imaging findings, or new treatments. Most studies won't replicate and there will be many seemingly promising, but very blind alleys. All this said, we should also not underestimate

the current necessity of psychiatric diagnosis and its clinical utility in treating patients.

The DSM-III was a response to a serious crisis in confidence in the credibility of psychiatry. It introduced two major innovations that radically changed psychiatric diagnosis and temporarily restored confidence: operational criteria to increase reliability of psychiatric diagnosis and the multiaxial system to increase its breath. Everything since the DSM-III has been little more than a footnote, often causing more harm than good.

Let's do a brief report card of the positive and negative effects of DSM on the major domains of its influence:

*Clinical.* A reliable diagnostic system is essential to meaningful clinical communication. To the extent that DSM criteria sets improve reliability, they help clinicians to talk a common language and to relate research findings to clinical practice. But reliability does not inhere only to how the criteria are written; it also depends on how well they are used. Sad but true, many clinicians are not well schooled in the criteria sets and continue to speak idiosyncratic diagnostic tongues.

*Education.* The good news is that DSM criteria are a useful training tool in psychiatric diagnosis, but this is overwhelmed by the bad news that a reductionistic focus on criteria has often replaced what used to be a much more rounded evaluation of the person who has the symptoms. I don't trust clinicians who don't know DSM criteria, but I equally don't trust clinicians who focus only on DSM criteria and are blind to the complexity of life and human nature.

*Research.* The DSM system that seemed to offer such a promising research tool has failed to live up to expectations and no longer guides much of the latest psychiatric research. It turned out that the DSM mental disorders are too heterogeneous to allow for simple research answers. The Research Domain Criteria framework instituted in the U.S. by the National Institute of Mental Health is also now promising

much, but the lesson of the past is that brain research is exciting and essential, but extraordinarily difficult and often irrelevant to clinical practice. Progress in understanding mental illness has been, and will continue to be, frustratingly slow whatever method is used<sup>3</sup>.

*Epidemiology.* It was impossible to gather meaningful statistics on the rates of mental disorders before there was a reliable way of diagnosing them. Although helpful in epidemiology, the DSM criteria based system has been applied in a systematically biased way to overstate rates. At the inherently fuzzy boundary between normal and disorder, the only (if fallible) demarcation is the presence or absence of clinically significant distress or impairment. The large number of assessments necessary in epidemiological research preclude the use of expensive clinicians and therefore cannot evaluate for clinical significance. Mild symptoms thus get mislabeled as mental disorders, and reported prevalences are upper limits, not real rates<sup>4</sup>.

*Forensic.* The DSM-III seemed to provide a common language that might reduce the babel of opposing expert psychiatric testimony in forensic proceedings. To some degree, it has improved testimony, but is still as often misused as used well. The pressures created by the adversarial legal system encourage tortured misinterpretations of the criteria sets that the insufficiently precise DSM language is unable to prevent. Egregious misuses of psychiatric diagnosis remain a major problem in courtroom proceedings<sup>5</sup>.

I probably understand the weaknesses of DSM diagnosis as well as anyone, but still appreciate its value. Opponents of psychiatric diagnosis often have a more one-sided and single-minded purpose: to use its weaknesses to argue for the complete abolition of psychiatric diagnosis. The British Psychological Society's widely publicized report "Understanding Psychosis and Schizophrenia" is a prime example<sup>6</sup>. In its effort to show that psychiatric diagnosis is unnecessary and does more harm than good, the report misleadingly lumps together all the very different usages of "psychosis" and blurs the essential distinctions they offer, thus losing crucial prognostic and treatment precision.

"Psychosis" is used in at least six different ways, that can be teased out after careful differential diagnosis. Each has quite different implications regarding severity, chronicity, clinical significance, causality, and treatment: a) "psychosis" misused to describe anyone who occasionally experiences hallucinations (this overlooks the fact that 10% of the general public reports having had an hallucination, and 20% have had a direct encounter with an angel or devil; "psychosis" should be reserved only for those who are unable to reality test the hallucination and who also have accompanying significant distress and impairment in interpersonal and vocational functioning); b) psychosis caused by intoxication or withdrawal from alcohol, a medication, or a street drug; c) psychosis due to a medical or neurological disease; d) brief psychosis (a transient mental disorder with excellent prognosis and no reason to expect long-term im-

pairment); e) psychosis occurring (usually episodically) as part of bipolar or major depressive disorder; f) psychosis occurring as a primary, often debilitating and chronic feature in schizophrenia and delusional disorder.

The "Understanding Psychosis and Schizophrenia" report makes broad statements about the role of medication and psychosocial interventions that are essentially meaningless, because most certainly there is no one size that fits all the diagnoses loosely covered by the vague term "psychosis". The more precise language of psychiatric diagnosis saves precious information that is absolutely necessary for responsible clinical care.

However limited the explanatory power of our current diagnostic system, it is great folly to ignore its very great clinical utility. The excellent is sometimes the enemy of the good. Expecting too much from the diagnostic system leads critics to ignore its value and necessity. We should all feel grateful to A. Jablensky for his clear and scholarly delineation of the issues and resetting of expectations.

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## Against utility

*"The more palpable and practical the classification is, the better; if it cannot be perfect, let it be useful."*<sup>1</sup>

Jablensky's paper<sup>2</sup> makes a compelling case that current psychiatric diagnostic categories fail to achieve full single-etiology construct validity as measured by the zones-of-rarity test, an important

point that is broadly acknowledged. However, its further conclusions regarding utility as an alternative nosological goal are unwarranted.

Defense of nosological proposals based on utility is a recipe for fruitless arguments detracting from pursuit of scientific grounding for diagnosis. This was a problem with the DSM-5 debates. Disputes

about major proposals, such as elimination of the bereavement exclusion or adoption of the alternative DSM-5 model of personality disorder, that should have stayed focused on validity, strayed into swampy arguments about utility, obscuring crucial scientific issues.

Jablensky's arguments do not support his conclusions. His pivotal point is the

emphasis on zones of symptom rarity as the cardinal test of construct validity. The zones-of-rarity test, influentially put forward by Kendell and Jablensky<sup>3</sup>, has had momentous consequences for nosology: failure of current diagnostic categories to pass this test has supported the move towards dimensionalization that became one of DSM-5's signature goals, albeit one that was eventually mostly abandoned. For a doctrine of such importance, the zones-of-rarity test has been subject to surprisingly little critical discussion.

Note that the test addresses more than just symptom discontinuities. Having initially focused on a zones-of-symptom-rarity test to evaluate typologies of depression, Kendell realized the limitations of this approach and expanded the allowable evidence of validity to include not just zones of symptom rarity revealing discontinuous symptom distributions, but also continuous symptom distributions that had discontinuous correlates with variables such as outcome, course, and treatment response<sup>4</sup>. This expanded approach was used in classic studies to argue that, for example, subthreshold depression is not categorically different from major depression.

The problem with the zones-of-rarity test, however, is that, first, it gets wrong what is most essential in the quest for validly distinguishing disorders, namely, *explanatory discontinuity*, in which there are divergent etiologies (either one dysfunction versus another, or dysfunction versus normality); and second, it fallaciously assumes that such structural/explanatory discontinuities must be associated with superficial zone-of-rarity symptom/outcome discontinuities. Although zones of rarity suggest explanatory discontinuities, lack of such zones does not imply lack of explanatory discontinuity. As Kendell himself observed, "certainly, failure to demonstrate discontinuity in symptomatology can never prove that the conditions in question are not distinct entities"<sup>4</sup>.

There are myriad scenarios in which divergent dysfunction etiologies would not manifest themselves in zones of symptom/outcome rarity. Function/dysfunction discontinuities may exist, but not be

easily detectable against the normal-distribution background. Diagnostic criteria may mix indicators heavily overlapping with normality with other indicators that are more suggestive of pathology, so that discontinuities are obscured, a claim sometimes made about DSM major depression criteria. Significant numbers of false positives and false negatives on either side of a boundary can create the impression of continuity where none exists.

A more substantive reason is that mental modules responsible for different facets of psychological processing are richly linked, and there is a great degree of mutual penetrability by mental systems due to their high need for coordination. Consequently, a dysfunction in one module is likely to create "comorbid" symptoms in interacting modules, as dysfunction-generated outputs act as deviant inputs to linked systems. This would tend to create the appearance of symptom continuity despite etiological heterogeneity.

Additionally, the categorical distinction between dysfunction and normality can depend on very abstract theoretical considerations, such as the naturally selected range of a variable, and this abstract explanatory discontinuity may not be reflected in symptom or outcome distributions. So, for example, ability to detach at times from social rules may be adaptive as part of the social-relational repertoire, but if one has a strong tendency in that direction and this interacts with low levels of compensatory inhibitory and anxiety mechanisms, antisocial personality may result, and that may take the overall system outside the naturally selected range and undermine the biologically designed function of the social-relational mechanisms.

Given the challenges of achieving validity, some argue that diagnostic revisions should be based on cost-benefit analysis, clinical utility, user acceptability, and whatever helps patients. Certainly such considerations should be carefully weighed, but only as an after-the-fact pragmatic supplement to validity, with validity the overriding arbiter in formulating diagnostic criteria.

Utility and cost-benefit analysis involve subjective value judgments at their

core. Opponents on both sides of DSM-5 debates cited utility and benefits to clients as warrants for their positions, without any clear way to adjudicate such claims, rhetorically obscuring validity issues. Judging utility rather than sticking to validity unduly inflates the moral pretensions of the profession.

Attempts to define utility distinct from validity founder either on the Scylla of non-scientific triviality – because, once the "utility-as-separate-from-validity" door is opened, almost any idiosyncratic preference can come through it (e.g., user familiarity, reimbursement coverage) – or, if utility is defined more narrowly to make it diagnostically beneficial, the Charybdis of redundancy with partial validity.

Relying on historical precedents for credibility, Jablensky's dichotomy has the latter problem, yielding a distinction without a difference. Jablensky cites P. Meehl as having originated his utility notion, but in the quoted passage Meehl is simply explaining the utility of having valid diagnoses as against not diagnosing at all, with Meehl's "utility" defined by the cardinal validity features of "etiological and prognostic homogeneity"<sup>5</sup>. Similarly, Kendell and Jablensky<sup>3</sup> quoted R. Spitzer, but he actually equated clinical utility with validity and took both to reflect standard validity information about etiology, risk factors, course, family history, and response to treatment. Jablensky also cites Kraepelin's distinction between grouping disorders and establishing their pathological essence, but famously Kraepelin saw grouping as a path to validity. So, there is no support for a validity/utility distinction of fundamental nosological goals in these classic texts.

Jablensky's own definitional attempt fares no better. He says we are seeking syndromes with "*utility* for predicting course, outcome and likely response to available treatments", yet course, outcome, and response to treatment are intimately related to validity. Kraepelin famously used course and outcome to validate nosological distinctions, and Klein<sup>6</sup> famously used comparisons of treatment response ("pharmacological dissection") to reveal divergent diagnostic constructs and refine validity. So, Jablensky's claimed difference

between validity and utility seems to be merely the difference between more and less perfect forms of validity.

Jablensky's analysis makes the perfect the enemy of the good. He elevates the ideal goal of single-etiology validity to the only form of validity, when in fact validity is variegated, ranging from conceptual validity (successfully distinguishing normal vs. disordered conditions)<sup>7</sup>, through many forms of partial validity (marking various homogeneities among the dysfunctions underlying a domain of disorders), to single-etiology construct validity. Then, once validity is placed out of reach (and pushed further out of reach by the embrace of a spurious zone-of-rarity validity criterion), he argues for an alternative focus on utility.

As my epigraph from a paper published in 1843<sup>1</sup> reflects, the idea that the difficulties in achieving validity in nosological classification should induce us to refocus on utility is not new. However, instead of "if it cannot be perfect, let it be useful", I would suggest the motto "if diagnostic criteria cannot be perfectly valid, let them be as valid as possible". That should be our goal, and in the long term it serves utility.

Recent deployments of utility as a nosological rationale on both sides of various disputes suggest as well a paraphrase of W. James's comment about the unconscious<sup>8</sup>: utility "is the sovereign means for believing what one likes in psychology, and of turning what might become a science into a tumbling ground for whimsies".

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## Utility without validity is useless

A. Jablensky's paper<sup>1</sup> raises important questions of many kinds. In this commentary, due to space constraints, I will not consider the evidence regarding clinical course as a diagnostic validator in schizophrenia or the overlap between psychosis and mood conditions, nor the nosological views of K. Jaspers, except to note that other interpretations exist that would not agree with Jablensky's perspective. The main focus here will be instead on whether the concept of utility can or should be the basis of psychiatric nosology.

The central assumption in Jablensky's paper is the statement, made in passing, that medical classifications have as their *primary* purpose pragmatic needs, and only *secondarily* generation of new knowledge. Here is the heart of the validity versus utility debate. However, there is another way of thinking about the matter. Almost a century ago, A. Lewis<sup>2</sup> noted: "Classifications may be useful for the wrong ends... The clinician may never come to see how vicious are the uses to which he has been, contentedly, putting his classification". Reversing the DSM/ICD view, Lewis held that nosology had to be "valid and useful". If invalid, a nosology is not useful. He concluded:

"A valid classification is one which is not only useful, but useful for sound medical and scientific ends". Put another way, the *primary* source for diagnostic classification should be our best scientific knowledge, i.e., classification should be valid scientifically, first and foremost, and also clinically relevant. Only secondarily, in rare cases, can purely utilitarian diagnosis be justified when there is compelling clinical need but zero scientific evidence. DSM/ICD reverses the terms, with hundreds of scientifically unjustified utilitarian diagnoses, versus only a dozen or two with some scientific bases.

This is the kernel of the problem: should validity be central to the diagnostic process, or can we just give up on it, and happily celebrate utility?

To answer this question, let's go back for a history lesson. The original justification for the radical changes of DSM-III in 1980 was that it represented a common language, providing "reliability" and utility. This was not the final goal, though. The claim was made repeatedly that this reliability/utility would be a way-station to validity<sup>3</sup>. In other words, we would get to validity more effectively by having a reliable common language. We would change this language with further scien-

tific research, each revision of DSM moving gradually closer to validity. However, as Jablensky admits, the DSM project has failed to achieve validity. And now we are told that we should change our goal to pure utility, an attempt to make a virtue out of defeat.

Recent debates around DSM-5 have exposed some ideas which previously were expressed mainly behind closed doors. We learned that our DSM leaders have important post-modernist assumptions: they have given up entirely on the whole concept of validity<sup>4</sup>.

Contrary to initial DSM-III claims about achieving gradual validity in the future, we now have 40 years of the converse experience. The DSM-IV and 5 leadership stated very explicitly to their task forces that they should make as few changes as possible<sup>4</sup>. This is an anti-scientific attitude. Scientists do not make and test hypotheses by saying to themselves: "Now, let's make as few changes to prior beliefs as possible". DSM classification is now a pure paean to utility, entirely "pragmatic", in the worst meaning of the term: an extremist utilitarianism that has no purpose other than to reflect the wishes and beliefs of the American Psychiatric Association or

DSM leadership, or the loudest interest groups. This statement is documented by historians who have reviewed internal DSM documents<sup>5,6</sup>.

Besides its basic anti-scientific attitude, DSM revisions have used higher and higher thresholds for making changes based on research, making it harder to move toward empirically-based validity. Call it the “Sisyphus problem”: researchers obtain data, rolling the boulder of knowledge up the hill of ignorance; then DSM leaders say it is not good enough. Another generation of researchers adds to that knowledge, and, if their results pass the DSM task force itself, they are vetoed in the American Psychiatric Association by the Scientific Review Committee, or the Board of Trustees.

We have an unimpeachable example of this Sisyphus problem in the work of the great psychiatric researcher J. Angst. For a century, ever since Kraepelin, the standard view in world psychiatry was that it did not matter if patients were manic (bipolar) or depressed (unipolar), but rather that all mood episodes reflected the same single manic-depressive illness. Angst’s Zürich cohort, collected in the early 1960s, suggested that bipolar and unipolar groups differentiated on diagnostic validators of course and genetics<sup>7</sup>. Hence the underappreciated radical anti-Kraepelinian change in DSM-III: the creation of bipolar disorder and major depressive disorder out of Kraepelin’s concept of manic-depressive illness. In the intervening decades, with over 40 years of more data, Angst now finds that his Zürich cohort does *not* differentiate well into bipolar and unipolar based on course and other diagnostic validators<sup>8</sup>. The same Zürich dataset, now even more valid with complete prospective follow-up of the entire lifetime of its subjects, is rejected by the DSM-5 task force. What was considered acceptable to make very radical changes in the 1970s is now rejected decades later for even minor changes (like duration of hypomania or definition of mixed states). Much more radical changes in the past were made with much less science.

There is not even a utilitarian justification for this resistance. DSM-5 field

trials now indicate that, after four decades, major depressive disorder has poor reliability<sup>9</sup>, even worse than in the past. Our current nosology of major depression is *both* false and useless.

Angst, being a true scientist, falsifies his own hypotheses, something the DSM/ICD leadership has been unwilling to do, which brings us to the most baneful consequence of the rejection of science/validity in favor of pragmatism/utility: because of DSM/ICD, all research, both clinical and biological, is doomed to failure. This self-fulfilling prophecy is then used by DSM advocates of pragmatism/utility to justify further their rejection of science-based classification. We reach a dead end in obtaining further new knowledge precisely because obtaining new knowledge is “secondary” to the pragmatism that ensures that no new knowledge will be achieved. Psychiatric progress never occurs, because it cannot occur with these anti-scientific attitudes.

To state it otherwise: DSM/ICD is a “social construction”. That’s what the concept of utility means. It is created for social – professional, insurance, forensic, economic, ideological, political, cultural – purposes. It is not, as admitted by Jablensky, primarily based on scientific research. The fact that DSM/ICD is a social construction reflects its underlying philosophy, post-modernism<sup>10</sup>.

If we create diagnostic categories based on social, economic and political considerations, why should genes correlate with those categories? Why should neuroanatomy correlate with wishes for insurance reimbursement? When DSM/ICD phenotypes for biological studies are purely social constructions, it should be no surprise that hardly any major genes/biomarkers for DSM/ICD diagnoses are identified. Four decades of failure in DSM-based research are hard to ignore. Recent change in the U.S. National Institute of Mental Health (NIMH) policy, such that DSM criteria are no longer acceptable for research<sup>11</sup>, is an institutional verification that an emphasis on utility actually *prevents* ever achieving validity.

Because DSM failed, one should not conclude, as the NIMH leadership does, that the whole clinical research project

failed. In fact, because of DSM pragmatism, clinical research has *not* been the main basis of our diagnostic system for 40 years. Let us now not draw the false conclusion that clinical research into psychiatric diagnosis has failed, when instead it has been ignored.

Nor will it do to resort to prayer – wishing for a gene, or a brain circuit, that will someday, somehow, split the Red Sea. The gene/biological marker miracle will never happen as long as DSM/ICD fails to put science first<sup>12</sup>.

The explicitly vague term “disorder” reflects post-modernist cynicism about the disease concept<sup>13</sup>. The attempt to base “disorder” definitions on functional impairment and severity of symptoms is not conceptually, biologically, or scientifically sound. There are many medical diseases that do not cause functional impairment (such as silent cancers), or involve mild rather than severe symptoms. Some medical diseases even are associated with some benefits, rather than only harms (e.g., decreased malaria risk with sickle cell trait). The extremist DSM/ICD ideology of rejecting mild symptoms does not solve the “false positives problem” nor improve predictive values of diagnosis<sup>14</sup>. Instead, it feeds into, and perhaps reflects, stigma against mental illness, an ironic result of DSM/ICD “pragmatism”, understandable as another baneful effect of cultural post-modernism.

In sum, my main critique is that a primarily utilitarian approach, in the end, is not useful, because it matters – cultural post-modernist assumptions notwithstanding – whether we are really right or wrong, i.e., whether our diagnoses are valid. In clinical medicine, where lives are in the balance and where scientific values are accepted, any other view is difficult to defend.

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## We need science to be useful too

Jablensky's notion of a fundamental contrast between utility and validity in psychiatric classification<sup>1</sup> probably bears a relation to the tensions between pragmatic and correspondence ideas of truth. Having both in play at once creates conundrums. Of particular relevance, if one supposes that truth is correspondence with reality as it really is, then mere pragmatic value – utility – will always look like it falls short.

In several key places, Jablensky refers to the shifting nature of utility, contrasted with “reality”, understood in this context as inner biological and psychological structure, or “essential structure”. There are plenty of places and times in the history of science when it has been reasonably supposed that theory grasped the essential nature of reality. To name but a few: Newtonian mechanics, the mature period table of elements, and the biomedicine of cholera. Also, by way of contrast, in plenty of occasions it did not seem so, such as in the relation between general relativity and quantum mechanics, the models of global warming, the developmental pathology of most medical conditions, the biomedicine of some cancers, and most or all psychiatric conditions.

From a pragmatic point of view, the difference here is a matter of how much the science predicts: in the former kind of case, the theory predicts everything of interest (at the time), while in the latter the theory doesn't at all, or we have a range of sub-theories predicting more or less within sub-domains of interest, but no unified theory. When the idea of truth as correspondence is working in the background, however, the theories which predict everything of interest (at the time) appear as its exemplars, illustrating that our concepts can and therefore should

grasp the nature of reality as it really is. In practice, in the sciences, it has become obvious, since the demotion of Newtonian mechanics and the absence of a unified physics, that scientific theories don't stay the same but evolve for many reasons, so it would be rash – misconceived – to say that science grasps reality as it really is, once and for all. We can say that it provides better and better approximations, but this comes down to: it gets better at predicting. Prediction is useful in its own right, but of special interest are predictions that help us solve problems, those that underpin interventions. Science is closely tied to utility and technology.

Psychiatric classification is supposed to have clinical utility. A particular diagnosis is supposed to provide some information useful for clinical management, such as course and prognosis with and without particular treatment(s). By all means diagnoses are only partly successful in this, more or less so depending on the condition, subtype and which treatment. Nevertheless, in the clinic, we suppose that the current diagnostic system guides management somewhat, even if imperfectly, better than nothing, and better than any other system on offer.

Onto this shifting problem domain of clinical utility, Jablensky proposes two criteria of “validity”. One of them is that to be valid a condition must be *discrete*, separated from others by a “zone of rarity”. This sounds to me like the correspondence theory of truth at work again, because this theory supposes that *facts* and therefore their representations are discrete, each identical to itself and to no other thing. So far as utility is concerned, however, fuzzy overlapping categories can still be useful, more or less, and might be all we have to go on. The weather can be

forecast, more or less well, for a limited time ahead, by cloud-shape types (by all means not by shapes of individual clouds), even though not precisely defined and sometimes muddled together.

The other criterion of validity Jablensky proposes is mapping on to the science. He cites the diverse criteria for establishing validity of diagnoses proposed by Robins and Guze, Kendler, and Andreasen. These include, to name but a few, familial aggregation, typical precipitants, psychological tests, neurochemical assays, as well as rates of relapse and recovery, and response to treatment. In these lists, clinical utility appears as validation marker, which, in the view being proposed here, it should, there being no fundamental conceptual distinction between utility and validity. Both utility and validity come to the issue of how much of interest is predicted, and among that, the critical issue of how the predictions guide action and underpin technological solutions.

So what do we expect of scientific validity criteria such as genetic, neurochemical, neurological or neuropsychological? We expect these to be useful too and value them for this reason. We do not expect them just to “map onto reality”, otherwise understood. As mentioned earlier, the biomedical model of cholera can be reasonably described as pinning down the real nature of the disease, but this description is underpinned by the fact that the model delivers everything of interest, specifically models of and technologies for treatment and primary prevention.

Increasingly we know that the causes of psychiatric conditions – along with the causes of many general medical conditions – are not singular but multi-factorial, and moreover may have a development from

birth, given that genetic predispositions are life-long, some modifiable by epigenetic mechanisms. Models of these multifactorial life-longitudinal pathways, for example for cardiovascular disease or clinical depression, are more complex than for infectious diseases, but what we expect of them is the same, namely, identification of correlations and modifiable targets for treatment and primary prevention.

The science – behavioural or molecular genetics, psychological tests, neurochemical assays, neuroimaging findings – has to be judged against these pragmatic criteria, just as psychiatric classification has to be judged against findings in the science. The argument cuts both ways.

It has turned out that there is a poor mapping between emerging genetic, neurological and neuropsychological biomarkers and current psychiatric classification. For a while this of course looked like bad news for the biomedical model's application to psychiatry, until the reali-

zation that the poor fit could just as well be interpreted as bad news for the classification system. This latter interpretation drives the U.S. National Institute of Mental Health's Research Domain Criteria project<sup>2,3</sup>.

Current diagnostic criteria no longer are a gold standard; they have to prove their worth in the new sciences, to be conducted on the presumed underlying biopsychological structures and functions themselves. Nonetheless, the pragmatic demands – the requirement of clinical utility, broadly conceived, to include also early detection and primary prevention – remain. Ultimately health science, as opposed to science conducted for some other interest and technical application, has to relate to *health and disease*. In this connection the Research Domain Criteria project has been challenged for losing firm grip on “disease”, both conceptually<sup>4</sup> and for the purposes of global mental health strategy<sup>5</sup>.

The current psychiatric classifications, whatever other shortcomings they may have in relation to clinical utility and biomarkers, do at least serve the major practical purpose of defining *diseases* (illnesses, dysfunctions or disorders), conceived as conditions typically associated with significant burden of distress and impairment of functioning, hence requiring health care attention, and which are the essential outcomes of interest for health care provision and prevention strategies, and for national economies.

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## Would the use of dimensional measures improve the utility of psychiatric diagnoses?

Accepting A. Jablensky's<sup>1</sup> assessment that establishing the validity of either discrete categorical psychiatric diagnoses or dimensional measures of clusters of psychiatric symptoms is a very long-term (or, possibly, unachievable) objective, what should nosologists and diagnosticians be doing to improve the utility of the categories we are currently using?

One issue debated at length during the deliberations for DSM-5 was the use of dimensional measures to supplement the standard categorical diagnoses (e.g., for schizophrenia) or, possibly, as a replacement for the categorical diagnoses (e.g., personality disorders). In the end, the final version of DSM-5 retained the categorical diagnostic structure of previous classifications, largely relegating the dimensional measures to the Emerging Measures and Models section (Section III) of the volume.

But there is continuing debate about the potential clinical utility of converting the current categorical diagnostic system to a dimensional system of classification which would be closer to the observed continuous nature of the severity, duration, and disability associated with psychiatric symptoms<sup>2,3</sup>. To achieve this long-term goal, the Research Domain Criteria (RDoC) project of the U.S. National Institute of Mental Health specifically aims to selectively fund research that will replace current psychiatric diagnostic systems based on descriptive phenomenology with “new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures”<sup>3,4</sup>.

Theoretically, dimensional measures could either be used to directly determine different diagnoses within a new dimensional classification network, or as

adjunctive measures to classify distinct subtypes of the psychiatric disorders in current categorical diagnostic systems (ICD or DSM). If dimensional measures could help to identify distinct clusters of symptoms with different clinical courses and responses to treatment, the use of such measures could increase the utility of diagnostic classifications. But is it realistic to think that they can be used in this way?

There are several problems with using dimensional scores to directly assign diagnoses. Many currently available dimensional measures are highly correlated, so to achieve the goal of a diagnostic system with improved utility, current dimensional measures would either need to be substantially revised or diagnoses would need to be defined as specific patterns of dimensional scores.

Neither of these tasks is simple. Using



a cut-off score of a dimensional measure to assign a diagnosis would collapse that measure into the traditional dichotomized diagnostic labels – the main problem dimensional measures are supposed to resolve. Moreover, the scores of most dimensional measures change frequently either in response to treatment or as part of the natural course of the condition, so diagnoses based on dimensional scores would need to change frequently.

Let's assume that it is possible: a) to develop relatively independent dimensional measures, b) to identify points (or ranges) of rarity on the continuous dimensional measures that would justify specifying a score above which symptoms are to be considered “diagnostically relevant”, and c) to indicate the time(s) in the course of the condition when the dimensional scores would be used to determine a diagnosis (e.g., prior to initiating treatment). Even in that case, assigning diagnoses for all dimensions for which the dimensional score exceeds a specified diagnostically relevant level would result in an unmanageable number of diagnostic categories. Assuming only 10 symptom/diagnostic dimensions, there would be 10 single-dimension disorders, 45 dual-dimension disorders, 360 triple-dimension disorders, 2520 quadruple-dimension disorders, and so forth.

Many of the cells in this matrix of dimension-based diagnoses would be empty, but determining the course and preferred treatment for each of the large number of cells with a substantial number of cases would require studies several orders of magnitude larger than the largest current studies. For individuals with diagnostically relevant scores in

more than one dimension, there would also be the difficulty of prioritizing the various conditions and deciding whether to administer relevant treatments simultaneously or sequentially.

The use of dimensional scores to classify subtypes of current criteria-based categorical diagnoses would require resolving several additional problems. Would there be a universal set of dimensions used for all patients, a menu of dimensions among which a specific subgroup would be used for each diagnosis, or diagnosis-specific dimensions? Would the diagnostic subtypes change as the dimensional scores change? And for diagnoses that consider four or more symptom-based dimensions, the potential number of subtypes (based on the number of dimensions for which the score exceeds a diagnostically relevant level) would be unmanageable. The complex diagnostic algorithms needed to address these issues would likely make the diagnostic criteria unusable in routine clinical practice.

One other potential use of dimensional measures would be to directly determine treatment. If treatments in psychiatry were immediately effective (like antihypertensives) and available treatments were uniquely targeted on specific symptom clusters, then it would be reasonable to regularly change treatments based on patients' current symptom profiles as assessed by narrowly defined dimensional measures. But, for the foreseeable future, neither of these conditions is satisfied, so dimensional measures can only be used to assess the effectiveness of different treatment strategies, *not* to select specific treatment strategies.

The use of dimensional measures of symptom severity to monitor changes in symptoms over time is clinically useful, because they provide a reasonably accurate assessment of the current clinical state of patients and of the effectiveness of specific treatments. But these measures are of limited use for predicting the course of a condition or for predicting the likely effectiveness of specific treatments – essential roles they would need to play if they were to be used to classify diagnoses or subtypes of categorical diagnoses.

The RDoC initiative to identify diagnostically relevant dimensions is intellectually appealing to clinicians and researchers who are frustrated by the inability of categorical diagnostic systems to reflect the complex reality they see every time they interact with patients. But current dimensional measures of behavioural, emotional or neurobiological processes (and the new dimensional measures that will emerge from the RDoC initiative) are correlated with each other and variable over time<sup>5</sup>. Their use will neither improve the validity nor the utility of the diagnoses we employ.

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## Variation and validation: the example of schizophrenia

A. Jablensky's paper<sup>1</sup> is a clear and powerful analysis of issues related to validity and utility in the psychiatric area. We might approach the issues he raises, focusing on the example of schizophrenia, from four somewhat different perspectives: one accepting in a provisional way classical

DSM schizophrenia, a second tolerating and using variation and “fuzziness” or more precisely “polytypicality”, a third considering the relation of validity and utility, and a fourth proposing that research be conducted both on the descriptive DSM-5 account as well as on some

contrasting and more etiological models of schizophrenia.

Though I would agree that a disorder such as schizophrenia may ultimately need to be further analyzed, and perhaps divided or reconfigured as several different disorders, there are some empir-

ical studies that do support the aggregation or “hanging together” of the diagnostic criteria for this and other traditional disorders.

One approach to seeking objective confirmation of a common pathology underlying typical DSM-clustering in six mental disorders was pursued by Kendler et al<sup>2</sup> using latent class analysis. More recently, Derks et al<sup>3</sup> used a similar approach and reported that, when they combined factor analysis and latent class analysis, 85% of the patients receiving a DSM-IV diagnosis of schizophrenia were assigned to the Kraepelinian schizophrenia class. My inference from these studies is that classical schizophrenia is a reasonable first approximation to diagnosing and beginning to develop a treatment plan for such patients, and that, based on the widespread acceptance of the DSM and ICD accounts, the classical picture also retains reasonable clinical “utility”.

But let us acknowledge the variation in several different dimensions (rather than discrete categories) in the schizophrenia area that Jablensky emphasizes. Should it be of that major a concern? Is there some way we might embrace the variation and fuzzy boundaries?

The notion that the entities that are fundamental in a scientific area need to be discrete and separable is an idea that works well in some sciences such as physics and chemistry. But these types of entities are rarely found in biology, where more “polytypic” or “polythetic” concepts reflect the variation in the entities that are fundamental in that science<sup>4</sup>. And medicine and psychiatry are similarly affected by variation<sup>5</sup>. Thus Jablensky’s critiques, though accurate, are in a sense not the real issue. I would suggest that we begin by accepting this polytypicality and then decide how to deal with it in psychiatry.

Perhaps it would be better to deal with variation as doctors do with blood pressure and blood sugar, using a com-

paratively few prototypes for hypertension and diabetes, with different thresholds for different modes of treatment and employing sliding scales. In a way, the psychosis symptom severity five point scales in the DSM-5, though not required for schizophrenia, are a start in this direction. Jablensky himself, in his fuzzy set analyses, has offered a more technical way to advance that approach<sup>6</sup>. For prodromal and early episode forms of schizophrenia, we might also consider proposals for a staging system<sup>7</sup>.

A recurrent theme in Jablensky’s paper is the distinction between validity and utility in psychiatry. Jablensky indicates that issues of utility (and reliability) seem to be progressing satisfactorily, though the same is not the case for validity. But it would seem that the distinction he urges between utility and validity is not quite as sharp. In fact, Jablensky himself cites Jaspers, reminding us “validity” may be a Kantian type of idea. There, Jablensky notes that, though validity is a most elusive endpoint, it may well be best approached by “progressive refinement of the *utility* of the diagnostic concepts and tools”.

This type of approach seems also to be supported by the way the psychiatric “validator” literature has developed in the DSM context<sup>8</sup>. The set of validators that were putatively used in all of DSM-5, and which are very likely to continue being used in DSM 5.1, include three high priority “predictive validators”. These are “diagnostic stability, course of illness, and response to treatment”. This set of validators evokes the notion of predictive validity, and also resonates with received views of clinical utility. First<sup>9</sup> remarks that two (of four) important components of clinical utility are “implementing effective intervention” and “predicting the future” of the patient’s needs and outcomes. This merging of aspects of validity with utility seems both sound, and in the spirit of philosophical pragmatism, and points the way forward.

Finally, there are also more recent etiological approaches to schizophrenia, such as the work of Lewis<sup>10</sup>, and the Psychiatric Genomics Consortium’s suggestions of neuronal, immunological, and epigenetic etiological pathways<sup>11</sup>, as well as the circuit-based approach recommended by the U.S. National Institute of Mental Health’s extensive Research Domain Criteria initiative<sup>12</sup>. Jablensky notes some of these, but is more skeptical of the pursuit of them than I believe warranted.

For the present, and as indicated above, however, there are some very suggestive empirical reasons for retaining the DSM-5 approach to schizophrenia and other major disorders for clinical use. From a symptom aggregational view, the DSM-5 criteria work fairly well in providing a diagnosis and a therapeutic plan. For research, however, more etiological approaches are likely to be more fruitful. This entails that psychiatrists should be pluralistic and select whichever approach seems likely to yield progress in their area of interest.

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# Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a “need for care”

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*Individuals reporting persistent psychotic experiences (PEs) in the general population, but without a “need for care”, are a unique group of particular importance in identifying risk and protective factors for psychosis. We compared people with persistent PEs and no “need for care” (non-clinical, N=92) with patients diagnosed with a psychotic disorder (clinical, N=84) and controls without PEs (N=83), in terms of their phenomenological, socio-demographic and psychological features. The 259 participants were recruited from one urban and one rural area in the UK, as part of the UNIQUE (Unusual Experiences Enquiry) study. Results showed that the non-clinical group experienced hallucinations in all modalities as well as first-rank symptoms, with an earlier age of onset than in the clinical group. Somatic/tactile hallucinations were more frequent than in the clinical group, while commenting and conversing voices were rare. Participants in the non-clinical group were differentiated from their clinical counterparts by being less paranoid and deluded, apart from ideas of reference, and having fewer cognitive difficulties and negative symptoms. Unlike the clinical group, they were characterized neither by low psychosocial functioning nor by social adversity. However, childhood trauma featured in both groups. They were similar to the controls in psychological characteristics: they did not report current emotional problems, had intact self-esteem, displayed healthy schemas about the self and others, showed high life satisfaction and well-being, and high mindfulness. These findings support biopsychosocial models postulating that environmental and psychological factors interact with biological processes in the aetiology of psychosis. While some PEs may be more malign than others, lower levels of social and environmental adversity, combined with protective factors such as intact IQ, spirituality, and psychological and emotional well-being, may reduce the likelihood of persistent PEs leading to pathological outcomes. Future research should focus on protective factors and determinants of well-being in the context of PEs, rather than exclusively on risk factors and biomarkers of disease states.*

**Key words:** Persistent psychotic experiences, need for care, psychosis, hallucinations, first-rank symptoms, psychosocial functioning, social adversity, childhood trauma, protective factors

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The continuum view of psychosis<sup>1</sup> proposes that psychotic symptoms are the severe expression of “schizotypal” traits that are normally distributed in the general population. Large-scale surveys have confirmed that psychotic experiences (PEs) in the general population are relatively common, with a recent meta-analysis yielding a prevalence of 7.2%.<sup>2</sup> Qualitative similarities between high “schizotypes” and psychosis patients have been shown on psychopathological<sup>3</sup>, epidemiological<sup>4,5</sup>, and neurobiological<sup>6,7</sup> measures. Approximately 20% of people with PEs report persistent, rather than transient, experiences. Although a minority of this subgroup may eventually develop a psychotic disorder<sup>8</sup>, in most cases these experiences are not associated with distress, and do not lead to a malign outcome<sup>4</sup>.

However, some authors<sup>9</sup> have argued that subclinical or psychosis-like experiences in the general population are distinct from true symptoms of psychosis, as they are often too mild and transient to be clinically meaningful<sup>10</sup>, and are not specific to schizophrenia<sup>11</sup>. This issue can be addressed by targeting individuals whose PEs are persistent and relatively severe, but who are not distressed by them, have never been diagnosed with a psychotic disorder, or sought help from mental health services (i.e., they do not have a “need for care”)<sup>4</sup>.

A number of studies have compared persistent PEs in individuals with and without a need for care. Auditory verbal hal-

lucinations in non-clinical and clinical samples are broadly phenomenologically similar, but differ in content, emotional valence, and appraisals about their omnipotence<sup>12</sup>. Jackson et al<sup>13,14</sup> found that intense spiritual experiences reported by some individuals could not be distinguished phenomenologically from psychotic symptoms; the differences lay in the interpretation and meaning given to these experiences, and in their emotional and behavioural correlates. Similarly, Brett et al<sup>15</sup> found that the positive symptoms present in psychosis patients and individuals at ultra-high-risk for psychosis were similar to the PEs reported by a non-clinical group, with only “cognitive” anomalies (inability to concentrate, loss of automaticity of thinking skills) being more common in both help-seeking groups. However, the groups differed in the way they appraised and responded to their PEs<sup>16</sup>, which predicted the extent to which PEs were associated with distress<sup>17</sup>. Specifically, several studies suggest that PEs occur in the absence of paranoid appraisals in people with no need for care<sup>16,18,19</sup>, while odd beliefs tend to lead to worse outcome than anomalous experiences<sup>20</sup>.

Stress-vulnerability and integrated cognitive models<sup>21,22</sup> posit a role for social, environmental and psychological factors in the aetiology of psychosis, in addition to genetic and neurodevelopmental features such as a family history of psychosis and low

intelligence quotient (IQ). For instance, negative schemas about self and others are common in psychotic populations<sup>23</sup>, as are dysfunctional attachment styles<sup>24</sup>. Childhood adversity<sup>25,26</sup>, and interpersonal trauma specifically<sup>27</sup>, have been linked to the development of PEs, and there is evidence linking current adverse environments – characterized by racial discrimination<sup>28</sup>, migrant status<sup>29</sup> and low social capital<sup>30</sup> – with psychosis. There seems to be a synergistic interplay between different risk factors, such as between childhood abuse and adult life events, as well as cannabis use<sup>31,32</sup>, suggesting that exposure to childhood and adult disadvantage may combine in complex ways to push some individuals along the pathway to psychotic disorder. Sommer et al<sup>33</sup> compared non-clinical voice-hearers with controls and showed that higher schizotypy scores, lower education, and higher family loading for psychiatric disorders, but not presence of voices, were associated with lower global functioning, illustrating the importance of disentangling the contribution of biopsychosocial factors to psychotic experiences from poor functioning and potential “need for care”. On the other hand, childhood and interpersonal trauma have been consistently associated with the presence of voices<sup>34-36</sup> and other anomalous experiences<sup>18</sup>, irrespective of need for care.

Studies with people reporting persistent but benign PEs provide a means of examining both risk and protective factors for the development of psychosis. On the one hand, the persistence of psychotic phenomena implies the sharing of risk factors for psychotic disorders. On the other, such individuals lead unperturbed lives without needing clinical care, suggesting they possess or have been exposed to protective factors absent in psychotic populations.

The aim of the present study was to characterize people with persistent, non-distressing PEs by comparing them with psychosis patients and controls without PEs, recruited as part of the UNIQUE (Unusual Experiences Enquiry) study. We tested three specific hypotheses, based on cognitive models of psychosis<sup>21,37</sup> and previous studies on differences in clinical, environmental, and psychological characteristics. We postulated that people with persistent PEs would not differ socio-demographically or psychologically from controls and, compared to patients diagnosed with psychotic disorders, would have: a) similar types of positive symptoms, but fewer subjective cognitive deficits, paranoid delusions, and negative symptoms; b) lower levels of social and environmental adversity, with the exception of childhood trauma<sup>18,34</sup>; c) greater emotional and psychological well-being, and healthier parental relationships.

## METHODS

### Participants

Three groups of adults were recruited from one urban (South London and environs) and one rural (Bangor and environs, North Wales) area over a period of 23 months: a) individuals with PEs without a “need for care” (non-clinical group);

b) patients diagnosed with a psychotic disorder (clinical group); c) controls with no PEs. Exclusion criteria for all groups were: age < 18; insufficient command of English; history of neurological problems, head injury or epilepsy; primary substance dependence. Participants were screened over the phone by research workers, or face-to-face in the case of inpatients.

### Non-clinical group (N=92)

This group comprised healthy individuals with enduring PEs who had never been diagnosed with, or treated for, a psychotic disorder (London site: N=51, 55.4%; Bangor site: N=41, 44.6%).

The majority (N=82, 89.1%) were recruited using our previous sampling strategy<sup>16,19,38-40</sup> targeting specialist sources in London, North Wales and their respective environs. Advertisements were placed in psychic and spiritualist fora (including: College of Psychic Studies, The British Astrological and Psychic Society, The International Academy of Unconsciousness, Spiritualist Association of Great Britain, Society of Psychical Research, London College of Spirituality, Unitarian Church, Two Worlds, Open Arms Spiritualist group, and Bangor Spiritualist Church), usually through the relevant organization leaders (or via Facebook pages). Interested individuals would then contact the team and proceed with screening of eligibility. A number of individuals were also recruited from a research register held by the first author, who had consented to being contacted about research following participation in previous studies. Lastly, an advert was circulated using the King's College London circular email list. In all cases a snowballing method was adopted in which participants were encouraged to pass on information about the study to contacts whom they considered appropriate.

A further 10 participants (10.9%) were recruited from an epidemiologically representative community sample (South East London Community Health Study<sup>41</sup>) and general practitioner (GP) registers selected from the same geographical area as our South London clinical sample.

Individuals were invited to participate if they: a) reported one or more PEs (secondary item) on the Psychosis Screening Questionnaire (PSQ)<sup>42</sup>, and “occasional” (at least monthly) experiences of any positive and Schneiderian first-rank symptom on the Unusual Experiences Screening Questionnaire (UESQ)<sup>16</sup>, within the last month, in the absence of drug use and in clear consciousness; b) had experiences occurring for more than 5 years (to avoid including individuals who may be prodromal); c) had never been in contact with mental health services/GPs in relation to their PEs (nor had someone else on their behalf); d) had never been in contact with secondary mental health care; e) did not score 2 (“unmet need”) on items covering basic self-care and the psychological distress dimension (in relation to their PEs) of the Camberwell Assessment of Need Short Appraisal Schedule (CAN-SAS)<sup>43</sup>; f) were judged by the research worker, in consultation with the study coordinator, to not be in need of care.

Only individuals with current positive PEs (score of 2 or above on at least one item of the Scale for the Assessment of

Positive Symptoms (SAPS)<sup>44</sup> at the time of recruitment) were included. People who had received diagnoses of, and/or treatment for, common mental health problems (such as anxiety and depression) or had been in contact with primary care services for issues unrelated to their PEs (N=16, 17.4%) were not excluded from the study.

There were 25 men (27.2%) and 67 women (72.8%), with a mean age of 46 years (range of 18-80).

### **Clinical group (N=84)**

This group was recruited from routine inpatient (N=29, 34.5%) and community (N=55, 65.5%) services of the South London and Maudsley NHS Foundation Trust (N=43, 51.2%) and Betsi Cadwaladr University Health Board (N=41, 48.8%) concurrently.

Consultant psychiatrists, care coordinators or primary nurses were asked to identify patients under their care eligible for the study, who were then approached by the research workers to ascertain their willingness to participate. Only patients with current positive symptoms (score of 2 or above on at least one item of the SAPS at the time of recruitment) and a psychotic disorder diagnosis (ICD-10 categories F20-39) were included.

The diagnosis was schizophrenia in 53 patients (63.1%), schizoaffective disorder in 13 (15.5%), and psychosis not otherwise specified in 6 (7.1%), while 11 patients (13.1%) had a diagnosis belonging to F30-39 categories. Seventy-six patients (90.5%) were on an antipsychotic medication. Patients had a mean of 4.4 (median=4; SD=3.6) prior hospital admissions.

There were 55 men (65.5%) and 29 women (34.5%), with a mean age of 42 years (range of 20-78).

### **Control group (N=83)**

The control participants were volunteered directly by non-clinical participants (N=18, 21.7%), or recruited using research registers held by members of the team (including a local GP register) or advertisements placed in various community settings (e.g., newsagents and community centres) in the South London area, the King's College London circular email list, the Bangor University "research participation panels" and the Bangor Network News Magazine (N=65, 78.3%). Interested individuals would then contact the team and proceed with screening of eligibility.

Only individuals with no PEs (endorsed no items on UESQ and PSQ), and scoring no higher than one standard deviation above the Unusual Experiences subscale mean of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)<sup>45</sup>, were invited to participate. Controls were broadly matched to the non-clinical group in age, gender, ethnicity, and education level, and also included people who had received diagnoses of, and/or treatment for, common mental health problems (N=5, 6.0%), but not those who had been in contact with secondary mental health care.

There were 26 men (31.3%) and 57 women (68.7%), with a mean age of 46 years (range 21-76).

## **Assessments**

### **Screening tools**

Screening tools were not routinely administered to the clinical group, who were screened through clinicians and/or case-note review. The CANSAS was administered to the non-clinical group only, and the O-LIFE to the control group only.

The PSQ<sup>42</sup> assesses PEs in the preceding year and comprises five sections covering hypomania, thought disorder, paranoia, strange experiences and hallucinations. Each section has an initial probe, followed by secondary questions that are designed to establish the psychotic quality of experiences. The PSQ has been validated in two national surveys in the UK<sup>46,47</sup>. As we were specifically interested in PEs, items on hypomania were discarded.

The UESQ consists of nine items derived from the Appraisals of Anomalous Experiences Interview (AANEX)<sup>16</sup>, assessing the presence of a range of positive and Schneiderian first-rank symptoms (such as hallucinations, thought interference, delusional perception), within the last month, in the absence of drug use and in clear consciousness.

The CANSAS<sup>43</sup> is a comprehensive assessment of clinical and social needs. Only items 1-4 (relating to accommodation, food, home, and self-care), and item 9 (psychological distress in relation to unusual experiences) were used. Scores range from 0 to 2 (0=no problem; 1=met need; 2=unmet need).

Of the O-LIFE<sup>45</sup>, a standardized schizotypy questionnaire, we used only the Unusual Experiences subscale. This includes 30 items describing perceptual aberrations, magical thinking, and hallucinations, and is phenomenologically related to positive symptoms of psychosis. Items are scored "yes" or "no", with a potential range of scores from 0 to 30. O-LIFE norms<sup>45</sup> indicate a mean of 8.8 and SD of 6.2. The cut-off score for this study was 15.

### **PE assessments**

Clinical assessments were performed in the clinical and non-clinical groups only.

The AANEX semi-structured interview<sup>16</sup> was used to elicit participants' current PEs and their associated emotional and cognitive correlates. The first part of the interview (AANEX-Inventory, short form<sup>18</sup>) consists of 17 anomalous experiences that are rated for both presence and severity in the person's lifetime and currently (within the last month). Each item is rated on a 3-point scale (1=not present; 2=unclear; 3=present). Possible total scores range from 17 to 51 for both lifetime and current experiences.

Five factor scores are also generated via summation of individual item scores<sup>15</sup>: a) meaning-reference (which reflects manic or hypomanic states and experiences, ideas of reference, insight, and prominent "revelatory" experiences); b) paranormal-hallucinatory (which reflects alterations in sense of agency and passivity, somatic hallucinations, and paranormal experiences

such as mediumship, clairvoyance and magic, and perception of other entities/energies); c) cognitive-attention (which reflects non-specific subjective changes or deficits in thinking and attention, such as thought blockages and loss of automatic skills); d) dissociative-perceptual (which reflects dissociative experiences such as depersonalization and derealization, along with other global perceptual changes); and e) first-rank symptoms (which includes specific auditory hallucinations, experiences of weakened boundaries between self and other such as thought transmission, receptivity, and “made” emotions).

The anomalous experiences elicited by the first part are then used to anchor the second part of the interview (AANEX-CAR (Context, Appraisals & Response)), which covers emotional and cognitive factors associated with the anomalous experiences, and the context in which they occurred. Additional items were added to assess “belief flexibility”, derived from the Maudsley Assessment of Delusions Scale (MADS)<sup>48</sup>. Only AANEX-Inventory data are reported here.

The SAPS<sup>44</sup> and the Scale for the Assessment of Negative Symptoms (SANS)<sup>49</sup> were used to assess positive and negative psychosis symptoms. The SAPS consists of 35 items subdivided into four sections: hallucinations, delusions, bizarre behaviour, and positive formal thought disorder. The SANS consists of 25 items subdivided into five sections: affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, and attention. Scores for each item reflect level of severity and frequency, and range from 0 (none) to 5 (severe). Each subscale produces a global rating (also 0-5). The total range of scores is 0-175 for SAPS, and 0-125 for SANS.

### **Socio-demographic and environmental factors measures**

A demographic form was used to record the following information from all participants: age, gender, ethnicity, current socio-economic status (SES), years in education, current employment status, migrant status, first language, current and past relationship status, number of children, religious/spiritual affiliation, current and past drug use. Age at onset and length of time of PEs were obtained from the clinical and non-clinical groups. Current medications, diagnosis, and number of admissions were checked through case-note review for the clinical group.

The Social-Environmental Assessment Tool (SEAT)<sup>50</sup> was adopted to assess social capital. It consists of four subdomains: civic disorder (i.e., thefts, vandalism, truancy); impact of civic disorder (i.e., how concerned respondents feel about crime and disorder); informal social control (i.e., how likely people are to take action about civic disorder); and social cohesion and trust (i.e., whether people can be trusted, are willing to help, will cooperate to campaign for local issues, feeling part of the community). The first three domains consist of four items, and the fourth of 11 items (all items are scored 1-5). Sum-scores for each subdomain are z-standardized, and an overall social capital score is created using a weighted sum of the z-scores for each subdomain.

A short form of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III)<sup>51</sup> was used, consisting of one subtest of each cognitive index: information (verbal comprehension), block design (perceptual organization), arithmetic (working memory), and digit symbol (processing speed). The four subtest scaled scores were summed and divided by the total number of subtests (11) to generate a WAIS estimation total score, which was then converted into an estimated IQ score.

The Victimization Experiences Schedule (VES)<sup>52</sup> was developed for this study. It is a semi-structured interview incorporating the two categories of interpersonal trauma and perceived discrimination. Relevant items from a number of existing scales – Childhood Experience of Care and Abuse<sup>53</sup>, Trauma History Questionnaire<sup>54</sup>, Discrimination Interview<sup>55</sup> – were selected to cover the range of victimization experiences relevant to psychosis. The first category consists of nine items: sexual abuse (divided into sexual intercourse, and unwanted sexual contact); physical abuse; physical attack (with, and without, a weapon); threat of assault; bullying; psychological abuse; parental neglect. The second category consists of five items assessing everyday perceived discrimination (unfairly treated: at work, by the police, by the court system, by neighbours and/or family, when receiving medical care). Three scores can be obtained for each category: total number of interpersonal trauma/discrimination experiences in childhood, in adulthood, and across the lifespan. Scores across categories can also be summed to provide total victimization scores. Only the childhood interpersonal trauma and lifespan discrimination scores are reported here.

### **Psychological characteristics**

The Beck Depression and Anxiety Inventories (BDI-II<sup>56</sup> and BAI<sup>57</sup>) were used to assess depression and anxiety symptoms, respectively. They both consist of 21 items, and respondents are asked to rate the severity of each item in the last week on a 4-point scale (potential range of scores 0-63; higher scores represent higher pathology).

The Perceived Stress Scale (PSS)<sup>58</sup> was adopted to explore perceived levels of stress in the last month. This includes 10 items, each rated on a 5-point scale from “never” to “very often”, with a potential range of score of 0-40 (higher scores represent higher levels of perceived stress).

The Brief Core Schema Scale (BCSS)<sup>23</sup> was used to assess long-term held beliefs (i.e., “schemas”) about the self and others. This includes 24 items, rated on a 5-point scale from “don’t believe it” to “believe it totally”. Four scores are obtained relating to “positive self”, “negative self”, “positive others”, and “negative others”, each with six items (potential range of scores 0-24; higher scores represent stronger schemas for each subscale).

The Questionnaire for Evaluation of Self (QES)<sup>59</sup> was used to assess self-esteem. This is a 21-item questionnaire based on the modified Self-Evaluation and Social Support Interview<sup>60</sup>, assessing positive, negative, and self-acceptance attributes. Each subscale has seven items rated on a 4-point scale from

“disagree” to “agree very much” (range of scores 7-28; higher scores represent stronger attributes for each subscale).

The Southampton Mindfulness Questionnaires (SMQ)<sup>61,62</sup> were adopted to assess participants’ habitual responses to distressing thoughts and images (all groups), and to voices (clinical and non-clinical groups only). Each of these questionnaires consists of 16 items rated on a 7-point scale, from “agree totally” to “disagree totally”, with a potential range of scores of 0-96 for each questionnaire (higher scores represent better ability to respond to thoughts/images and voices mindfully).

The Satisfaction with Life Scale (SWLS)<sup>63</sup> was used to assess satisfaction with life. This is a 5-item self-report measure. Each statement is rated on a 7-point scale, ranging from “strongly disagree” to “strongly agree”, with a potential range of scores of 5-35 (high scores represent higher life satisfaction).

The Psychological Well-Being-Post-Traumatic Changes Questionnaire (PWB-PTCQ)<sup>64</sup> explores any positive sequelae to traumatic experiences, and was adapted in this study to identify positive changes occurring as a result of PEs. It is an 18-item self-report measure, with six subscales (self-acceptance, autonomy, purpose in life, relationships, sense of mastery, personal growth). Each item is rated on a 5-point scale, from “much more so now” to “much less so now”, with a range of scores of 18-90 (higher scores represent higher psychological well-being). This scale was not administered to the controls.

The Parental Bonding Questionnaire (PBQ)<sup>65</sup> was used to evaluate the participants’ retrospective perceptions of parental attitudes and behaviours towards them in the first 16 years of life. This scale consists of two 25-item forms (one for mother and one for father), each comprising a subscale on protection (13 items) and one on care (12 items). Each item was rated on a 4-point scale (“very like” to “very unlike”). Potential range of scores for the protection scale is 0-39, and for care 0-36. Low scores on the protection scale relate to perceived acceptance of autonomy, whereas high scores reflect perceived intrusion and excessive control. Low scores on the care scale relate to indifference and rejection; high scores relate to perceived warmth and affection.

## Procedures

Ethical approval for the UNIQUE study was obtained from the London-Westminster National Research Ethics Service Committee (12/LO/0766); the South London and Maudsley NHS Foundation Trust/King’s College London Institute of Psychiatry, Psychology and Neuroscience Research and Development (R&D2012/047); and the Betsi Cadwaladr University Health Board Research and Development (Jackson/LO/0766). Following written informed consent, eligible participants completed all assessments with the research workers. At the end of the study participants were debriefed, and given £30 honorarium.

Interviews were audio-recorded for scoring, with the participant’s consent. Interrater reliabilities (ascertained using 35 interviews across sites and groups, rated by the study coordinator and the individual research workers) for the three

AANEX-Inventory totals indicated almost perfect agreement (intra-class correlation, ICC=.995-.998). Interrater reliability for the combined SAPS and SANS (ICC=.904) and for the VES (ICC=.99) also showed almost perfect agreement.

## Analytic strategy

The distribution of continuous variables was checked to ensure basic assumptions of parametric testing were met. Where deviations from a normal distribution were found, variables were either dichotomized or non-parametric testing was carried out. One-way ANOVAs or t-tests (socio-demographic and environmental factors; psychological characteristics), MANOVAs (AANEX, SEAT) or Kruskal-Wallis (VES) were used to test for significant differences between the groups, followed by post-hoc least significant difference comparisons or Mann-Whitney tests (SAPS and SANS) between specific groups where appropriate. Categorical variables were tested using  $\chi^2$  tests. Significance level was set at  $p < 0.01$  for analyses of PEs due to multiple testing on related constructs.

## RESULTS

The groups did not differ in age ( $F_{2,256}=2.5$ ,  $p=0.09$ ), but there were more men in the clinical than in the other two groups ( $\chi^2=31.3$ ,  $df=2$ ,  $p < 0.001$ ). Results are presented in Tables 1-3.

### Types of PE (see Table 1)

The non-clinical group had a younger age of onset of their PEs than the clinical group, and had lived with their experiences for longer. Over 75% in both groups reported having heard voices during their lifetime. Both groups reported hallucinations in all modalities, although commenting and conversing voices were rare in the non-clinical individuals, while somatic/tactile and (at trend level) olfactory hallucinations were more frequent in the non-clinical sample. The latter also scored significantly higher on both the AANEX lifetime and current paranormal-hallucinatory factor than the clinical group, reflecting a greater frequency of magical and precognitive experiences, somatic hallucinations and passivity experiences.

First-rank symptoms, especially thought insertion, mind reading, and feelings of being controlled, were also commonly reported in the non-clinical group, although they had a higher lifetime (but not current) frequency in the clinical group. The non-clinical individuals showed few signs of being paranoid or deluded, apart from ideas of reference, which were commonly reported, but still less frequently than in the clinical group.

Compared with the clinical group, the non-clinical sample reported fewer negative symptoms and cognitive difficulties, both currently and over their lifetime. In particular, their average score was  $< 0.5$  for all individual SANS items. They also scored

**Table 1** Types of persistent psychotic experiences (PEs) in the non-clinical and clinical groups

	Non-clinical (N=92)	Clinical (N=84)	Statistics
Age at onset of PEs (years, mean±SD)	15.0 ± 12.3	22.0 ± 10.4	<b>t<sub>174</sub>=3.9, p&lt;0.001</b>
Length of time with PEs (years, mean±SD)	31.2 ± 15.3	20.2 ± 12.9	<b>t<sub>174</sub>=5.1, p&lt;0.001</b>
Lifetime auditory hallucinations (%)	77.2	88.1	X <sup>2</sup> =3.6, df=1, p<0.06
SAPS total (mean±SD)	12.3 ± 7.2	27.5 ± 15.5	<b>U<sub>173</sub>=1433, p&lt;0.001</b>
SAPS hallucinations global rating (mean±SD)	2.5 ± 1.3	3.2 ± 1.9	<b>U<sub>173</sub>=2494, p&lt;0.001</b>
SAPS delusions global rating (mean±SD)	2.3 ± 1.4	3.7 ± 1.2	<b>U<sub>173</sub>=1618, p&lt;0.001</b>
SAPS bizarre behaviour global rating (mean±SD)	0.1 ± 0.4	0.7 ± 1.1	<b>U<sub>173</sub>=2718, p&lt;0.001</b>
SAPS thought disorder global rating (mean±SD)	0.1 ± 0.3	1.0 ± 1.3	<b>U<sub>173</sub>=2227, p&lt;0.001</b>
SANS total (mean±SD)	3.0 ± 3.3	22.7 ± 13.4	<b>U<sub>173</sub>=250, p&lt;0.001</b>
SANS global ratings total (sum of five global ratings) (mean±SD)	1.5 ± 1.7	9.3 ± 4.3	<b>U<sub>173</sub>=216, p&lt;0.001</b>
SAPS somatic/tactile hallucinations (mean±SD)	2.1 ± 1.7	1.4 ± 1.7	<b>U<sub>173</sub>=2845, p=0.002</b>
SAPS delusions of reference (mean±SD)	1.7 ± 1.7	2.9 ± 1.7	<b>U<sub>173</sub>=2436, p&lt;0.001</b>
SAPS visual hallucinations (mean±SD)	1.6 ± 1.7	1.3 ± 1.8	U <sub>173</sub> =3392, p=0.17
SAPS thought insertion (mean±SD)	1.6 ± 1.7	1.9 ± 1.9	U <sub>173</sub> =3483, p=0.29
SAPS auditory hallucinations (mean±SD)	1.4 ± 1.4	2.8 ± 2.2	<b>U<sub>173</sub>=2407, p&lt;0.001</b>
SAPS mind reading (mean±SD)	1.1 ± 1.4	1.7 ± 1.9	U <sub>173</sub> =3152, p=0.03
SAPS olfactory hallucinations (mean±SD)	0.7 ± 1.2	0.4 ± 1.1	U <sub>173</sub> =3273, p=0.03
SAPS feelings of being controlled (mean±SD)	0.5 ± 1.1	1.1 ± 1.8	U <sub>173</sub> =3265, p=0.03
SAPS voices commenting (mean±SD)	0.3 ± 1.0	1.6 ± 2.1	<b>U<sub>173</sub>=2505, p&lt;0.001</b>
SAPS thought broadcast (mean±SD)	0.2 ± 0.6	1.5 ± 2.0	<b>U<sub>173</sub>=2412, p&lt;0.001</b>
SAPS voices conversing (mean±SD)	0.2 ± 0.6	1.1 ± 1.8	<b>U<sub>173</sub>=2751, p&lt;0.001</b>
SAPS grandiose delusions (mean±SD)	0.2 ± 0.7	0.8 ± 1.5	<b>U<sub>173</sub>=3132, p=0.003</b>
SAPS thought withdrawal (mean±SD)	0.1 ± 0.5	0.8 ± 1.5	<b>U<sub>173</sub>=2962, p&lt;0.001</b>
SAPS religious delusions (mean±SD)	0.1 ± 0.4	0.8 ± 1.5	<b>U<sub>173</sub>=2884, p&lt;0.001</b>
SAPS persecutory delusions (mean±SD)	0.1 ± 0.4	1.9 ± 1.6	<b>U<sub>173</sub>=1438, p&lt;0.001</b>
SAPS inappropriate affect (mean±SD)	0.03 ± 0.3	0.3 ± 0.9	<b>U<sub>172</sub>=3410, p=0.006</b>
SAPS delusions of jealousy (mean±SD)	0.01 ± 0.1	0.3 ± 0.7	<b>U<sub>173</sub>=3258, p&lt;0.001</b>
SAPS delusions of sin/guilt (mean±SD)	0.01 ± 0.1	0.7 ± 1.3	<b>U<sub>173</sub>=2932, p&lt;0.001</b>
SAPS somatic delusions (mean±SD)	0.01 ± 0.1	0.3 ± 0.9	<b>U<sub>173</sub>=3349, p=0.001</b>
AANEX total current (mean±SD)	28.6 ± 5.1	30.1 ± 6.2	F <sub>1,172</sub> =2.9, p=0.088
AANEX total lifetime (mean±SD)	34.8 ± 4.9	36.3 ± 6.4	F <sub>1,172</sub> =2.8, p=0.098
AANEX meaning-reference, current (mean±SD)	7.7 ± 2.1	7.5 ± 2.2	F <sub>1,172</sub> =0.7, p=0.41
AANEX meaning-reference, lifetime (mean±SD)	9.1 ± 2.1	8.7 ± 2.3	F <sub>1,172</sub> =1.5, p=0.23
AANEX first-rank symptoms, current (mean±SD)	7.5 ± 1.9	8.1 ± 2.5	F <sub>1,172</sub> =2.8, p=0.096
AANEX first-rank symptoms, lifetime (mean±SD)	8.9 ± 1.6	9.7 ± 2.0	<b>F<sub>1,172</sub>=9.5, p=0.002</b>
AANEX paranormal-hallucinatory, current (mean±SD)	5.9 ± 1.7	5.1 ± 1.9	<b>F<sub>1,172</sub>=9.3, p=0.003</b>
AANEX paranormal-hallucinatory, lifetime (mean±SD)	7.5 ± 1.4	6.5 ± 2.1	<b>F<sub>1,172</sub>=17.7, p&lt;0.001</b>
AANEX dissociative-perceptual, current (mean±SD)	3.8 ± 1.4	4.5 ± 1.8	<b>F<sub>1,172</sub>=7.5, p=0.007</b>
AANEX dissociative-perceptual, lifetime (mean±SD)	5.3 ± 1.9	5.8 ± 2.0	F <sub>1,172</sub> =2.9, p=0.093
AANEX cognitive-attentional, current (mean±SD)	3.8 ± 1.6	5.1 ± 1.7	<b>F<sub>1,172</sub>=28.4, p&lt;0.001</b>
AANEX cognitive-attentional, lifetime (mean±SD)	4.1 ± 1.6	5.7 ± 1.8	<b>F<sub>1,172</sub>=38.3, p&lt;0.001</b>

SAPS – Scale for the Assessment of Positive Symptoms, SANS – Scale for the Assessment of Negative Symptoms, AANEX – Appraisals of Anomalous Experiences Interview–Inventory

Significant differences are highlighted in bold prints; SAPS items are listed in order of severity rating in the non-clinical group



**Table 2** Socio-demographic and environmental factors in the three groups

	Controls (N=83)	Non-clinical (N=92)	Clinical (N=84)	Statistics
Ethnicity (%)				White vs. others: $\chi^2=20.1$ , <b>df=2</b> , <b>p&lt;0.001</b> (clinical < non-clinical = controls)
White	90.4	87.0	65.5	
Mixed	2.4	3.3	4.8	
Asian	2.4	2.2	2.4	
Black	3.6	6.5	26.2	
Other	1.2	1.1	1.2	
Migrant (%)	12.1	15.2	26.2	$\chi^2=6.4$ , <b>df=2</b> , <b>p=0.04</b> (clinical > non-clinical at trend level; non-clinical = controls)
English first language (%)	89.0	91.2	88.1	$\chi^2=0.5$ , <b>df=2</b> , <b>p=0.79</b>
Education (years, mean±SD)	17.1 ± 4.0	16.8 ± 4.2	14.7 ± 5.8	<b>F<sub>2,254</sub>=6.3</b> , <b>p=0.002</b> (clinical < non-clinical = controls)
Employed/in training (%)	78.3	69.6	16.7	$\chi^2=76.1$ , <b>df=2</b> , <b>p&lt;0.001</b> (clinical < non-clinical = controls)
Current employment* (%)				$\chi^2=100.8$ , <b>df=8</b> , <b>p&lt;0.001</b> (clinical < non-clinical = controls)
Salaried	28.9	18.9	0	
Intermediate	21.7	21.1	0	
Working class	6.0	13.3	6.0	
Never worked/long-term unemployed	22.9	32.2	90.5	
Unclassifiable	20.5	14.4	3.6	
Married/partner (%)	47.0	50.0	21.4	$\chi^2=17.6$ , <b>df=2</b> , <b>p&lt;0.001</b> (clinical < non-clinical = controls)
Ever had relationship (%)	92.8	96.7	75.0	$\chi^2=22.5$ , <b>df=2</b> , <b>p&lt;0.001</b> (clinical < non-clinical = controls)
Children (one or more, %)	59.0	57.6	35.7	$\chi^2=11.6$ , <b>df=2</b> , <b>p=0.003</b> (clinical < non-clinical = controls)
Family history of psychosis (%)	5.0	10.2	24.7	$\chi^2=14.0$ , <b>df=2</b> , <b>p=0.001</b> (clinical > non-clinical = controls)
Family history of mental health problems (%)	28.0	31.5	43.0	$\chi^2=4.4$ , <b>df=2</b> , <b>p=0.11</b>
Religion (%)				$\chi^2=68.2$ , <b>df=4</b> , <b>p&lt;0.001</b> (clinical ≠ non-clinical ≠ controls)
None	57.8	34.8	19.0	
Mainstream	33.7	20.7	65.5	
Non-traditional	8.4	44.6	15.5	
Spiritual (%)	41.0	91.1	76.5	$\chi^2=54.2$ , <b>df=2</b> , <b>p&lt;0.001</b> (non-clinical > clinical > controls)
Cannabis use, past (%)	41.0	33.7	53.6	$\chi^2=7.2$ , <b>df=2</b> , <b>p=0.027</b> (clinical > non-clinical; clinical = controls; non-clinical = controls)
Cannabis use, present (%)	4.8	2.2	10.7	$\chi^2=6.1$ , <b>df=2</b> , <b>p=0.048</b> (clinical > non-clinical; clinical = controls; non-clinical = controls)
Other drug use, past (%)	25.3	12.0	36.9	$\chi^2=14.9$ , <b>df=2</b> , <b>p=0.001</b> (non-clinical < clinical = controls)
Other drug use, present (%)	2.4	0	2.4	$\chi^2=2.3$ , <b>df=2</b> , <b>p=0.32</b>
SEAT total (mean±SD)	0.20 ± 2.6	0.04 ± 2.9	-0.13 ± 2.6	<b>F<sub>2,250</sub>=0.3</b> , <b>p=0.73</b>
SEAT civic disorder (mean±SD)	0.05 ± 0.9	0.21 ± 0.9	-0.27 ± 1.1	<b>F<sub>2,250</sub>=5.2</b> , <b>p=0.006</b> (clinical < non-clinical = controls)
SEAT impact of civic disorder (mean±SD)	0.08 ± 1.0	0.02 ± 1.0	-0.10 ± 1.1	<b>F<sub>2,250</sub>=0.7</b> , <b>p=0.49</b>
SEAT informal social control (mean±SD)	-0.04 ± 1.0	-0.12 ± 1.0	0.18 ± 0.9	<b>F<sub>2,250</sub>=2.0</b> , <b>p=0.14</b>
SEAT social cohesion and trust (mean±SD)	0.16 ± 0.9	-0.05 ± 1.1	-0.10 ± 1.0	<b>F<sub>2,250</sub>=1.7</b> , <b>p=0.19</b>
IQ (mean±SD)	112.0 ± 16.5	105.0 ± 14.0	85.0 ± 14.2	<b>F<sub>2,247</sub>=71.1</b> , <b>p&lt;0.001</b> (clinical < non-clinical < controls)
VES childhood interpersonal trauma (mean±SD)	2.4 ± 2.2	3.0 ± 2.4	2.6 ± 2.5	<b>K=4.8</b> , <b>df=2</b> , <b>p=0.09</b> (controls < non-clinical; non-clinical = clinical; clinical = controls)
VES lifetime discrimination (mean±SD)	1.0 ± 1.2	1.2 ± 1.4	1.9 ± 1.7	<b>K=16.2</b> , <b>df=2</b> , <b>p&lt;0.001</b> (clinical > non-clinical = controls)

\*Classified according to the European Socio-economic Classification (ESeC)<sup>66</sup>

SEAT – Social Environment Assessment Tool, VES – Victimization Experiences Schedule

Significant differences are highlighted in bold prints

**Table 3** Psychological characteristics in the three groups

	Controls (N=82)	Non-clinical (N=91)	Clinical (N=83)	Statistics
Beck Depression Inventory-II (mean±SD)	5.9 ± 8.2	6.7 ± 7.1	20.9 ± 14.0	<b>F<sub>2,251</sub>=57.3, p&lt;0.001</b> (clinical > non-clinical = controls)
Beck Anxiety Inventory (mean±SD)	3.7 ± 5.0	6.8 ± 7.2	17.4 ± 12.8	<b>F<sub>2,251</sub>=52.8, p&lt;0.001</b> (clinical > non-clinical > controls)
Perceived Stress Scale (mean±SD)	13.5 ± 7.0	13.7 ± 7.2	20.1 ± 7.4	<b>F<sub>2,246</sub>=22.0, p&lt;0.001</b> (clinical > non-clinical = controls)
QES positive attributes (mean±SD)	21.3 ± 3.5	21.8 ± 3.7	19.0 ± 4.9	<b>F<sub>2,251</sub>=11.2, p&lt;0.001</b> (clinical < non-clinical = controls)
QES negative attributes (mean±SD)	8.9 ± 2.2	8.7 ± 2.4	11.7 ± 4.2	<b>F<sub>2,251</sub>=25.4, p&lt;0.001</b> (clinical > non-clinical = controls)
QES self-acceptance, lack of (mean±SD)	12.0 ± 3.5	11.7 ± 2.9	16.5 ± 5.6	<b>F<sub>2,252</sub>=34.4, p&lt;0.001</b> (clinical > non-clinical = controls)
BCSS positive self (mean±SD)	14.2 ± 5.5	14.9 ± 7.0	10.2 ± 6.9	<b>F<sub>2,252</sub>=13.0, p&lt;0.001</b> (clinical < non-clinical = controls)
BCSS negative self (mean±SD)	1.8 ± 3.2	2.0 ± 3.2	6.0 ± 6.2	<b>F<sub>2,253</sub>=24.0, p&lt;0.001</b> (clinical > non-clinical = controls)
BCSS positive others (mean±SD)	13.6 ± 5.4	12.9 ± 4.9	11.0 ± 6.0	<b>F<sub>2,250</sub>=5.3, p=0.006</b> (clinical < non-clinical = controls)
BCSS negative others (mean±SD)	3.8 ± 5.4	4.8 ± 5.3	9.1 ± 6.8	<b>F<sub>2,251</sub>=19.6, p&lt;0.001</b> (clinical > non-clinical = controls)
Satisfaction With Life Scale (mean±SD)	23.3 ± 7.1	23.6 ± 6.7	17.2 ± 7.9	<b>F<sub>2,251</sub>=21.1, p&lt;0.001</b> (clinical < non-clinical = controls)
Psychological Well-Being-Post PEs Questionnaire (mean±SD)		72.9 ± 11.9	61.5 ± 14.3	<b>F<sub>1,169</sub>=32.7, p&lt;0.001</b>
SMQ thoughts/images (mean±SD)	58.9 ± 15.6	63.4 ± 15	47.0 ± 12.7	<b>F<sub>2,228</sub>=24.6, p&lt;0.001</b> (non-clinical > controls > clinical)
SMQ voices* (mean±SD)		69.2 ± 14.5	48.0 ± 13.3	<b>F<sub>1,88</sub>=51.8, p&lt;0.001</b>
PBQ protection, mother (mean±SD)	12.6 ± 8.0	14.5 ± 9.3	15.6 ± 7.9	F <sub>2,247</sub> =2.6, p=0.076 (clinical > controls; controls = non-clinical; clinical = non-clinical)
PBQ protection, father (mean±SD)	11.4 ± 8.0	11.4 ± 7.6	14.8 ± 8.6	<b>F<sub>2,225</sub>=4.0, p=0.02</b> (clinical > non-clinical = controls)
PBQ care, mother (mean±SD)	23.2 ± 9.4	22.7 ± 10.3	24.3 ± 9.9	F <sub>2,247</sub> =0.6, p=0.55
PBQ care, father (mean±SD)	21.8 ± 9.6	21.4 ± 11.3	23.7 ± 9.2	F <sub>2,225</sub> =1.1, p=0.35

\*Only voice-hearers were administered this questionnaire (non-clinical: N=41; clinical: N=49)

QES – Questionnaire for Evaluation of Self, BCSS – Brief Core Schema Scales, PEs – persistent psychotic experiences, SMQ – Southampton Mindfulness Questionnaires, PBQ – Parental Bonding Questionnaire

Significant differences are highlighted in bold prints

lower on bizarre behaviour and thought disorder (although these were not common in the clinical group either). On SAPS and SANS total and global scores, the non-clinical individuals had lower ratings than their clinical counterparts, although there were no significant differences on the AANEX-Inventory totals, either current or lifetime.

### Socio-demographic and environmental factors (Table 2)

The non-clinical sample differed in the predicted direction from the clinical group on 16 (+1 trend) of the 25 socio-demographic and environmental factors measured. They were less likely than the clinical group to: belong to British minority ethnic groups and be a migrant (at trend level); come from a working class background and live in areas with civic disorder (although there was no difference in terms of overall social capital); have a family history of psychosis (although not of general mental health problems). They had a higher IQ, were more educated, and more likely to be employed or in training, with higher professional grades; they were more likely to be in/have had a long-term relationship and to have children; they were less likely to use drugs.

The non-clinical participants were selected to be matched to the controls on age, gender, ethnicity and education, and therefore did not differ on those variables. In addition, they did not differ from the controls on most of the other variables examined (19 out of 23), apart from the non-clinical group having a slightly lower IQ, a greater proportion reporting being spiritual and following non-traditional religions, and to tend to take fewer drugs, than the controls.

In relation to victimization, there were no differences between the clinical and non-clinical groups in number of childhood interpersonal traumatic events, with the latter group scoring higher than the controls (although the overall group difference was at trend level only). However, the clinical individuals reported significantly more lifetime discrimination than the other two groups.

### Psychological characteristics (Table 3)

The non-clinical sample differed in the predicted direction from the clinical group on 15 of the 18 characteristics examined. Compared with the non-clinical sample, the clinical group was more anxious, depressed and stressed, reported lower self-esteem, and scored higher in negative schemas about

the self and others. Furthermore, non-clinical participants showed more self-acceptance and were more likely to perceive themselves as having positive attributes, scored higher on positive schemas about the self and others, were more satisfied with life, and scored higher on mindfulness than even the control group. They reported high psychological well-being as a result of their PEs, and non-clinical voice-hearers were more able to accept their voices and have a mindful response style than their clinical counterparts.

Although non-clinical participants were slightly more anxious than the controls, their mean score on the BAI was still within the minimal anxiety range (0-7). The only psychological domain where differences between the clinical and other groups were either absent or equivocal ( $p > 0.01$ ) was perception of parental relationships, although the clinical group had notably more individuals who did not have any kind of paternal relationship (18%) than the other two groups (non-clinical = 3%; controls = 6%).

## DISCUSSION

In the largest study of its kind, and broadly in line with our hypotheses, we found: a) a distinctive pattern of similarities and differences on individual PEs between the clinical and non-clinical groups, suggesting that some types of PEs are more benign than others; b) that specific socio-demographic and environmental factors may protect against the development of “need for care”; c) that it is possible to be psychologically and emotionally healthy while experiencing persistent PEs. These results support biopsychosocial models<sup>21,22,37</sup> that emphasize the importance of environmental and psychological factors in the aetiology of psychosis and need for care.

The main limitation of the study was that recruitment of the majority of the persistent PEs group was not implemented in an epidemiological way; rather we targeted a selective sample from specialist interest organizations, who tend to be high functioning and immersed in sub-cultural groups that are likely to provide validation and acceptance of their PEs. Therefore, our sample may not be representative of the broader group of individuals with PEs in the general population, who may be distressed by their experiences<sup>67,68</sup> and have unmet mental health needs<sup>69</sup>. While an epidemiological sample would have been preferable, this is logistically difficult as individuals with persistent, as opposed to transient, PEs are rare. Nevertheless, the aim of the present study was not to characterize a representative, general population sample with PEs, but to compare individuals with poor and good outcomes of persistent PEs, hence our results are still informative within this context.

### Types of PEs

The majority of the non-clinical group reported hearing voices in their lifetime, and hallucinations in all modalities were

common, with some types being more frequent than in the clinical group. First-rank symptoms were also reported, such as passivity experiences, thought insertion and mind reading, and there were marked ideas of reference. The experiences were far from transitory (average duration was 31 years), with an earlier age of onset than in the clinical group, replicating other studies that typically show a childhood or adolescent onset of PEs in these individuals<sup>18,19,33</sup>. There were, however, some individual positive symptoms that may be more pathological than others: voices commenting and conversing, for instance, and experiences suggesting a loss of control over one's own thoughts (such as withdrawal and broadcast), were rarely present in the non-clinical group. Furthermore, an important difference between the groups was severity: even when clear-cut positive symptoms were present, they were not as severe/frequent in the non-clinical group, suggesting that the relentlessness of such experiences may be an important factor in leading to distress and need for care<sup>70</sup>.

Participants in the non-clinical group were almost completely devoid of negative symptoms, bizarre behaviour and thought disorder, consistent with data from healthy voice-hearers<sup>33</sup>. They were also less likely to report cognitive and attentional difficulties than the clinical group, which is now a well-replicated finding<sup>17,18,39,71</sup>. These results are in line with recent evidence that positive symptoms in individuals at ultra-high-risk for psychosis are weaker predictors of transition to psychosis and a poor functional outcome than negative and disorganized symptoms<sup>72</sup>, and subjective cognitive difficulties<sup>73,74</sup>.

Finally, as predicted, non-clinical participants were much less paranoid than their clinical counterparts, and displayed relatively few delusions overall, apart from ideas of reference. The presence of PEs in the absence of delusions may be a crucial distinction between the phenomenology of non-clinical and clinical groups: other studies have also shown that a paranoid world view and threatening/maladaptive appraisals of anomalous experiences differentiate the two groups<sup>16,18,19,39</sup>, and may therefore determine whether an individual will develop a full-blown psychosis.

### Socio-demographic and environmental factors

As expected, the two PE groups were highly distinct demographically, with the non-clinical sample resembling the controls on most variables examined. Overall, non-clinical individuals were less socially disadvantaged than the psychosis patients, and had more socially-valued roles. They had greater cognitive resources than the clinical group, and reported less drug-taking than even the controls. Although it is not possible to determine direction of causality, taken together these findings suggest tentatively that a lack of social and environmental adversity may be protective against malign outcomes of PEs.

One notable exception was the prevalence of childhood trauma, which did not differ between the clinical and the non-clinical group, with the latter scoring higher than the controls. An association between childhood trauma and the presence of

PEs replicates previous findings<sup>18,34,35</sup>, although the link was weaker in this study (the overall group difference did not reach significance). Nevertheless, these results demonstrate the importance of identifying which particular types of adversity may be related to the presence of PEs<sup>36</sup>, and differentiating from those that are associated with a need for care. Our results are in line with Morgan et al's report<sup>31,32</sup> of a complex interplay between different environmental risk factors, suggesting that it is the synergy of social adversity and other factors such as drug abuse and familial risk which, in combination with exposure to childhood trauma, may push individuals beyond the threshold for psychotic disorder.

A greater proportion of the non-clinical participants (>90%) described themselves as spiritual (in a non-mainstream religious way) than both the control and clinical samples. Spirituality may be a key factor in the development of positive appraisals of PEs and in facilitating their social validation. The combination of enhanced spirituality with the above socio-demographic findings may represent a specific psychosocial buffer against the potential noxious impact of persistent PEs; or, put another way, it is likely that persistent PEs only become problematic in the context of pre-existent vulnerabilities, as suggested by contemporary aetiological models of psychosis<sup>21,22,37</sup>.

## Psychological characteristics

Participants in the non-clinical group did not report current emotional problems, had intact self-esteem, displayed self-acceptance and healthy schemas about self and others, and showed high life satisfaction. They were indistinguishable from the controls on any measure, apart from being slightly more anxious, although their BAI score was still within the minimal anxiety range. Findings about parental relationships were more equivocal, with a tendency for the non-clinical group to report being more likely to have a paternal relationship, and to perceive their parents as less overprotective, than the clinical group. These results require replication, potentially with a more robust measure of attachment<sup>75</sup>.

The non-clinical group reported relating more mindfully to voices than the clinical group, and to potentially distressing internal events than even the control group. Similarly to spirituality, a mindful response style may therefore represent a protective factor against problematic outcomes of PEs. Overall, these findings provide robust evidence that even persistent PEs are not necessarily associated with mental ill-health, at least in individuals who present with a range of protective environmental and psychological factors.

## Clinical implications

Our findings have potential implications for the clinical management of people with PEs, including individuals at ultra-high-risk for psychosis. Psychological therapies (including cognitive behaviour therapy for psychosis and third-wave

therapies such as acceptance and commitment therapy and mindfulness) all have a normalizing and accepting approach to PEs as a central tenet<sup>76,77</sup>. Since PEs can occur without pathological outcomes, the aim of therapy may not necessarily be to eliminate such experiences, but to appraise them in a less threatening and paranoid way, or to deal with them differently<sup>78</sup>. These results also have clear implications for ultra-high-risk services. Whilst traditionally the diagnosis of the high risk state has been heavily weighted towards the presence of positive PEs, the lack of negative symptoms and subjective cognitive deficits in the non-clinical sample is consistent with recent evidence that these features are particularly associated with an increased risk of transition to psychosis<sup>79</sup>. Importantly, psychological and emotional problems were shown to be key factors in differentiating the groups, confirming that they merit intervention in their own right<sup>80</sup>, whether they are the consequences of, or contributors to, PEs<sup>81-83</sup>.

We hope that these findings will pave the way for a paradigm shift in psychosis research, which has traditionally been overly focused on illness models and identifying risk factors/biomarkers for disease states, to looking at protective factors and determinants of well-being in the context of PEs<sup>84</sup>.

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# Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records

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*It is unclear which maintenance treatment for bipolar disorder is superior in clinical practice. Randomized controlled head-to-head trials of available drugs either do not exist or are inconclusive. We aimed to compare rates of monotherapy treatment failure in individuals prescribed lithium, valproate, olanzapine or quetiapine by a population-based cohort study using electronic health records. 5,089 patients with bipolar disorder were prescribed lithium (N=1,505), valproate (N=1,173) olanzapine (N=1,366) or quetiapine (N=1,075) as monotherapy. Treatment failure was defined as time to stopping medication or add-on of another mood stabilizer, antipsychotic, antidepressant or benzodiazepine. In unadjusted analyses, the duration of successful monotherapy was longest in individuals treated with lithium. Treatment failure had occurred in 75% of those prescribed lithium by 2.05 years (95% CI: 1.63-2.51), compared to 0.76 years (95% CI: 0.64-0.84) for those prescribed quetiapine, 0.98 years (95% CI: 0.84-1.18) for those prescribed valproate, and 1.13 years for those prescribed olanzapine (95% CI: 1.00-1.31). Lithium's superiority remained in a propensity score matched analysis; when treatment failure was defined as stopping medication or add-on of a mood stabilizer or antipsychotic; and when treatment failure was restricted to more than three months after commencing the study drug. Lithium appears to be more successful as monotherapy maintenance treatment than valproate, olanzapine or quetiapine. Lithium is often avoided because of its side effect profile, but alternative treatments may reduce the time to being prescribed more than one drug, with potential additive side effects of these treatments.*

**Key words:** Bipolar disorder, maintenance treatment, lithium, valproate, olanzapine, quetiapine, electronic health records, cohort study

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Bipolar disorder is a lifelong recurrent illness with high rates of hospitalization, suicide and comorbidity<sup>1</sup>. It is the sixth most common cause of disability in the world, responsible for the loss of more disability-adjusted life years than all forms of cancer or major neurological conditions such as epilepsy and Alzheimer's disease<sup>2</sup>. Long-term drug treatment is often required to prevent relapse or recurrence. Even with treatment, the proportion of people who remain in remission is low<sup>3</sup>.

A number of drug treatments are recommended for maintenance in bipolar disorder. In the UK, the most commonly used medications are lithium, valproate, olanzapine and quetiapine<sup>4</sup>. This reflects previous National Institute for Health and Care Excellence (NICE) guidance on first-line monotherapy maintenance treatment, which suggested equivalence of these drugs<sup>5</sup>. Globally, there is a range of prescribing advice, which includes additionally lamotrigine, carbamazepine, oxcarbazepine, aripiprazole and other second generation antipsychotics<sup>6–8</sup>. Recent meta-analyses and network meta-analyses have highlighted the superiority of lithium<sup>9,10</sup>, and these results have contributed to the change in NICE guidance in September 2014, where lithium is presented as first line<sup>11</sup>. However, no randomized controlled trial (RCT) has conclusively proved the benefit of lithium over other drugs, and there are no trials that compare valproate vs. olanzapine, valproate vs. quetiapine or olanzapine vs. quetiapine directly.

The applicability of RCT results to people with bipolar disorder in the real world may be limited by the exclusion criteria adopted in those trials, and by diagnostic heterogeneity, diagnosis or treatment rejection, and complex presentations of the

illness occurring over the life course<sup>12,13</sup>. These concerns have been raised when considering RCTs in other areas of medicine: applying their results to managing a lifelong illness of unpredictable course is not straightforward<sup>14,15</sup>. Necessary trials are also costly and difficult to run for sufficient periods in relation to the time course of bipolar disorder<sup>16</sup>. Electronic health records offer an opportunity to augment RCT findings with head-to-head comparison studies which include large numbers of patients, representative of real world clinical practice, and long follow-up periods.

Using data from a large UK primary care database, The Health Improvement Network (THIN), we aimed to compare rates of stopping medication or add-on of another psychotropic drug in individuals prescribed lithium, valproate, olanzapine or quetiapine as maintenance monotherapy for bipolar disorder. This outcome represents a combination of both effectiveness and tolerability of the study medication, and is similar to that used in many RCTs of maintenance treatment for bipolar disorder<sup>9,10</sup>.

## METHODS

### Study design and setting

This was a prospective study of primary care data collected between January 1, 1995 and December 31, 2013. The scheme for THIN was approved by the National Health Service South-

East Multicentre Research Ethics Committee, and scientific approval for this study was obtained from Cegedim Strategic Data (CSD) Medical Research's Scientific Review Committee.

THIN is a UK primary care database that contains anonymized patient information from routine clinical consultations<sup>17</sup>. General practitioners (GPs) use Read codes, a hierarchical coding system, to record information in THIN<sup>18</sup>. These codes include diagnoses (which map onto ICD-10 codes), symptoms, examination findings, referrals, test results and information from hospital specialists, creating a longitudinal record for each patient<sup>19</sup>. In the UK, GPs are responsible for issuing all drug prescriptions if treatment is ongoing, following advice from a psychiatrist, and this information is also available<sup>20</sup>.

At the time this cohort was extracted, THIN contained records for over 11 million people<sup>17</sup>. Patients in the database have been shown to be broadly representative of the UK population, and GPs contributing data have been shown to be representative in terms of consultation and prescribing statistics<sup>21,22</sup>. Approximately 98% of the UK population is registered with a GP practice<sup>23</sup>. The incidence rate of bipolar disorder in THIN has been shown to be similar to other European cohorts<sup>24</sup>, and validity of severe mental illness diagnoses held in primary care has been established<sup>25</sup>.

## Participants

Patients with a diagnosis of bipolar disorder were included if they had at least one 28-day prescription of lithium, valproate, olanzapine or quetiapine after January 1, 1995, or after the date at which the GP practice met quality assurance criteria for data entry (based on computer usage and mortality recording rates)<sup>26,27</sup>. Patients were excluded if they received a diagnosis of schizophrenia at any time. They were also excluded if they were prescribed another of the study drugs, or any other mood stabilizer, antipsychotic, antidepressant or benzodiazepine at the start of follow-up, or in the month before this. The cohort was therefore one in which the intention was to treat with lithium, valproate, olanzapine or quetiapine monotherapy. Patients were censored at date of death, leaving the GP practice or the end of the study period (December 31, 2013).

## Main outcome

Patients were followed up until they stopped the study drug, or had a mood stabilizer, an antipsychotic, an antidepressant or a benzodiazepine added to their treatment regimen. Date of first prescription was taken as the start of exposure time. The end of the prescription was calculated from the prescription length and prescribing instructions coded by the GP.

Patients were considered to have a period of continuous prescribing if another prescription for the same drug was

issued within three months of the predicted end date. If this did not occur, the date of stopping the study drug was the end date of the final prescription.

## Observed pre-treatment variables for propensity score estimation

Socio-demographic, psychiatric and physical health characteristics at baseline were extracted from each patient's electronic health record. Psychiatric and physical health problems were considered present if referenced in the patient notes. If a patient had multiple entries of the same (or similar) Read codes, the start date of the condition was taken as the earliest date of entry.

A propensity score (PS) for each individual was estimated using variables defined *a priori*, based on existing research<sup>28,29</sup>. The PS attempts to account for all of the covariates that predict receiving a particular study drug<sup>29,30</sup>. The PS was then checked by comparison of covariate balance across treatments, within strata. The included variables were: gender; age at start of treatment with the study drug; year of entry to the cohort; ethnicity (grouped as White, Black, Asian, mixed, other, with missing values coded as White); physical health history at baseline (ischemic heart disease, myocardial infarction, cerebrovascular event, hypertension, renal disease, thyroid disease, liver disease, type 2 diabetes mellitus, epilepsy, history of alcohol dependence, history of illicit drug use); smoking status (grouped as never-smoker, ex-smoker, current smoker); body mass index (BMI) (grouped as healthy weight, overweight (BMI 25 to 30), obese (BMI over 30)); mental health history at baseline (history of anxiety symptoms, hypomania as most proximal diagnosis code, history of depressive symptoms, sleep disturbance, previous treatment with the study drug before baseline, incident diagnosis of bipolar disorder); and clustering by GP practice. These variables were selected because they represent factors influencing prescribing choice (such as risk factors for adverse effects with a particular study medication)<sup>11</sup>.

Although PS estimation cannot remove all bias, it has been postulated to also reduce confounding from unmeasured variables, because of their association with measured covariates<sup>31,32</sup>. Therefore in this study, for a given PS, exposure to lithium, valproate, olanzapine or quetiapine is presumed to have been at random<sup>33</sup>.

## Statistical analysis

Cox regression analyses were conducted comparing the rates of stopping the study drug or add-on of another psychotropic medication in the four treatment groups. Analyses were adjusted for gender, age, ethnicity and calendar year. Time to treatment failure was summarized by Kaplan-Meier curves. The proportional hazards model was tested formally with analysis of Schoenfeld residuals<sup>34</sup>.



**Table 1** Characteristics of patients with bipolar disorder prescribed lithium, valproate, olanzapine or quetiapine monotherapy

	Lithium	Valproate	Olanzapine	Quetiapine
Patients	1,505	1,173	1,336	1,075
Female, N (%)	860 (57.1)	631 (53.8)	733 (54.9)	735 (68.4)
Age at entry to the cohort, median (IQR)	44.9 (35.4-58.7)	41.6 (31.4-53.7)	40.9 (31.9-52.7)	38.5 (29.3-49.8)
Total years of follow-up, median (IQR)	4.2 (1.5-8.6)	3.0 (1.1-6.3)	3.6 (1.4-6.9)	2.1 (0.9-3.9)
GP practice contacts per year of follow-up, median (IQR)	12.1 (7.1-19.7)	14.8 (8.7-23.7)	14.3 (8.8-24.6)	17.9 (11.8-26.9)
Non-White ethnic background, N (%)	44 (2.9)	50 (4.3)	65 (4.9)	35 (3.3)
Health at baseline, N (%)				
Ischemic heart disease, myocardial infarction, cerebrovascular event history	76 (5.0)	80 (6.8)	58 (4.3)	41 (3.8)
Renal disease history	51 (3.4)	36 (3.1)	33 (2.5)	42 (3.9)
Thyroid disease history	161 (10.7)	89 (7.6)	89 (6.7)	75 (7.0)
Diabetes	77 (5.1)	87 (7.4)	42 (3.1)	71 (6.6)
Epilepsy	29 (1.9)	82 (7.0)	37 (2.8)	34 (3.2)
Obesity (BMI>30)	617 (41.0)	488 (41.6)	482 (36.1)	467 (43.4)
Previous anxiety symptoms	98 (6.5)	102 (8.7)	133 (10.0)	154 (14.3)
Previous alcohol dependence	7 (0.5)	3 (0.3)	12 (0.9)	7 (0.6)
Current smoker	518 (34.4)	462 (39.4)	571 (42.7)	425 (39.5)
Bipolar disorder characteristics at baseline, N (%)				
Incident diagnosis	318 (19.6)	396 (34.0)	543 (41.7)	416 (40.8)
Previous depressive episode	845 (56.1)	701 (59.8)	826 (61.8)	788 (73.3)
Hypomania as most recent diagnosis	234 (15.5)	154 (13.1)	238 (17.8)	125 (11.6)
Previous record of taking study drug	936 (62.2)	507 (43.2)	463 (34.7)	328 (30.5)

GP – general practitioner, IQR – interquartile range, BMI – body mass index

The PS was calculated using multinomial logistic regression using the covariates described as independent variables, with drug treatment as the dependent variable. The PS was then used as a linear term in a Cox regression analysis that also included age and calendar year<sup>35</sup>. This model was shown to be superior to stratifying on PS using Akaike information criterion and Bayesian information criterion<sup>36</sup>, and was a more efficient use of data than PS matching, because it uses all patients.

Analysis using PS matching was then completed. Although matched analyses may include a non-representative sample of patients receiving treatment, they may provide a more valid

estimate of treatment effect as they compare patients with similar observed characteristics<sup>35,37</sup>. Pairwise matching was performed for each patient in the valproate, olanzapine and quetiapine groups with individuals in the lithium treated group. Patients were matched on a one-to-one basis if their PS was within 0.01 of each other; all other patients were dropped from the analysis.

Supplementary analyses excluding benzodiazepine and antidepressant add-on as a source of treatment failure were carried out. A supplementary analysis excluding patients who stopped the study drug or had psychotropic medication

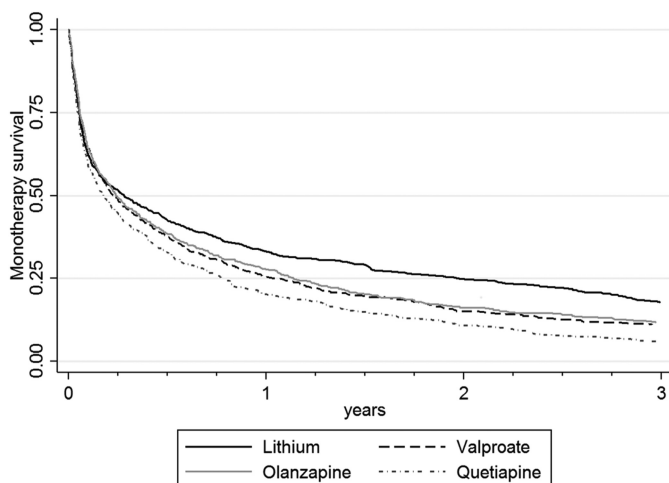
**Table 2** Rates of treatment failure by drug

	N events	Person years at risk	Rate per 100 person years at risk	Treatment failure, hazard ratio (95% CI)			
				Unadjusted	Model 1	Model 2	Model 3
Lithium	1,151	1,570	73.3 (65.5-81.8)	1	1	1	1
Valproate	909	777	116.9 (102.9-132.4)	1.25 (1.14- 1.37)	1.22 (1.11-1.34)	1.19 (1.09-1.31)	1.20 (1.10-1.32)
Olanzapine	977	893	109.4 (96.3-123.7)	1.19 (1.08-1.30)	1.19 (1.08-1.30)	1.16 (1.05-1.28)	1.17 (1.07-1.29)
Quetiapine	814	457	177.9 (157.9-199.8)	1.48 (1.35-1.62)	1.31 (1.19-1.44)	1.30 (1.18-1.44)	1.32 (1.20-1.45)

Model 1: adjusted for clustering by primary general practitioner (GP) practice, age, gender and calendar year

Model 2: adjusted for propensity score, clustering by GP practice, age and calendar year

Model 3: propensity score matched (pairwise matching with lithium) adjusted for clustering by GP practice, age and calendar year



**Figure 1** Time to treatment failure (stopped treatment or add-on of mood stabilizer, antipsychotic, antidepressant or benzodiazepine) (unadjusted)

added-on within the first three months of follow-up was also performed.

All analyses were completed using STATA 13<sup>38</sup>.

## RESULTS

A total of 14,396 individuals had a diagnosis of bipolar disorder. Of these, 5,089 were prescribed monotherapy with one of the study drugs at the start of cohort follow-up: lithium was prescribed to 1,505 people, valproate to 1,173, olanzapine to 1,366 and quetiapine to 1,075 people. Individuals prescribed lithium tended to be older than other groups, with more years of follow-up data and fewer GP practice contacts during this period. They were less likely to have a previous record of depression in their notes and less likely to be an incident case (Table 1).

In unadjusted analyses, the overall rate of treatment failure was increased for valproate, olanzapine and quetiapine when compared to lithium (Table 2). Treatment failure had occurred in 75% of those prescribed lithium by 2.05 years (95% CI: 1.63-2.51), compared to 0.76 years (95% CI: 0.64-0.84) for those prescribed quetiapine, 0.98 years (95% CI: 0.84-1.18) for those prescribed valproate, and 1.13 years for those prescribed olanzapine (95% CI: 1.00-1.31). The median time to treatment fail-

ure in the lithium monotherapy group was 0.28 years (95% CI: 0.23-0.35), compared to 0.17 years (95% CI: 0.14-0.21) in the quetiapine group, 0.22 years (95% CI: 0.19-0.27) in the valproate group, and 0.24 years (95% CI: 0.21-0.28) in the olanzapine group. The differences between treatments became more apparent the longer the duration of treatment (Figure 1).

Lithium's superiority remained after adjustment for clustering by GP practice, age, gender, calendar year, and ethnicity. It also remained after adjusting for PS, age and calendar year, and after matching by PS (Table 2), with olanzapine having the least elevated hazard ratio (HR) (1.16, 95% CI: 1.05-1.28). Compared to olanzapine, quetiapine had an increased rate of monotherapy failure (HR 1.12, 95% CI: 1.02-1.23) in the PS adjusted model. Compared to valproate, olanzapine and quetiapine had similar rates of treatment failure (HR 0.97, 95% CI: 0.89-1.06 and HR 1.09, 95% CI: 0.99-1.19, respectively). The proportional hazards assumption held for all analyses. Before pairwise matching, PS scores were most different for lithium (median 0.45, interquartile range, IQR 0.25-0.61) and quetiapine (median 0.14, IQR 0.08-0.25). After matching, the median PS was 0.21 (IQR 0.13-0.30) for lithium and 0.14 for quetiapine (IQR 0.08-0.25).

Individuals prescribed lithium or valproate were more likely to require antipsychotic add-on (19.53% and 18.41%, respectively) than those prescribed olanzapine or quetiapine monotherapy (10.25% and 9.02%, respectively). Conversely, individuals prescribed olanzapine and quetiapine were more likely to require mood stabilizer add-on (14.07% and 12.56%, respectively) compared to lithium and valproate (6.71% and 5.20%, respectively).

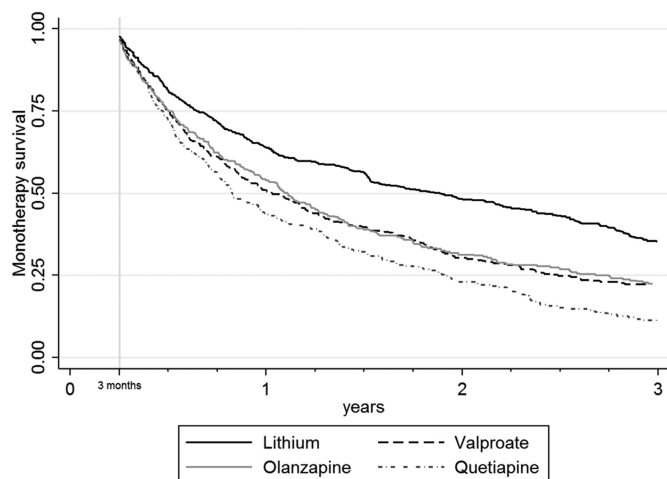
Supplementary analyses produced similar results to the primary analyses. If treatment failure was restricted to stopping the study drug or add-on of a mood stabilizer or antipsychotic medication, PS adjusted HRs were elevated for all drugs compared to lithium (Table 3). The same was true if patients failing in the first three months of follow-up were excluded from the analysis (Table 3, Figure 2).

## DISCUSSION

As far as we are aware, this study represents the only head-to-head comparison of the four most common maintenance treatments for bipolar disorder, and has the longest follow-up

**Table 3** Supplementary analyses using propensity score adjusted model

	Treatment failure, hazard ratio (95% CI)		
	Excluding benzodiazepine add-on	Excluding benzodiazepine and antidepressant add-on	Excluding failures in the first three months of treatment
Lithium	1	1	1
Valproate	1.25 (1.14-1.37)	1.18 (1.08-1.29)	1.22 (1.06-1.40)
Olanzapine	1.10 (1.00-1.22)	1.17 (1.07-1.28)	1.26 (1.09-1.45)
Quetiapine	1.25 (1.13-1.38)	1.15 (1.03-1.25)	1.20 (1.04-1.40)



**Figure 2** Time to treatment failure (excluding failures in the first three months of treatment) (unadjusted)

and largest cohort of any direct comparison of treatments for bipolar disorder. RCTs making these comparisons do not exist and are unlikely to be conducted.

The overall rate of treatment failure (represented by stopping index medication or requiring add-on of a mood stabilizer, antipsychotic, antidepressant or benzodiazepine) was increased for valproate, olanzapine and quetiapine when compared to lithium. This was also true if failures within the first three months were excluded (i.e., once the patient had been stabilized on the prescribed drug). These results suggest that monotherapy with lithium may be more successful than the other recommended drugs. The rate of treatment failure was also elevated for quetiapine compared to olanzapine, while it was not possible to separate the other drugs from each other.

The use of contemporaneous, representative medical records avoided the risk of potential biases relating to selection into the study. Information bias should partially have been avoided by the use of prescribing data as exposure: in the UK, GPs are responsible for all ongoing prescribing within the national health system<sup>20</sup>, which is detailed and well recorded in THIN. However, exposure to the study drug was approximated through prescriptions issued to patients, and may not reflect how the patient used the medication. Poor adherence to prescribed drug regimens is a problem with all medications, and this is particularly true if side effects are unpleasant, as can be the case with all of the study drugs<sup>39,40</sup>. In this study, stopping the drug will be reflected in the outcome, but erratic adherence cannot be detected. It is possible that erratic adherence is more likely for drugs other than lithium (as this is more closely monitored through regular blood tests). This may have contributed to lithium's perceived superiority, but we found that patients prescribed lithium had fewer GP contacts, and other longitudinal cohort studies have not shown differential adherence<sup>40</sup>.

Treatment failure was defined as stopping the study drug or add-on of any mood stabilizer, antipsychotic, antidepressant or benzodiazepine. It is likely that addition of a mood stabilizer

or antipsychotic represents more serious treatment failure than addition of an antidepressant (which would only occur during a depressive relapse) or a benzodiazepine (which may be used short term to avoid a relapse). A supplementary analysis excluding addition of these drugs had similar results. It may be the case that both of these outcomes fail to capture what is important to patients in terms of relapse, recurrence, functioning and quality of life. However, through examining monotherapy treatment failure, we believe we have described a proxy for these important outcomes which captures both tolerability and effectiveness and highlights very common need for adjunctive drug treatments. This outcome has also been used in a number of RCTs of maintenance drug treatment for bipolar disorder and therefore comparison with these results is possible. For example, the largest trial of lithium vs. valproate treatment had a primary outcome of "time to new intervention for an emerging mood episode"<sup>41</sup>. This trial found similar results to our study (HR 1.41, 95% CI: 1.00-1.92), but was not powered to directly compare lithium and valproate.

A limitation of interpretation of data from cohort studies is the inability to rule out important confounding effects. We attempted to account for confounding by indication by building a PS model that included important clinical predictors of treatment allocation<sup>30</sup>. This included physical health variables which may lead a clinician to avoid a certain drug because of its side effect profile, e.g. renal disease with lithium or cardiovascular disease with olanzapine. Characteristics such as gender, age and BMI were also included, as valproate is contraindicated (though commonly prescribed) in women of child-bearing potential<sup>5</sup>, and olanzapine has the potential to cause rapid weight gain<sup>42</sup>. Adjusting for the GP practice should account for physician preference for a particular drug. Once these covariates were adjusted for, there was a similar propensity for patients to be prescribed valproate, olanzapine or quetiapine, with patients prescribed lithium having slightly higher scores. Despite this, we cannot rule out the possibility that these confounders were imperfectly adjusted for, or that other important confounders were not included in the PS model.

Unfortunately, we were unable to separate treatment failure relating to emergent manic (or hypomanic) episodes from depressive episodes, and there is evidence that the study drugs may be differentially effective in preventing a particular polarity of illness<sup>9</sup>. However, an ideal "mood stabilizer" would protect against both polarities of relapse<sup>43</sup>, and this is what our study captures. We were also unable to examine the physician's reason for treatment initiation, and it may be that quetiapine's apparent inferiority is because in some patients it is prescribed as maintenance treatment, but for shorter term indications (which we hoped to capture in the supplementary analysis). There were too few patients on monotherapy with other recommended maintenance treatments, such as lamotrigine or aripiprazole, to include these drugs in the analysis.

In conclusion, this study provides necessary supplementary and complementary evidence to RCT findings for maintenance treatments for bipolar disorder. In real world clinical

practice, lithium appears to be the most effective treatment to prevent relapse or recurrence of bipolar disorder and may prolong the time before adjunctive prescribing is necessary. This finding echoes the results of recent meta-analyses that suggest lithium is superior to other drugs in protecting against both manic and depressive relapse<sup>9,10</sup>. This is important as lithium is often avoided because of its side effect profile<sup>44</sup>, but monotherapy with valproate, olanzapine or quetiapine is more likely to fail sooner and may result in patients experiencing the additive side effects of multiple psychotropic drugs.

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# Bereavement after sibling death: a population-based longitudinal case-control study

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*The objective of this study was to examine mental disorders and treatment use among bereaved siblings in the general population. Siblings (N=7243) of all deceased children in the population of Manitoba, Canada who died between 1984 and 2009 were matched 1:3 to control siblings (N=21,729) who did not have a sibling die in the study period. Generalized estimating equations were used to compare the two sibling groups in the two years before and after the index child's death on physician-diagnosed mental disorders and treatment utilization, with adjustment for confounding factors including pre-existing mental illness. Analyses were stratified by age of the bereaved (<13 vs. 13+). Results revealed that, in the two years after the death of the child, bereaved siblings had significantly higher rates of mental disorders than control siblings, even after adjusting for pre-existing mental illness. When comparing the effect of a child's death on younger versus older siblings, the rise in depression rates from pre-death to post-death was significantly higher for siblings aged under 13 (p<0.0001), increasing more than 7-fold (adjusted relative rate, ARR=7.25, 95% CI: 3.65-14.43). Bereaved siblings aged 13+ had substantial morbidity in the two years after the death: 25% were diagnosed with a mental disorder (vs. 17% of controls), and they had higher rates of almost all mental disorder outcomes compared to controls, including twice the rate of suicide attempts (ARR=2.01, 95% CI: 1.29-3.12). Siblings in the bereaved cohort had higher rates of alcohol and drug use disorders already before the death of their sibling. In conclusion, the death of a child is associated with considerable mental disorder burden among surviving siblings. Pre-existing health problems and social disadvantage do not fully account for the increase in mental disorder rates.*

**Key words:** Sibling, bereavement, epidemiology, depression, suicide, mental disorder

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Most children have a sibling<sup>1</sup>. While fertility rates are lower in Western nations and family sizes have diminished in recent decades, the majority of households with children in the U.S. in 2010 had two or more children<sup>2</sup>. Each year more than 40,000 children and adolescents die in the U.S., leaving a substantial number of bereaved siblings<sup>3</sup>.

Sibling bereavement is an experience with a very sparse literature and thus the consequences of losing a sibling are unclear. A series of Swedish national cohort studies revealed increased mortality of bereaved siblings when compared to non-bereaved controls<sup>4-8</sup>. These analyses, however, were restricted to adult sibling populations and did not examine outcomes other than death.

Other smaller studies have examined bereavement experiences related to specific causes of sibling death, namely cancer and suicide, with mixed findings<sup>9-12</sup>. One study of cancer-related bereavement showed no differences in anxiety and depression between bereaved and non-bereaved siblings<sup>13</sup>, while other descriptive case series found anxiety, substance misuse, depression, and social difficulties among bereaved siblings<sup>14-16</sup>.

Taken together, the extant literature suggests that sibling bereavement is an emotionally damaging experience and may result in premature death. However, the vast majority of studies are limited by sampling bias and small numbers of subjects, and many lack a control group. As such, the true impact of losing a sibling remains unknown.

The current study sought to extend the understanding of this experience by examining, for the first time, the mental health outcomes of bereaved siblings in the general population. Furthermore, by focusing on siblings of decedents who were under age 18 and examining relatively short time frames (two years before and after the death), it was designed to capture emotional consequences in the period of acute grief among siblings who were likely still living in the same dwelling as the deceased child.

Through the use of validated physician-generated diagnoses, non-bereaved matched controls, longitudinal follow-up, and a representative dataset of a population with universal access to free medical care, this study was able to overcome many of the limitations of prior research. We hypothesized that bereaved individuals would have elevated rates of depression and anxiety within two years following the death of their sibling when compared to controls and to pre-death rates.

## METHODS

### Data sources

The data in this study were drawn from the Population Health Research Data Repository at the Manitoba Centre for Health Policy at the University of Manitoba in Canada. The repository contains health, Census, Vital Statistics, and other

social databases for the 1.2 million residents in the province of Manitoba. Individual-level data are linked through these datasets by a personal health information number that is scrambled to ensure anonymity. Linkage accuracy in the databases is excellent<sup>17</sup>.

The following data sources were included in this study: physician claims (providing diagnoses for mental and physical disorders from virtually all physician contacts), hospital discharge abstracts (inpatient admission contacts and disorders), population registry (age, sex, region of residence, specification of family structure), Statistics Canada Census data (income quintile), and Vital Statistics (mortality data).

Manitoba provides universal free medical care to all residents, and thus virtually all persons in the population are included in the datasets; exceptions include active military personnel and incarcerated persons. The study period was 1984-2009, based on completeness of the available data for that period, and was approved by the University of Manitoba research ethics board.

### Cohort formation

Figure 1 presents a flowchart that describes how the cohort of bereaved siblings was composed. All children under the age of 18 who died in Manitoba during the study period were identified from the Vital Statistics dataset. If several children in a family died, only the first was included in the study and considered the index death. Using the shared family registration number, only decedents with a sibling at time of death were included in the study.

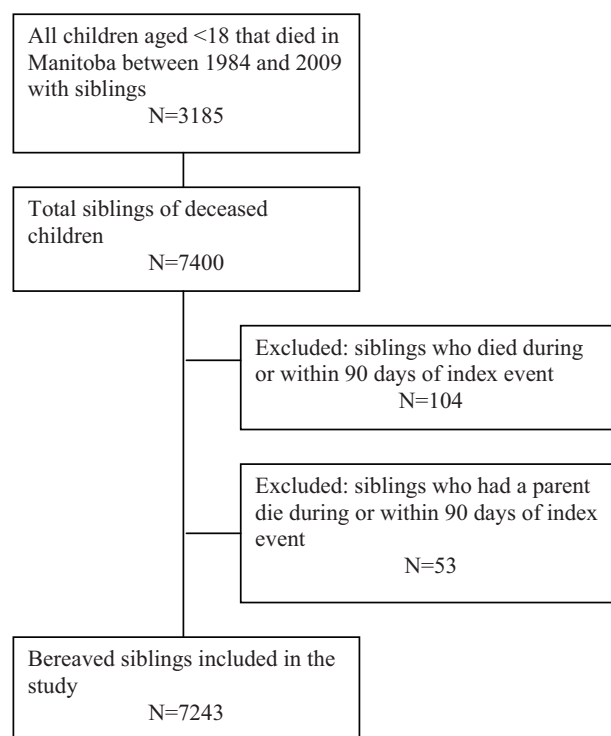
Seven thousand four hundred bereaved siblings were identified. Siblings who died during the same index event (e.g., a house fire) or within 90 days of the index death were excluded (N=104), along with siblings who suffered the death of a parent during or within 90 days of the index event (N=53). This resulted in a bereaved cohort of 7,243 siblings. Of this group, 59 had lost multiple siblings in the same index event. In families where there was more than one surviving sibling, all were included in the bereaved sibling cohort.

These bereaved siblings were matched 1:3 to non-bereaved siblings based on sex and age at date of death (date of death=index date), relation (brother, sister), age ( $\pm 3$  years), family income quintile, and region of residence at the index date. Control siblings were excluded if they had suffered the loss of a sibling or parent at any point between 1984 and two years after the index date, or if they died within 90 days of the index date. There were 21,729 non-bereaved siblings included in analyses.

### Outcomes of interest

#### Mental disorders

The conditions of interest included depression (unipolar and bipolar), anxiety disorders, alcohol use disorders, drug use



**Figure 1** Development of bereaved sibling cohort

disorders, attention deficit hyperactivity disorder (ADHD), and suicide attempts. “Any mental disorder” included all people who met criteria for any of the above disorders. These disorders were defined using ICD-9 Clinical Modification (ICD-9-CM) and ICD-10 Canada (ICD-10-CA) codes derived from inpatient hospital discharge abstracts and outpatient physician billing records, and were coded using previously validated disorder definitions<sup>18</sup>.

Based on previous work, the time periods for calculating the rates of these disorders were the two years prior to index date and the two years after index date<sup>19</sup>.

#### Health service utilization

There were four types of health service use examined. These included two measures of outpatient services (outpatient physician visits for mental health or for any reason) and two measures of inpatient admissions (hospitalization for mental health or for any reason).

Rates of each type of service use were based on the total sum of contacts within each sibling group during each time period of interest. Hospitalization was based on spending more than one day in hospital and did not include hospitalization for birth.

#### Covariates

The following variables were included as covariates: whether the bereaved sibling was the only remaining offspring in the

family (vs. 2+ remaining offspring), sibling sex (brother, sister), sibling marital status (married, single), low income, age of index child at time of death (0-4, 5-17), age of sibling at time of index child's death (0-4, 5+), presence of any previously diagnosed mental disorder (yes, no), and presence of any previously diagnosed physical disorder (yes, no).

Physical conditions examined in this study included cardiovascular disease, cancer, asthma, and diabetes. Validated definitions from previous studies were used to establish physical disease presence<sup>20</sup>.

Family income level was calculated by aggregating household income based on dissemination areas in Census data, and then grouping them into five income quintiles (1 being poorest and 5 being wealthiest)<sup>21</sup>. Each quintile contains approximately 20% of the population. Individuals who could not be assigned an income quintile from Census data were assigned to the unknown group (e.g., people in prison). Low income was defined as quintiles 1 and unknown (vs. the remaining four quintiles combined as the reference group).

## Statistical analysis

Analyses were conducted using SAS version 9.3. Chi-square tests were used to compare characteristics of bereaved and non-bereaved sibling controls across demographic and social measures. Outcomes of interest were compared using adjusted relative rates (ARR) obtained from a generalized estimating equation model using negative binomial or Poisson distributions.

The initial set of analyses examined only bereaved siblings, comparing rates of outcomes in the two years after the death of the index child to rates in the two years before the death. Based on disorder rate differences in children and adolescents, an interaction term for age (13+ vs. <13) by time period (post- vs. pre-death) was introduced in the model. Significance of the interaction term guided the need for age-stratified analyses.

The second set of analyses compared bereaved and non-bereaved siblings on outcome rates across time periods (post-index date vs. pre-index date). These analyses were likewise stratified by age. An interaction term of sibling group (bereaved vs. non-bereaved) by time period (pre-index date vs. post-index date) was included in the models as a method to account for rates in the pre-index date period. The interaction between sibling groups across the time periods effectively compares the rate changes between the two groups across time, therefore controlling for conditions present prior to the death/index date.

Relative rates in all analyses were adjusted for the above-listed covariates, conditionally entered into models based on the outcome of interest and model fit.

## RESULTS

The characteristics of the children decedents and siblings are provided in Table 1. Of the 7,243 siblings of interest, there was an almost equal split of bereaved brothers and sisters. The

majority of bereaved siblings (and hence income-matched controls) were from financially disadvantaged families, with 3,102 (43%) being in the lowest income quintile. Sixty-two percent (N=1,961) of the deceased children died under the age of 5, with a median age of 1.4. The leading cause of death was accidents. Diseases in infancy (perinatal conditions, congenital abnormalities) also accounted for many deaths. The bereaved siblings ranged in age from 0 to 39 years, with a median age of 8 years and 95% of the sample being under age 24.

Adjusted mental disorder prevalence among bereaved and control siblings in the pre- and post-death/index periods is presented in Figure 2. The percentage of bereaved siblings with any physician-diagnosed mental disorder rose from 4.9 to 8.0 after the death. Corresponding prevalence figures among control siblings were 4.0% before index date and 5.3% afterwards. This rate change across the time periods among bereaved siblings was significantly greater than the rate change among control siblings (pre-post x sibling group interaction term:  $p < 0.001$ ). Twenty-five percent of the 13+ age group were diagnosed with a mental disorder in the two-year period after the death of their sibling, compared to 16.5% of control siblings.

Table 2 compares outcomes in the two years after sibling death to the two years prior among the bereaved group. Significant age interactions were noted for outcomes of depression, ADHD, any mental disorder, physician visit for mental illness, and physician visit or hospitalization for any reason. While both age groups had elevated rates of depression in the post-death period, siblings under 13 years of age showed a more than 7-fold increased rate compared to the pre-death period (ARR=7.25, 95% CI: 3.65-14.43), and this rate increase was significantly greater than the rate doubling observed in the 13+ age group (ARR=2.27, 95% CI: 1.89-2.73, interaction  $p < 0.0001$ ). Bereaved siblings under 13 years of age also had increased rates of anxiety disorders, ADHD, and any mental disorder. The under-13 age group had 3-fold rate increases in physician visits and hospitalizations for mental illness, but less health care service utilization in general. Similar findings in mental disorder outcomes were observed in bereaved siblings aged 13+, albeit with smaller magnitudes. Differences in this age group were the 40% increased risk of drug use disorders in the post-death period (ARR=1.40, 95% CI: 1.11-1.76), and the likelihood of ADHD reduced by half (ARR=0.47, 95% CI: 0.29-0.77).

Table 3 displays the comparison between bereaved and non-bereaved siblings across the pre- and post-index date, by age group. For the pre-adolescent sibling group, bereavement was associated with significant rate increases in depression, any mental disorder, outpatient physician visits for mental illness, and physician visits and hospitalization for any health reason (based on significant interaction terms). Bereaved siblings had higher rates of depression in the two years after the death compared to controls (ARR=2.71, 95% CI: 1.94-3.79). The significant interaction analysis ( $p < 0.0001$ ) accounts for pre-death depression rates and confirms that these higher post-death depression rates among bereaved siblings also indicate a pre-post rate increase that is significantly different

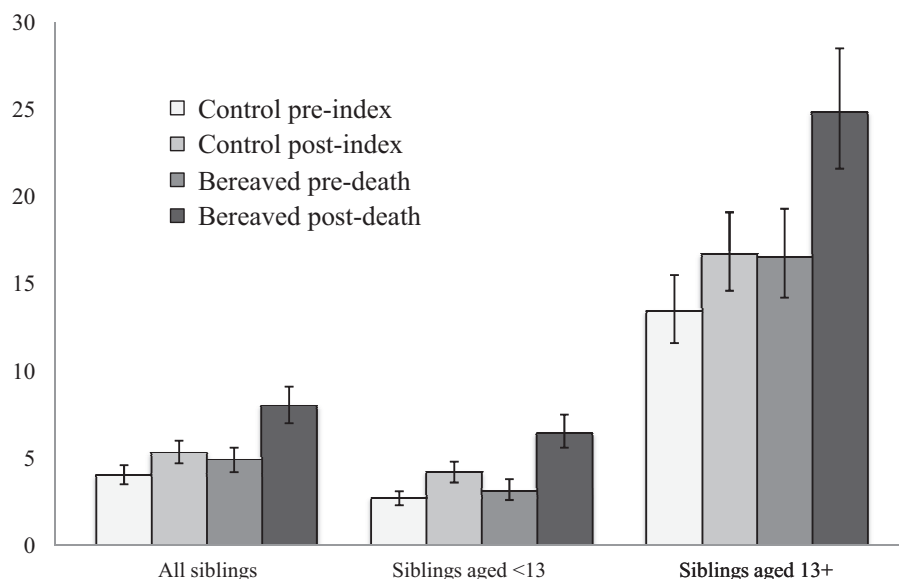
**Table 1** Characteristics of index children and sibling groups

	Index children (N=3,185)		
Age of index child at death (years)			
Mean ± SD	5.6 ± 6.7		
Median	1.4		
0-4, N (%)	1,961 (61.6)		
5-17, N (%)	1,224 (38.4)		
Cause of death of index child, N (%)			
Accidents	712 (22.4)		
Other diseases <sup>a</sup>	711 (22.3)		
Perinatal conditions	571 (17.9)		
Congenital anomalies	539 (16.9)		
Suicide	204 (6.4)		
Sudden infant death syndrome	161 (5.1)		
Malignant neoplasms	156 (4.9)		
Other external causes of death <sup>b</sup>	131 (4.1)		
	Bereaved siblings (N=7,243)	Non-bereaved sibling controls (N=21,729)	X <sup>2</sup>
Relation of sibling to index child, N (%)			
Brother	3,616 (49.9)	10,848 (49.9)	0.00
Sister	3,627 (50.1)	10,881 (50.1)	
Marital status of sibling at index child's death, N (%)			
Married	170 (2.3)	493 (2.3)	0.15
Single	7,073 (97.7)	21,236 (97.7)	
Total number of children in the family (excluding the index child), N (%)			
1	1,325 (18.3)	1,290 (5.9)	1010.1*
2+	5,918 (81.8)	20,439 (94.1)	
Age of sibling at time of index child's death (years)			
Mean ± SD	9.6 ± 7.3	NA	NA
Median	7.8	NA	
0-4, N (%)	2,523 (34.8)	NA	
5+, N (%)	4,720 (65.2)	NA	
Income quintile of sibling at time of index child's death, N (%)			
Lowest quintile	3,102 (42.8)	9,339 (43.0)	1.38
Second lowest quintile	1,412 (19.5)	4,232 (19.5)	
Middle quintile	1,044 (14.4)	3,152 (14.5)	
Second highest quintile	890 (12.3)	2,662 (12.3)	
Highest quintile	717 (9.9)	2,143 (9.9)	
Unknown	78 (1.1)	201 (1.0)	

\*p&lt;0.001, NA – not available

<sup>a</sup>Non-external causes not captured by any of the other categories<sup>b</sup>Causes not classified as accidental or self-inflicted (e.g., abuse, homicide, injuries of undetermined cause)





**Figure 2** Adjusted prevalence (%) of any mental disorder diagnosis among control and bereaved siblings in the 2-year periods before and after the index date. Error bars indicate confidence intervals. Pre-post rate changes were significantly greater for bereaved siblings compared to controls, based on pre-post x sibling group interaction terms, with the following levels of significance: all siblings ( $p < 0.001$ ), siblings aged <13 ( $p < 0.05$ ), and siblings aged 13+ ( $p < 0.01$ )

from the pre-post rate change among the control siblings. Rates of drug use disorders were significantly higher after sibling death when compared to non-bereaved controls. However, the non-significant interaction term reflects the higher pre-death rates among the bereaved cohort. Bereaved children were more likely to be hospitalized in both periods, with

these higher rates significantly increasing after the death of their sibling.

There was a slightly different pattern for the bereaved siblings who were adolescent age and older. Like their pre-adolescent counterparts, they suffered significant rate increases in depression and any mental disorder when compared to their non-

**Table 2** Pre-death and post-death comparisons of mental disorders and treatment utilization among bereaved siblings aged <13 and bereaved siblings aged 13+

	Post-death outcome rates vs. pre-death outcome rates		
	Bereaved siblings <13 (N = 5,150) ARR (95% CI)	Pre-post time period x sibling age group interaction (p value)	Bereaved siblings 13+ (N = 2,093) ARR (95% CI)
<b>Mental disorders</b>			
Depression	7.25 (5.65-14.43)**	<0.0001	2.27 (1.89-2.73)**
Anxiety disorder	2.17 (1.48-3.17)**	NS	1.48 (1.26-1.75)**
Alcohol use disorder	1.00 (0.25-4.00)	NS	1.37 (0.98-1.91)
Drug use disorder	1.71 (0.75-3.92)	NS	1.40 (1.11-1.76)*
ADHD	1.69 (1.34-2.12)**	<0.0001	0.47 (0.29-0.77)*
Suicide attempt	6.08 (0.73-50.55)	NS	1.20 (0.73-1.97)
Any mental disorder	2.06 (1.71-2.48)**	0.0026	1.50 (1.34-1.67)**
<b>Treatment utilization</b>			
Physician visit for mental illness	3.06 (2.40-3.91)**	0.0005	1.66 (1.31-2.09)**
Physician visit for any reason	0.90 (0.87-0.93)**	<0.0001	1.08 (1.02-1.13)*
Hospitalization for mental illness	3.78 (1.47-9.72)*	NS	1.33 (0.96-1.85)
Hospitalization for any reason (other than birth)	0.75 (0.66-0.86)**	0.0003	1.05 (0.92-1.20)

\* $p < 0.01$ , \*\* $p < 0.001$ , NS – non-significant

ARR – Adjusted relative rate, CI – confidence interval, ADHD – attention deficit hyperactivity disorder

**Table 3** Pre-death and post-death comparisons of bereaved siblings and non-bereaved matched sibling controls, by age group

	Bereaved sibling ages <13 (N=5,150) vs. non-bereaved siblings (N=15,450)			Bereaved sibling ages 13+ (N=2,093) vs. non-bereaved siblings (N=6,279)		
	2 years pre-death ARR (95% CI)	Pre-post time period x sibling interaction (p value)	2 years post-death ARR (95% CI)	2 years pre-death ARR (95% CI)	Pre-post time period x sibling interaction (p value)	2 years post-death ARR (95% CI)
<b>Mental disorders</b>						
Depression	0.57 (0.28-1.17)	<0.0001	2.71 (1.94-3.79)***	1.20 (0.97-1.48)	<0.0001	2.27 (1.94-2.65)***
Anxiety disorder	1.07 (0.73-1.59)	NS	1.43 (1.08-1.88)*	1.16 (0.98-1.37)	NS	1.35 (1.17-1.54)***
Alcohol use disorder	3.26 (0.84-12.62)	NS	1.09 (0.35-3.42)	2.17 (1.51-3.13)***	NS	2.15 (1.56-2.96)***
Drug use disorder	3.64 (1.22-10.82)*	NS	2.34 (1.11-4.95)*	1.44 (1.13-1.84)**	NS	1.55 (1.25-1.91)***
ADHD	1.11 (0.84-1.47)	NS	1.19 (0.96-1.48)	1.27 (0.78-2.04)	NS	0.76 (0.40-1.46)
Suicide attempt	-	-	-	1.72 (1.06-2.80)*	NS	2.01 (1.29-3.12)**
Any mental disorder	1.17 (0.95-1.45)	0.0153	1.53 (1.32-1.78)***	1.23 (1.10-1.39)***	0.004	1.48 (1.35-1.63)***
<b>Treatment utilization</b>						
Physician visit for mental illness	0.73 (0.55-0.99)*	0.0034	1.18 (0.91-1.54)	1.22 (0.92-1.61)	NS	1.48 (1.15-1.91)**
Physician visit for any reason	0.93 (0.91-0.96)***	<0.0001	1.02 (0.98-1.05)	1.01 (0.95-1.08)	NS	0.99 (0.93-1.05)
Hospitalization for mental illness	2.86 (0.80-10.18)	NS	2.42 (1.03-5.69)*	1.57 (1.14-2.17)**	NS	1.78 (1.37-2.30)***
Hospitalization for any reason (other than birth)	1.34 (1.19-1.51)***	0.0134	1.63 (1.42-1.86)***	1.29 (1.13-1.48)***	NS	1.19 (1.06-1.35)**

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, NS – non-significant

ARR – Adjusted relative rate, CI – confidence interval, ADHD – attention deficit hyperactivity disorder

bereaved matches over the same time period. However, this age group had marked differences in mental disorder comorbidity in the pre-death period, with higher rates of alcohol use disorders (ARR=2.17; 95% CI: 1.51-3.13), drug use disorders (ARR=1.44; 95% CI: 1.13-1.84), and suicide attempts (ARR=1.72; 95% CI: 1.06-2.80) even before the death of their sibling. These higher rates compared to non-bereaved controls continued in the post-death period, resulting in a pattern of considerable mental disorder burden across almost all outcomes.

A sensitivity analysis was performed to examine the influence of being bereaved from multiple sibling losses, as well as index events that resulted in injury to the bereaved sibling in addition to the death of the index child. There were 59 siblings who lost multiple siblings in the same event, and 19 siblings who were hospitalized with an injury related to the cause of death of their sibling (such as a motor vehicle collision). Removing these siblings (and their corresponding controls) did not alter statistical significance of any of the interaction terms in Table 2 or Table 3. Among the statistically significant ARRs in Tables 2 and 3, most were unchanged in the sensitivity analysis, but three were slightly attenuated and only achieved borderline significance: bereaved siblings under age 13 diagnosed with drug use disorder in the two years post-death (ARR=2.14, 95% CI: 1.00-4.58, p=0.051) and hospitalized for mental illness in the two years post-death (ARR=2.33, 95% CI: 0.97-5.99, p=0.058), and bereaved siblings ages 13+ attempting suicide in the 2-year pre-death period (ARR=1.59, 95% CI: 0.97-2.61, p=0.068).

## DISCUSSION

This study provides the first findings on mental health outcomes of bereaved siblings in the general population. It deepens the knowledge of bereavement effects by separately examining outcomes among children and adolescents, revealing that, while some experiences are similar, there are important differences depending on the age at which one loses a sibling. The results emphasize bereavement as a period of vulnerability and thus an important focus for treatment and public awareness efforts.

Our results suggest that bereavement experiences vary according to the age of the surviving sibling. Of particular concern were the higher rate increases in depression in pre-adolescent children versus the 13+ age group. Losing a sibling led to a more than 7-fold rate increase in physician-diagnosed depression among the under-13 age group when compared to rates before the death. This finding could indicate an enhanced vulnerability to the damaging emotional consequences of bereavement among younger children, or may reflect the lower baseline population incidence of mood disorders in this age group, although the lack of significant pre-death rate differences in depression in both age groups when compared to controls argues against the latter hypothesis.

Very few studies have compared sibling reactions based on age. Risk for behavioral and emotional problems has been reported to be higher in adolescent age groups<sup>22</sup>, whereas

younger children have been found to have social difficulties including being more isolated, less accepted, and having fewer friends<sup>23</sup>. The current study provides information that supports both perspectives. When compared to non-bereaved controls, bereaved siblings aged 13 or older had higher rates of almost every mental disorder examined. They also had a higher likelihood of both inpatient and outpatient treatment. This concerning profile of poor health, however, was not restricted to adolescents. Children younger than 13 had higher post-death rates of depression, anxiety, and drug use disorders when compared to age-matched non-bereaved controls. These outcomes suggest that the effects among young children are not limited to measures of social connectedness. This presents important considerations for general practitioners and pediatricians managing the care of young bereaved children, highlighting the importance of evaluation and treatment in a population that might otherwise not raise a high index of suspicion for serious mental disorders.

A striking finding from this study is the health and social adversity faced by siblings even before the death of their brother and sister. At the time of the child's death, almost half of the affected families occupied the lowest income quintile, demonstrating a marked over-representation of income inequality. Even prior to their siblings' death, children under 13 who were to become bereaved were already diagnosed with drug use disorders at a rate almost four times that of the non-bereaved controls. The older group of soon-to-be bereaved siblings had an even more concerning profile of mental health adversity compared to controls, including higher rates of alcohol and drug use disorders and suicide attempts in the two years prior to their sibling's death. Together these findings present a picture of substantial disadvantage for these families, both socially and health-related. Adjusting analyses by income did not attenuate the health findings, which emphasizes that social deprivation is not the sole explanatory factor. Shared genetic factors likely contribute in a complex interplay with unmeasured environmental variables such as tobacco use, poor nutrition, and low health literacy, all factors that share relationships with mental and physical disorders, infant mortality, and poverty<sup>24,25</sup>.

There are some limitations that should be considered in this study. Stratifying analyses by factors such as sibling sex or age of death of index child were not conducted. These factors were examined as covariates, however, and not found to correlate with the outcomes examined, hence the decision to not perform additional stratification. This study examined all bereaved siblings from the population, and therefore, in families where there were several bereaved siblings, all were included in the cohort. Sibling pairs in the bereaved cohort were not matched to non-bereaved sibling pairs in the general population, which could introduce some confounding. Parental illness was not included and could influence outcomes. The cause of death could be a marker of family pathology and likewise influence the mental health of the bereaved sibling. These are certainly important avenues for future research, but would introduce a

level of complexity that was felt beyond the scope of this first examination of sibling bereavement in the population.

This study examined bereavement related to any cause of death, thereby grouping together people bereaved by sudden death along with those who had a sibling die as a result of a prolonged illness. While these represent very different situations, we decided to examine sibling bereavement broadly as it is the first population study on health outcomes. The birth of a new child into the family may have influenced bereavement reactions, and this was not accounted for in this study. The outcomes of this study were dependent on treatment seeking and thus do not capture all health outcomes in the population. Administrative data cannot assess certain emotional consequences such as complicated grief, which may be highly prevalent in bereaved siblings<sup>26</sup>. Post-traumatic stress disorder represents another outcome that is not accurately captured in the datasets; this is a significant limitation given the traumatic nature of sibling loss. Not all people with mental disorders seek care despite a perceived need<sup>27</sup>, and therefore the results of this study likely underestimate the true burden of bereavement.

In summary, bereavement among siblings is clearly a distressing experience with consequent risk for mental disorders, especially depression. The sibling relationship is a close bond for many and often the longest interpersonal connection a person will have, and these results show that its disruption even early in life leads to profound impairment among the survivors. Families who lose a child frequently struggle with impoverishment and illness among their offspring, yet the death of the child exerts a damaging effect on the remaining siblings that exceeds the pre-existing health and social adversity. Practitioners, both within mental health and general medicine communities, should be aware of these vulnerabilities.

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# Lessons learned from unintended consequences about erasing the stigma of mental illness

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*Advocates and scientists have partnered to develop and evaluate programs meant to erase the egregious effects of the different forms of stigma. Enough evidence has been collected to yield lessons about approaches to stigma change. Some of the most insightful of these lessons emerge from unintended consequences of good intentioned approaches, and are the focus of this paper. They include the limited benefits of education especially when compared to contact, beating stigma is more than changing words, beware pity as a message, understand the competing agendas of stigma change, replace ideas of normalcy with solidarity, and avoid framing self-stigma as the problem of people with mental illness and not of society. The paper ends with consideration of the back seat role that psychiatrists and other mental health providers should have in stigma change.*

**Key words:** Stigma, mental illness, unintended consequences, education, contact, public stigma, self-stigma, label avoidance, services agenda, rights agenda, solidarity

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Eliminating stigma's egregious effects on people labeled "mentally ill" has become a major public health priority across the world, with many countries combating stigma over the past ten years via nationwide campaigns.

During this time, research on stigma and stigma change has grown exponentially, from just six papers in the four year period in which A. Farina instituted the first empirical work on mental illness stigma circa 1970, to 22 papers in the time B. Link began his important program of research in the early 1980s, to 1,008 papers since 2010.

The interface of national campaign evaluations with empirical research found in the professional journals has led to several lessons that might be heeded in moving forward to erase stigma. Some of these are discussed here. The paper begins with brief answers to "What is stigma?", focusing especially on its harmful impact. Given the breadth and complexity of the stigma experience, this discussion is mostly limited to the egregious effects of public stigma on the person with mental illness. The paper then focuses on ways to eliminate stigma, largely focusing on negative lessons – good intentioned approaches that nevertheless yield little or even harmful impact.

Why the focus on unintended consequences? Stigma is largely an issue of social injustice and as such attracts people with progressive agenda. Progressive philosophy in the U.S., for example, called for using science and social forces to erase the ills that lead to poverty and discrimination<sup>1</sup>. Progressives rally energetically against egregious social phenomena, but often do so without consideration of effective approaches, sometimes worsening the status quo. For example, B. Clinton promoted "Don't ask; don't tell" in the 1990s as a way to decrease homophobia in the American military. Unfortunately, this promoted closetedness and secrecy in the gay community. Avoiding errors is as important an effort in tackling stigma as erasing discrimination, hence the need to learn from good intentioned strategies gone awry. Reviewing unintended consequences makes us better able to recognize potentially beneficial approaches.

## WHAT IS STIGMA?

Several models have emerged to explain stigma, including Link and Phelan's approach<sup>2</sup> that unpacks the complicated elements of the phenomenon, and Pescosolido et al's framework<sup>3</sup> integrating normative influences on stigma. I expand in Table 1 on a two dimensional matrix representing cognitive constructs that emerge from social psychology and a typology of impact.

Social cognitive models have outlined various constructs that describe the generic stigma experience across all disrespected groups (racism, sexism and homophobia) and include stereotypes, prejudice and discrimination<sup>4</sup>. Stereotypes are knowledge structures that evolve as part of "normal" development in a culture. They are often framed as seemingly fact-based beliefs with a negative evaluative component. Stereotypes become prejudice when people agree with the belief followed by negative emotions and evaluations of the group involved<sup>5,6</sup>. Discrimination is the behavioral result of prejudice, typically punitive in form and experienced as taking away a rightful opportunity or reacting to the group aversively.

Research has identified a variety of prejudices and discriminatory behaviors reflecting the stigma of mental illness. Several of these are listed in Table 1, including those most commonly reported in the research literature<sup>7-10</sup>. Perhaps most damning is that of dangerousness: that "those people" are potentially violent felons. Dangerousness is highly associated with fear, which leads to avoidance and withdrawal, the discriminatory result.

The three types of stigma summarized in Table 1 are public stigma, self-stigma and label avoidance.

Public stigma occurs when the general population endorses the stereotypes of mental illness and acts upon them in a discriminatory manner. The most troubling form of discrimination is avoidance and withdrawal. In order to escape the risks of associating with people with mental illness, members of the general public will seek to avoid them. Avoidance is especially hurtful when acted on by employers who do not hire people with mental illness and landlords who do not rent to them.

**Table 1** A two dimensional matrix for understanding stigma: types by social cognitive constructs

<b>TYPOLOGY FOR HEALTH IMPACT</b>				
<b>CONSTRUCTS</b>		<b>PUBLIC STIGMA</b>	<b>SELF-STIGMA</b>	<b>LABEL AVOIDANCE</b>
COGNITIVE	<b>PREJUDICE (stereotypes)</b>	“He is dangerous”	“I am unreliable”	Diagnosis of mental illness means “crazy”
BEHAVIORAL	<b>DISCRIMINATION</b>	Employer refuses to hire person with mental illness	Person with mental illness does not take on new tasks	Individual refrains from going to the clinic to seek help

Self-stigma occurs when people internalize prejudice and discriminate against themselves. Self-stigma has been divided into progressive stages known as the three As: aware, agree and apply<sup>11,12</sup>. Is the individual with mental illness *aware* of the stereotypes? For example, does the person know the stereotype that individuals with mental illnesses are childlike, incompetent, and so will not meet the demands of their job? Does the person *agree* with the stereotype? (“Yes, people with mental illness are incompetent and not capable of keeping up with the demands of competitive employment”). Do they then *apply* the stigma to themselves? (“I have a mental illness so I must be incompetent”). Applying or internalizing stereotypes has two harmful effects. Cognitively and emotionally, internalizing stigma can hurt self-esteem (“I am not a good employee; I cannot keep up with the demands of my job because I have a mental illness”) and lessen self-efficacy (“I can’t keep up with my job because I am an incompetent person with mental illness”). Behaviorally, the three As lead to the “why try” effect<sup>13,14</sup>: “Why should I try to get a promotion? I am not worthy of it”; “Why try to seek out a job? I am unable to be successful”.

Label avoidance refers to a third type of stigma; namely, stigma undermines service use for individuals in need of psychiatric care. One way in which people are publicly labeled is by associating with a mental health program: “Hey, that’s Karen. She is coming out of that psychiatrist’s office. She must be nuts!”. To avoid labeling, some people refrain from seeking services that would be helpful, or do not continue to use services once initiated.

**WHAT LESSONS HAVE BEEN LEARNED TO CRAFT ANTI-STIGMA EFFORTS?**

Although explaining stigma and its negative impact is a research priority, the ethical imperative driving this work

comes from advocacy efforts meant to erase it. Just as the most effective clinical interventions arise in a partnership of researchers and line-level practitioners, so effective research programs on stigma change rely on partnership between advocates with lived experience and social scientists.

Based on a review of the social psychology literature, approaches to changing public stigma have been divided into protest, education and contact strategies<sup>15</sup>. Protest relies on an appeal to a moral authority (shame on us for disrespecting people with mental illness), leading to a call for suppressing these thoughts. Education seeks to decrease stigmatizing myths of mental illness by contrasting them with facts. Contact tries to erase the prejudice and discrimination of mental illness through interactions between the “public” and people in recovery. Most of the research on public stigma change has examined education and contact; hence, these two approaches are the focus of the remainder of the paper.

**Education or contact**

Education has a seductive appeal to many countries: address social ills by teaching people about them. And in fact, efforts that promote mental health literacy may help people to better consume services, because they better understand how psychiatric disorders can challenge life goals and how these disorders can be overcome<sup>16</sup>.

Research suggests, however, that education has little impact on the prejudice and discrimination that limit a person’s rightful opportunities. Schomerus et al<sup>17</sup> reviewed sixteen population studies that tracked evolution in knowledge about mental illness and corresponding change in stigma from 1990 to 2006. Results showed significant increase in population knowledge

that illnesses such as depression and schizophrenia are genetic in origin and hence brain disorders. For example, a median 75% of respondents in 2006 agreed that schizophrenia is a brain disorder compared to about 55% in 1990. Despite this change, no improvement in the stigma of depression was observed, and the stigma of schizophrenia actually worsened. Stigma was defined here as accepting a person labeled schizophrenic as a neighbor or coworker. Acceptance of coworkers labeled with schizophrenia decreased from 50% to about 30% during the 16-year span of data. Despite increases in knowledge, stigma has not changed, or it has actually gotten worse.

Unintended effects of education emerge when considering programs that frame “mental illness as a brain disorder”. Summaries by Read and colleagues show that endorsement of this view is highly associated with beliefs that people with mental illness are dangerous and incompetent<sup>18,19</sup>. A study by Phelan et al<sup>20</sup> demonstrated the specific effects of teaching the public about genetic models of mental illness. The good news was, as expected, that this kind of education decreased blame: “People do not choose to have a mental illness; it is biological in origin”. However, genetic models also lead the public into believing that people will not recover; that the mental illness is “hard wired”. Poor prognoses result which are more likely to predict whether an employer will hire people with mental illness or a landlord will rent to them.

Several research studies have directly contrasted effects of education and contact. Results of a meta-analysis with thirteen randomized controlled trials showed that contact, compared to education, yielded significantly greater change in attitudes and behavioral intentions from pre- to post-test. Moreover, follow-up effects were significantly greater for contact than education<sup>21</sup>. By the way, research from the meta-analysis also showed that *in vivo* contact had better impact than contact that occurs through some medium<sup>21</sup>. Specifically, face-to-face interactions with people with mental illness has greater impact than hearing their story through video.

### Beating stigma is more than changing words

Stigma related to mental illness is often understood in terms of labeling; e.g., tagging people with the diagnosis of schizophrenia brings upon the negative impact of stigma. As a result, professionals and advocates have called for changing labels of mental illness in order to reduce its stigma<sup>22</sup>. This has been done for other disorders: dementia is now Alzheimer’s disease, mental retardation is intellectual disability, and manic-depressive illness is bipolar disorder.

Name changes for schizophrenia have been proposed by several East Asian professional associations, in part to highlight the optimism of recovery in prognosis. This is a relatively new endeavor, so research on its impact is still evolving, much of it from Japan, which changed the disrespectful name for schizophrenia to “integration disorder”. Research shows that psychiatrists and other mental health providers soon learned new labels<sup>23</sup>. Awareness of the new diagnostic label was in-

versely associated with conscious and unconscious measures of social distance<sup>23,24</sup>.

Still, even if renaming mental illness could show some stigma change, the effort fundamentally misunderstands the pernicious effects of prejudice and discrimination. Whether people with serious mental illness are labeled with schizophrenia, or a more benign and informed label like integration disorder, the person may still be marked as different. The harm of stigma arises from both the mark and the difference<sup>25</sup>.

Racism did not disappear in America because the majority now call black people African Americans. Social scientists called putative changes like these “modern racism”, where obvious forms of discrimination may disappear – for example, media, politicians or marketing experts no longer refer to groups of color using egregious terms – but discrimination continues in subtle forms, e.g., opposing busing for elementary school students<sup>26</sup>. Diagnosing people with integration disorder may not lessen the discrimination they experience from landlords, employers and legislators.

In addition, promoting diagnostic relabeling to erase stigma makes the anti-stigma agenda look easy. All we need to do is change the words. Unfortunately, believing stigma change is easy has its consequences. Funding bodies like the U.S. National Institute of Mental Health are modifying their priorities, and support for research in stigma has waxed and waned over the past decade. Some professional groups believe anti-stigma programs are no longer needed<sup>27</sup>. Diagnostic relabeling encourages word police, prodding media and others to improve their language. Research shows, however, that protest efforts to stop inappropriate words do not diminish stigma, and sometimes even worsen it<sup>15</sup>.

### Beware pity: it’s about parity

The symptoms and disabilities of mental illness, by their very definition, challenge happiness and hope. Reasonable reactions to mental illness include sadness and sympathy. Research suggests that educational programs focusing on biological causes may increase pity, or sympathy, for people with mental illness<sup>28-30</sup>.

Weiner<sup>31</sup> argued that sympathetically viewing a person as victimized by various health conditions – including cancer, HIV/AIDS and heart disease – is associated with willingness to provide help to that person. Research specific to psychiatric illness has shown that members of the general public who pity individuals with mental illness are more willing to offer a helping hand to them<sup>32</sup>.

Hence, pity might be used as a way to promote legislative movement for greater resources for mental health programs. In fact, research showed a significant relationship between viewing people with mental illness pitifully and endorsing the allocation of more funds for mental health services<sup>33</sup>. Further analyses showed, however, that it was greater resources for mandated treatment, and not rehabilitation services, that was associated with greater pity.

Pity may also produce negative effects, because of an over-reliance on or dramatization of what persons with illness and disability cannot do. Pity may create a different stigma, e.g., people with mental illness are incapable of making adult-level decisions<sup>20</sup>. Viewing people with illness as pitiful has been associated with the benevolence stigma, i.e., because people with mental illness are unable to competently handle life's demands, they need a benevolent authority who can make decisions for them<sup>34-37</sup>.

Advocates and researchers have argued that a major problem with many health systems is disempowering practices that prevent people with disabilities from pursuing life goals<sup>38-40</sup>. Appeals to sympathy must be replaced by calls for empowerment and self-determination. All decisions about life goals and the interventions to achieve those goals must stay in the hands of the person with mental illness. This message rests on the knowledge that people with mental illness often fail because of community and systemic inequities. Anti-stigma advocates need to cultivate empathy that leads to parity, not to condensation and exaggeration of difference. Advocates clearly voice the goal: parity, not pity!

### Competing goals in stigma change

The impact of public stigma, leading to prejudice and discrimination that undermine pursuit of life goals related to work, independent living and personal relationships, differs markedly from label avoidance, such that people do not seek out mental health services in order to avoid stigmatizing labels.

Targeting stigma to erase these different impacts may yield separate agenda: *the services agenda*, trying to remove stigma as a barrier to becoming engaged in evidence-based services, and *the rights agenda*, replacing discrimination that robs people of rightful opportunities with affirming attitudes and behaviors. Approaches to these agenda were developed and matured independently, leading to different purposes and processes.

### *The services agenda*

Decreasing label avoidance in order to promote mental health service seeking has become a major public health endeavor<sup>41</sup>. The Australian program called *beyondblue* tackles label avoidance and care seeking. It is a social marketing campaign which includes public service announcements framing depression as a treatable disease. It has been active in Australia for almost 15 years, and shown to have penetrated the population well, with 60% of Australians being aware of the program<sup>42</sup>. Campaign awareness was associated with better recognition of mental illnesses and greater understanding of treatment benefits<sup>43</sup>.

*Mental Health First Aid* is a mental health literacy program that also has sought to diminish label avoidance. It is an 8-hour course taught in a classroom setting that reviews basic information and skills, so that course participants can help others with mental health problems or crises. Outcome research on this program is promising: findings from a recent

meta-analysis show that people who complete first aid training are likely to have mastered information about mental illness and show diminished stigma<sup>44</sup>. This kind of information should boost care seeking.

### *The rights agenda*

Programs meant to erase public stigma are seeking to promote civil rights. Erasing discrimination is not enough; the population needs to replace prejudice with affirming attitudes and behaviors. Affirming attitudes promote recovery and pursuit of individual goals based on ideas of hope, empowerment and self-determination. Affirming behaviors are community actions that firm up recovery and self-determination. They include innovative ways to provide reasonable accommodations and meaningful supports.

*Opening Minds* is a nationwide effort in Canada that largely rests on contact-based interventions<sup>45</sup>. It sought to build networks of practice, collections of small contact-based programs from across the country that were reimbursed for local anti-stigma efforts. Preliminary analyses of this six-year initiative seem to suggest that contact programs have positive effects on targeted groups of youth, health care providers, Canadians in the workplace, and the media.

### *What is the significance of different goals?*

The two approaches to stigma change differ in fundamental purposes and processes. They differ in message. The services message seeks to destigmatize mental illnesses by framing them as treatable disorders. The rights message poses mental illness stigma in the same light as any civil right, calling for ending discrimination and promoting opportunities.

These messages lead to differences in expected benefits, which lead to differing research measures of their success. The services agenda is successful when evidence shows that people with mental illness are seeking out services more or becoming better engaged. The rights agenda is successful when, for example, there are more people with mental illness in the workforce receiving reasonable accommodations.

The different agendas may be driven by people with different roles in the mental health system. The services agenda is propelled by people who are confident that treatment helps: those who have benefited from interventions and their families. This approach is often supported by service providers and their professional organizations. The rights agenda is driven by those who have been victimized by discrimination, either directly or through the experiences of others.

Agendas may turn to different strategies to promote their goals. The services approach is dominated by health communication and public service campaigns meant to influence a broad population. The rights approach is more grassroots, using people with lived experiences and stories of recovery to challenge local examples of discrimination and promote community opportunities.



The different agendas may compete with each other. Summaries and evaluations of government programs with 5 to 10-year histories in the U.S., U.K., Canada and Australia show that they are limited by available funds. As a result, choices need to be made in budgets for social marketing campaigns to enhance service seeking versus those for grassroots efforts to promote rights. There is never sufficient money for all proposals, so benefits for one may limit the other.

### The nature of the message: normalcy versus solidarity

Goffman<sup>46</sup> characterized stigma as “undesired differentness” that results from a mark distinguishing and discrediting an out-group from the majority. People with mental illness are different from the norm, and hence, somehow broken. One way to erase stigma has been to accentuate similarities between people with mental illness and the rest of the population through an appeal to normalcy. “Despite his schizophrenia, Harold is just like everyone else”. In this light, Goffman believed stigmatized people can be active agents in diminishing difference through impression management, the strategic effort to minimize other’s perceptions of one’s self in order to promote individual goals<sup>46</sup>.

Impression management for psychiatric disabilities has largely taken the form of public education programs seeking to replace notions of the abnormal with normal. This is done by contrasting myths of serious mental illness with facts that challenge these myths. The normalcy frame is often used in social marketing campaigns addressing stigma. Australia’s *beyondblue* demystifies treatment by framing it as similar to other medical interventions.

Despite the promise of normalcy campaigns, there may be unintended effects. People with mental illness are fundamentally told to keep aspects of their identity secret. There are consequences to suppressing identity that harm a person’s mental and physical health, relationships and well-being<sup>47</sup>. Despite the risks, coming out has generally been found to yield improved mental and physical health for gays, lesbians, bisexuals and transgender (GLBTs)<sup>48</sup>. Keeping secrets only worsens health and wellness.

What does research suggest about identity and coming out for people with mental illness? Some people who identify with their mental illness may show lower self-esteem and greater pessimism<sup>49</sup>. However, effects of illness identity are influenced by perceived legitimacy of mental illness stigma<sup>50</sup>. Those who identify with mental illness, but also embrace the stigma of their disorder, report less hope and diminished self-esteem. Conversely, those who’s sense of self prominently includes their mental illness *and* who reject the stigma of mental illness not only show more hope and better self-esteem, but enhanced social functioning as well.

Identity can have positive or negative valences. People with mental illness may describe themselves negatively in terms of their distress, failures or symptoms. People might try to alter this kind of self-image in psychotherapy, spiritual endeavors, or related activities. Mental illness identity can also be posi-

tively valenced, leading to a sense of pride<sup>51</sup>. People experience pride in achieving a standard recognized by their culture (e.g., a medal for the runner) or set by themselves (e.g., a personal best race time). Overcoming challenges of mental illness, withstanding related societal stigma, and demonstrating a sense of resilience may lead to identity pride.

Pride also emerges from a sense of who one is; ethnic pride is an example. “I am Irish American” does not suggest any accomplishment *per se*, but rather an additional answer to the person’s search to understanding “Who am I?”. In this light, mental illness whose challenges have been overcome may be an identity of which some individuals might be proud.

This kind of identity promotes authenticity and recognition of one’s internal conceptualizations in the face of an imposing world. This might take the form of group identification. People with mental illness who more highly identify with “the group” are less likely to experience harm to self-esteem or self-efficacy as a result of internalized stigma<sup>52</sup>.

What then becomes the goal of stigma change programs? Might the public need to acknowledge positive aspects of some people’s mental illness identity and do this by standing in solidarity with them? Solidarity has two meanings here. First, research suggests that people with a stigmatized condition gain strength through association with peers: solidarity in a microcosm of the world. More broadly, however, it is the experience where the majority stands with people who are publicly out with their stigmatized identity: I am in solidarity with people in recovery.

The task that remains for future research and advocacy is to identify when normalcy or solidarity may be most useful for tearing down stigma. Perhaps normalcy messages are valuable to public service campaigns seeking to decrease the stigma of treatment by representing psychotherapy as “just like a visit to the family physician”. Perhaps solidarity is especially poignant for the person struggling with self-stigma, seeking a group of peers with whom to stand proud.

### Self-stigma: whose problem is it?

There is one unintended lesson worth learning in terms of tackling self-stigma. Educational and cognitive-behavioral strategies approach self-stigma as “the person’s problem”, rather than a problem of a society that breeds public stigma, prejudice and discrimination. As a result, educational and cognitive approaches may unintentionally pathologize the experience of self-stigma, framing internalized stereotypes as irrational beliefs that reside in the person<sup>53,54</sup>. Irrational beliefs demand professionally led treatment to correct dysfunctional cognitions. Pathologizing self-stigma may unintentionally promote secrecy, suggesting that people should not disclose mental health experiences.

The harm of sending people back to the closet was reviewed above; strategic disclosure programs have emerged to address this harm<sup>55</sup>. *Coming Out Proud (COP) to Erase the Stigma of Mental Illness* is a three session peer-led program helping to: a) consider the

pros and cons of disclosing in differing settings; b) learn relatively safe ways to come out; c) and craft one's coming out story<sup>56</sup>.

Two randomized controlled trials have documented benefits of COP. The first showed that participants completing COP, compared to a control group, recognized more benefits to disclosure and less need for secrecy<sup>57</sup>. This in turn was related to diminished stress related to self-stigma and disclosure, as well as being more willing to ask for help when in need. In the second, multisite study, women who completed COP showed significant reductions in depression compared to those in the control group<sup>58</sup>. These effects were mediated by significant reductions in self-stigma and stress related to self-stigma. In addition, COP completers showed significant increase in perceived resources to deal with stigma compared to the control group.

Strategic disclosure sends a different message than education and cognitive therapy. COP says that people with mental illness do not need to pass as normal nor conform to expectations based on self-stigma. Disclosure demands solidarity; that the public accepts and empowers friends, neighbors, coworkers and other acquaintances with mental illness.

## WHAT MIGHT PSYCHIATRISTS AND OTHER MENTAL HEALTH PROVIDERS DO?

If progressive people seek to tear down social injustices, what is the role of White progressives in correcting racist attitudes against Blacks? Or men in promoting opportunities for women? Or heterosexuals in addressing the social injustices experienced by the GLBT community?

People seeking to right social injustices are energized, wanting responsible roles in tackling these wrongs; they are vital resources for changing the social dialogue. A tough lesson, however, is for Whites, men and heterosexuals to pursue these goals from the back seat. Blacks need to be at the fore of the pursuit of racial justice; women of seeking gender equality; GLBTs of establishing gay rights. In the absence of Black, female and GLBT leaders, efforts to tear down racism, sexism and homophobia fail to capture the dynamic agenda of the community they are meant to empower.

Even more, righting stigma is fundamentally a task of power; Blacks, women and GLBTs need to hold the power. Excluding people from these communities from leadership unintentionally serves to disempower them.

So what might psychiatrists and other providers do to correct mental illness stigma? Start by getting into the back seat. People with lived experience need to be driving the effort to erase the stigma of mental illness. *Nihil de nobis sine nobis* ("Nothing about us without us") is an expression believed to have arisen in Central Europe during the Enlightenment which affirms that no policy or action should be taken about a group without full participation of that group. It is a slogan adopted by disabilities rights groups around the world. People with mental illness need to lead efforts to set policy and actions that affect their lives. This is consistent with what research has

shown about changing public stigma<sup>59,60</sup>. It is not the professional expert teaching facts of illness that changes stigma, but contact with people sharing stories of recovery.

Moving to the shadows to take a supporting role has been a hard lesson for professionals, especially when society charges them with leading health systems that provide the lens for understanding people with mental illness. However, the professionals' expertise in managing service systems is not synonymous with impacting the social sphere in which those systems operate. This is an especially poignant issue when considering where mental health professions land in response to surveys on public stigma.

Comprehensive reviews show that consumers and families often describe mental health professionals as more likely to focus on the disease while ignoring the person<sup>61,62</sup>. As many as half of professionals failed to endorse recovery as an outcome for serious mental illness<sup>63</sup>. Mental health providers often endorse stereotypes about mental illness, including perceptions of dangerousness, unpredictability and blame<sup>64,65</sup>. The point here is not to chastise professionals; stigmatizing the stigmatizer serves no benefit. Sensitivity to the issue, however, is likely to make professionals better supporting partners in erasing stigma.

Sitting in the back seat is neither irrelevant nor impotent. Mental health providers have significant resources to bring to anti-stigma efforts. They have a certain credibility in the public sphere. Professional voices of hope and self-determination behind a person's story of recovery, instead of gloomy prognosis that often colors media images, exponentially advances anti-stigma goals. In the process, providers may be able to rally other opinion leaders to counter stigma. One example of effective partnership goes back to President G.W. Bush's New Freedom Commission. That commission was a collection of people with lived experience, providers and other stakeholders charged with crafting a vision for mental health services moving into the new millennium.

There are service providers with their own story of recovery. Professionals advocating through their experiences as a service recipient may hold an especially powerful role in the stigma change agenda. Some professionals stepped up to share their stories in the recent book *Coming Out Proud to Erase the Stigma of Mental Illness: Stories and Essays of Solidarity*<sup>66</sup>. Psychiatrists and other mental health providers can stem the course of stigma when embracing roles like these.

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## Supported accommodation for people with mental health problems

The process of “deinstitutionalization” over recent decades has led to many countries developing supported accommodation services to enable people with mental health problems to live in the community. In the early days, most of these facilities were communal group homes or residences, but over time it became clear not only that people were often able to gain skills for more independent living, but also that many preferred not to live with other service users. In many countries, a range of provision has therefore evolved, including facilities that are highly staffed, 24 hours a day (such as residential care homes), as well as shared group homes and hostels that are less intensively staffed, apartment blocks where residents have their own private tenancy but there are staff on-site at least part of the day, and “floating” or “outreach” models, where staff who are based off-site visit service users in their own individual or shared homes, providing support of flexible intensity.

In some countries, services are now organized into a local “care pathway”, where people move from hospital to highly supported accommodation, graduating to more independent settings every few years as they gain skills and confidence. This has the advantage of providing clear goals for people to work towards and tailored support, but it also means that individuals have to keep moving home as they recover from their mental health problems. However, in other countries, buildings within the asylum campus were re-designated as “supported accommodation”, with no or few further options for people to move on to. Concerns about a lack of rehabilitative ethos in the more traditional communal residences have led some to assert that mental health services have undergone a process of “trans-institutionalization” rather than deinstitutionalization<sup>1</sup>.

Gaining accurate estimates of the number of people living in specialist mental health supported accommodation services is difficult as, in many countries, multiple providers (including statutory social services and voluntary sector organizations) are involved and there are no centralized registration requirements from which data can be extracted. In 2006, it was estimated that around 12,500 people with mental health problems were living in residential care homes in England<sup>2</sup>, and around 24,000 people were receiving specialist mental health floating outreach services<sup>3</sup>.

The people who need supported accommodation services often have severe, complex mental health problems, such as schizophrenia, with associated cognitive difficulties that impair their organizational skills, motivation and ability to manage activities of daily living<sup>4</sup>. The support they need to live successfully in the community is mainly of a practical nature, including assistance to manage medication, personal care, laundry, paying bills, shopping, cooking and cleaning<sup>5</sup>. Most are unemployed, socially isolated, and many do not participate in civil and political processes<sup>4</sup>. They may therefore also require encouragement and support to access community resources and to remain in touch with family and friends.

In England, the estimated average cost of providing floating outreach to one tenant is around £150 per week, and a place in residential care is estimated as being around £500 per week. Clearly the costs of providing supported accommodation run into billions when multiplied across the thousands of people using these services internationally. In addition, statutory community mental health services will often provide additional input to the residents and staff of supported accommodation services, and therefore both health and social care costs should be taken into account when considering the cost-effectiveness of this approach.

Despite the major investment in supported accommodation services for people with mental health problems, there is a paucity of high quality research investigating the effectiveness of different models. The only rigorous systematic literature review in this area reported the simple finding that no trials of adequate quality had been carried out<sup>6</sup>. This is understandable given the logistic difficulties of randomizing individuals to different types of supported accommodation when clinicians and service users may have strong preferences about the kind of support they feel is required. Nevertheless, there is evidence to suggest definite benefits compared to long-term hospitalization. A study of around 700 long-stay patients discharged to the community following the closure of the two large mental hospitals in north London in the 1990s found that the majority were not only able to sustain community tenure but most were able to move on successfully to less supported settings over the subsequent five years<sup>7</sup>. Similarly, the Berlin Deinstitutionalization Study found that patients’ quality of life improved after moving to the community<sup>8</sup>. One small study carried out in an area of London with a well-established mental health supported accommodation care pathway found that, over a five year period, 40% of people moved on to less supported (more independent) accommodation and 26% remained in the same accommodation, without requiring readmission to hospital and without any breakdown in their community placement; overall, 10% progressed to completely independent living in a permanent tenancy<sup>9</sup>.

A large survey of mental health supported accommodation across England found few differences in characteristics of users of the three main types: residential care, building based support, and floating outreach<sup>5</sup>. The majority were male, with a diagnosis of psychosis, and almost half also had a history of substance misuse. Most were prescribed psychotropic medication and all services provided support with personal care and activities of daily living. The types of service provided appeared to have little to do with the socio-demographic context of the local area and were mostly driven by different regional approaches to health planning and the availability of statutory mental health services. A national survey of mental health residential care in Italy also reported a lack of association between provision and the mental health needs of the local population<sup>10</sup>. This survey also found

low discharge rates and considered that many residential care services were operating as “homes for life”, providing little in the way of rehabilitation.

A number of studies have identified discrepancies between different “stakeholder” views about the level of support required, with service users tending to prefer more independent accommodation, while staff and family members tend to prefer their relatives live in staffed environments<sup>11</sup>. Whilst communal, staffed settings can reproduce institutional regimes<sup>12</sup>, some service users have found more independent accommodation, such as supported apartments, to make them feel lonely<sup>13</sup>.

In the U.S., the “Train and Place” approach (which provides a constant level of staffing on-site to a number of service users living in apartments, with the expectation of service users moving on to more independent accommodation as they gain living skills) was compared in a quasi-experimental study to the “Place and Train” approach (which provides off-site outreach support of flexible intensity to service users living in time-unlimited, independent tenancies). The latter approach was found to facilitate greater community integration and service user satisfaction<sup>14</sup>.

In Canada, the efficacy of a similar model, “Housing First”, which provides immediate access to a permanent tenancy for homeless people with mental health problems along with intensive, outreach support from a specialist multidisciplinary community mental health team, was assessed in a recent randomized controlled trial. Although participants receiving the model achieved greater housing stability than those receiving standard care at two year follow-up, there was no statistically significant difference between the two groups in quality of life<sup>15</sup>.

A five year programme of research, funded by the National Institute for Health Research in England, is now attempting to address some of the evidence gaps in this field. This project, named QuEST (Quality and Effectiveness of Supported Tenancies for people with mental health problems), includes detailed inves-

tigation of the provision, quality, clinical and cost-effectiveness of different forms of mental health supported accommodation services across England, and a feasibility trial comparing supported housing and floating outreach services ([www.ucl.ac.uk/quest](http://www.ucl.ac.uk/quest)).

In conclusion, many people with severe mental health problems reside in supported accommodation. There is great heterogeneity in the types of service provided and the content of care delivered within and between countries, and little evidence to guide clinicians and service planners. More research in this field is urgently required to establish the most effective models in which to invest.

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## New approaches to interventions for refugee children

The alarming global increase of persons forcibly displaced because of persecution, conflict, violence or human rights violation poses a number of challenges to health and other public sector services. Approximately 51.2 million individuals fall into this broad group, largely consisting of 33 million internally displaced, 17 million refugees and 1.2 million asylum seekers. Conflicts are no longer confined to regions, with the Syrian refugee crisis, for instance, spreading especially to Southern Europe, where Syrian refugees have already exceeded 1.5 million in Turkey alone, of whom 250,000 live in camps. Children under 18 years constitute around 50% of the refugee population, with a total of 25,000 unaccompanied minors applying for asylum annually across 80 countries.

In recent years, there has been increasing evidence on the prevalence of mental disorders in refugee children and the underpinning risk factors, but knowledge remains relatively limited about

resilience building, treatment and service efficacy. Studies arise from post-conflict areas or from Western countries with newly arrived (asylum seeking) or resettled (refugee) children and young people. The characteristics of these groups, societal contexts and service systems obviously differ, requiring a range of approaches.

Most epidemiological studies have focused on post-traumatic stress disorder, but when they have been extended to other conditions such as depression, the impact of both past trauma and current life adversities on child psychopathology has clearly emerged<sup>1</sup>. The mediating effect of parental mental illness and parenting capacity is prominent<sup>2</sup>, although surprisingly there has been less attention so far to the role of the quality of attachment relationships, including those with extended family members. Unaccompanied children have an elevated risk of psychopathology and lower service engagement compared to refugee children living with their parents<sup>3</sup>.

There has been less research on factors that promote mental health or that moderate stressors in this population, despite the acknowledgement of their direct relevance to planning interventions. Although not always theoretically driven, such studies have identified individual (spirituality, coping strategies, internal locus of control), family (financial circumstances, family acceptance and support) and community factors (neighbourhood safety, social support networks, school retention)<sup>4</sup>. These are important findings, but currently we lack a coherent model that connects them in order to inform the development of interventions and services.

In terms of children's multiple needs, services often aspire to a socio-ecological model, but this is not usually supported by research evidence, as most studies are still based on self-reports, and programmes are rarely implemented at individual, family and community levels. Interventions usually draw on a variety of psychological frameworks, which are largely trauma-focused, whether implemented individually or with groups, but without incorporating the family and community level<sup>5</sup>. They largely target re-experiencing and reconstructing trauma-related cognitions and emotions, and findings are not always exclusively based on refugee children, but rather on children exposed to war and political conflict, and living in a range of circumstances. The theoretical clarity and fidelity of interventions varies considerably, as well as their developmental perspective if adapted from adult programmes, or the demarcation between universal and targeted prevention<sup>6</sup>.

Overall, the clinical and socio-ecological fields are gradually converging. Therefore, we need to conceptualize intervention programmes and service development for refugee children in an integrated context. We should also take into consideration the vacuum or limitations of public services in most countries, where there is a huge mismatch between refugee numbers and resources, with this gap usually filled in part by non-governmental organizations (NGOs) of varying philosophies, missions, structures and funding streams. The development of a comprehensive model should also be informed by organizational, in particular implementation theory. The framework proposed by Greenhalgh et al<sup>7</sup> is useful, as it defines sequential stages, each with its own domains, i.e. innovation, adoption by individuals, assimilation by the system, diffusion, and dissemination.

A service distinction should be made between displaced refugee children in low-income countries and those resettled in high-income health care systems, as well as between the acute and the resilience building phases.

In low-income countries, the humanitarian crisis is usually tackled by the United Nations, governmental departments and international NGOs, and this period remains fluid in terms of acute needs and mobility. Group-based, particularly school interventions where possible, are the most cost-effective. A number of modalities have been used, and a small number of studies have employed experimental designs such as randomized controlled trials<sup>8</sup>. These have been based on play, creative-expressive, cognitive-behavioural, narrative exposure, interpersonal, and grief-focused therapies, with a tendency to broaden their scope

from only focusing on trauma<sup>9</sup>. This is a useful baseline, but it needs to be maximized through existing systems, predominantly communities and schools; non-specialist health community workers or lay counsellors supporting parents as mediators; and local empowerment<sup>10</sup>.

The delivery of interventions in the absence of specialist professionals is another key challenge. In reality, the majority of interventions can only be delivered by suitably trained teachers, NGO staff and volunteers, or lay counsellors, who would thus integrate new skills to their "therapeutic key working role" to form the crucial links with the other eco-levels<sup>11</sup>. This raises implications for consultancy, training and sustainability, e.g. through supervision, which will be the main focus of specialists in addition to using their sparse resources for acute and severe cases. Trauma-focused interventions require a varying degree of skills and training, and this is a major practice issue in balancing treatment fidelity with a large-scale impact on children.

Practitioners and volunteers should be clear on the objectives at different stages of trauma exposure. A tiered model can be clinically and economically effective. Psychoeducation on symptom recognition and management (for example, nightmares) can be put in place relatively early through schools or community settings, preferably by involving parents, who may require additional input in their own right. For children who require a more active intervention, groups of relatively brief duration can be implemented by non-specialist facilitators under clinical supervision, aiming at trauma reprocessing, and these should suffice for a substantial proportion of children. Those children who either do not respond or present with comorbid disorders that necessitate pharmacological treatment or more prolonged therapies, such as depression, should be the focus of the available specialist resources.

When children are resettled in low- or middle-income countries with limited specialist resources, similar approaches to those discussed previously can be adopted, particularly if they are placed in a relatively concentrated area. In high-income countries, service models for a range of vulnerable children with complex needs should be applied, namely direct access, outreach work, and links with refugee charities and employment training<sup>12</sup>. The balance of interventions has gradually shifted from predominantly focusing on the pre-flight trauma to more emphasis on resettlement factors, such as acquiring a new language and communication, socio-cultural adjustment and identity, peer relationships (which can lead to bullying and further victimization), and school inclusion.

Schools still provide an effective entry route into mental health services. Multi-faceted case management can be provided in addition to the described therapeutic interventions, and this can include parenting input or liaison with adult mental health services. Unaccompanied minors require policies and systems equivalent to those for children in public care, e.g. appropriately trained residential staff and foster carers. Reliance on interpreters for a variety of languages makes their training and consistent relationship with services essential.

Following recognition and referral to the appropriate service, a number of practice considerations should be made. Refugee children are likely to have different constructs of mental ill health, attributions that associate it with their asylum applications, and fears of stigma and deportation. Engaging them and alleviating such misconceptions is thus a major step towards a successful outcome. Their psychological mindedness will vary, as many refugee children first experience predominantly somatizing symptoms, and may require several attempts before accepting a trauma-focused treatment. Involving their carers and initially setting goals of, for instance, risk management while developing a trusting relationship can lead to a therapeutic phase, while they also become more adjusted in their country of reception.

In conclusion, refugee children and young people pose a significant public health challenge across the world. Their complex needs require closer collaboration between mental health and non-statutory services to maximize their respective skills and resources. A comprehensive multi-modal service should include

clear care pathways, case management, evidence-based trauma-focused interventions, consultancy, and training.

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## Why are some individuals more resilient than others: the role of social support

Trauma is an inextricable component of the human condition. Most individuals are exposed to one or more traumas during their lifetime, but there is great psychological and neurobiological variability in how people respond to these events. While the majority of individuals are largely psychologically resistant or resilient to the negative consequences of trauma, a significant minority develop chronic, debilitating psychological symptoms that markedly interfere with their capacity to function; others may initially develop symptoms and recover, or develop late or delayed symptoms over time.

What explains these differences? The answer is complex and only partially understood. Resilience is generally defined as the ability of an individual to bend but not break, to bounce back, and “to adapt well in the face of adversity, trauma, tragedy, threats or even significant sources of stress”<sup>1</sup>. However, this definition primarily focuses on the individual. In so doing, it fails to explicitly acknowledge that individuals are embedded in social systems, and that these systems may be more or less resilient in their own right, as well as more or less able to support the adaptive psychological capacities of the individual. Thus, responses to trauma and significant stressors are determined by multiple dynamic, interacting individual-level systems (e.g., genetic, epigenetic, developmental, neurobiological), which are embedded in larger social systems (e.g., family, cultural, economic, and political systems).

Like resilience, social support is a complex construct with many definitions. One is from Cohen, who defines it as “a social network’s provision of psychological and material

resources intended to benefit an individual’s capacity to cope with stress”<sup>2</sup>; another is from Eisenberger, who defines it as “having or perceiving to have close others who can provide help or care, particularly during times of stress”<sup>3</sup>. There are many facets of social support which, while overlapping to some extent, reflect unique aspects of this construct. These facets include: structural social support (i.e., the size and extent of the individual’s social network, frequency of social interactions); functional social support (i.e., the perception that social interactions have been beneficial in terms of meeting emotional or instrumental needs); emotional social support (i.e., behavior that fosters feelings of comfort leading the person to believe that he/she is loved, respected, and/or cared for by others); instrumental/material social support (i.e., goods and services that help solve practical problems); and informational/cognitive social support (i.e., provision of advice or guidance intended to help individuals cope with current difficulties). These facets of social support can be facilitated and maintained by different systems, including family, community, and state, national, and international systems. Notably, while social support is a key correlate of psychological resilience, it is not universally helpful, as its effectiveness may vary by the type of support provided and the extent to which it matches individual’s needs, which may change over time. For example, among Iraq/Afghanistan combat veterans, perceptions of family members’ understanding of deployment-related concerns (i.e., functional support) was more strongly related to mental health and resilience than structural and instrumental support<sup>4</sup>.

A large body of research has found that psychological resilience is generally fostered by environmental/caregiving conditions during childhood that are loving, emotionally responsive, consistent, and reliable<sup>5</sup>. This work suggests that, when the environment also provides ample opportunities to master challenges and stresses, it can have an “inoculating” or “steeling” effect, which can help promote resilience. Such social and environmental conditions can also support the development of individual attributes and skills commonly associated with resilience, including the ability to regulate emotions, self-soothe, solve problems under stress, form secure attachments, sustain friendships and intimate relationships, and acquire a realistic and positive sense of agency/self-efficacy<sup>5</sup>. However, when the caregiving environment is highly stressful and chaotic, animals and humans are at increased risk for developing exaggerated sympathetic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and emotional and behavioral responses to future stressors, which can persist into adulthood<sup>6</sup>.

Many features of personality are heritable and some of these, such as extraversion and dispositional optimism, are associated with one's capacity to seek and utilize social support. However, the social caregiving environment may influence whether and to what extent these inherited features are actually expressed. For example, short allele carriers of the serotonin transporter promoter polymorphism were found to be more susceptible to the influence of parenting than long carriers<sup>7</sup>. Positive social support was also shown to moderate genetic risk for depression in maltreated children<sup>8</sup>. There is also emerging evidence that one's social environment may moderate genetic vulnerability to stress by triggering epigenetic modification of genes implicated in the stress response system<sup>9</sup>.

Social support appears to be associated with resilience to psychopathology via a number of psychological and behavioral mechanisms, including motivation to adopt healthy and reduce risky behaviors; feelings of being understood; appraisal of potentially stressful events as being less threatening; enhanced sense of control or mastery; increased self-esteem; use of active coping strategies; and impact of social influence and social comparison. For example, in a study of individuals with cardiac disease, high functional and emotional social support (i.e., perceiving understanding from and confiding in family members, work employees, and the broader social network) was associated with increased use of active problem-solving, a coping mechanism that has been associated with resilience in several traumatized populations<sup>10</sup>.

An emerging body of research has shown that threats to social connectedness, such as rejection and loneliness, activate many of the same neurobiological systems associated with physical threats and fear, including the amygdala, dorsal anterior cingulate, dorsal medial prefrontal cortex, sympathetic nervous system, and HPA axis<sup>3</sup>. In contrast, positive social support has been shown to inhibit activation of fear-related neurobiological systems by activating the parasympathetic nervous system and brain regions, such as ventromedial pre-

frontal cortex, ventral anterior cingulate cortex, right dorsolateral prefrontal cortex, and caudate, which are implicated in the processing of safety cues<sup>3</sup>. Positive social support has also been shown to stimulate the release of oxytocin<sup>11</sup>, which is critical for social cognition and social behaviors, including accurate facial affect identification, social approach, affiliation, perceptions of trustworthiness, and sexual behavior<sup>11</sup>. Oxytocin has also been shown to have anxiolytic effects and to attenuate physiological, hormonal, and brain-level responses to aversive and potentially stress-inducing signals<sup>11</sup>. Overall, positive social support, through a variety of neurobiological mechanisms, can have a buffering effect on physiological stress responses, with a resultant salutary effect on mental (e.g., depression and post-traumatic stress disorder, PTSD) and physical health (e.g., cardiovascular disorders, immune function)<sup>3</sup>.

On the other hand, preclinical and clinical research finds that weak social support and isolation are associated with indicators of compromised physical and mental health. The magnitude of impact of poor social support on all-cause mortality is similar to that of obesity, cigarette smoking and physical inactivity. Social support also influences rates of mental disorders. For example, meta-analytic findings have reported that low post-trauma social support is a consistent risk factor for PTSD<sup>12</sup>.

Psychological interventions to increase individual resilience typically target personal skill development (e.g., training in physical fitness, cognitive reframing, mindfulness, social skills). However, they can also target family and community social systems<sup>13</sup>. For example, there is substantial evidence that one of the most effective ways to increase resilience in a child is to focus on the well-being and child-rearing skills of his/her parents<sup>6</sup>. A number of studies and programs have demonstrated that teaching at-risk parents to understand their own needs as well as the emotional and mental needs of their infant/child may enhance attachment security, and reduce a variety of later maladaptive outcomes, including child maltreatment and criminal behavior.

Social support from one's community can also help foster resilience in the individual. Community members are strongly affected by the coping strategies of other community members, as well as by the community's capacity to prepare for and deal with adverse events and conditions. This becomes apparent during disasters, when individuals who are linked to pre-existing organizations and communities that are well prepared to deal with adversity tend to fare better than those who are not connected to or supported by community<sup>13</sup>. Communities can also enhance resilience in the individual through policies and programs that promote safe neighborhoods, affordable housing, food and employment stability, access to healthcare, effective schools, emergency and disaster preparedness, and ample public spaces for relaxation and exercise.

Like other animals, humans have been endowed with great potential to weather and adapt to trauma and significant stressors. However, for natural protective systems to develop and



operate effectively in the individual, ample social and material resources are necessary. Because resilience is dependent on multiple individual-level systems, which are embedded in larger social systems, future advances in understanding resilience and how to best foster it will require a broad-based multidisciplinary approach.

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## Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder

Marked inconsistencies exist in how treatment response, remission, recovery and relapse are defined in clinical trials for obsessive-compulsive disorder (OCD). This impairs the comparability of results and communication in the field. Empirical methods (e.g., signal detection analyses) have been used to calculate the optimal amount of symptom improvement to classify an individual as a “responder” or “remitter”, both in adults<sup>1-4</sup> and children<sup>5</sup> with OCD. Unfortunately, this has led to different recommendations.

The concept of “recovery”, used in other mental disorders such as depression<sup>6</sup>, is rarely used in the OCD literature. “Relapse” has been defined in some OCD studies as a return to pre-treatment symptom levels and in others as a worsening of symptoms to a certain degree<sup>7</sup>. These inconsistent definitions make comparisons across studies and treatment modalities challenging, and have led to different estimates of treatment efficacy and relapse risk<sup>8</sup>. The Reliable Change Index<sup>9</sup>, a scale-standardized metric often used to alleviate this issue, also has limitations, including the inability to use relevant normative samples across studies, leading to different severity cut-off scores<sup>10</sup>.

Since these constructs are man-made rather than natural entities, expert consensus may be a more appropriate approach to their definition. However, previous proposals<sup>7</sup> have not been met with wide acceptance. A broader, international, multidisciplinary consensus can create investment in standardization and motivate field-wide adoption of the resulting definitions. Here we describe the results of a multi-round, web-based Delphi survey<sup>11</sup>, the aim of which was to facilitate a global, expert consensus regarding the conceptual and operational definitions of treatment response, remission, recovery and relapse for use in clinical trials of OCD.

First, second, last and corresponding authors of international peer-reviewed OCD papers published between 2007 and 2013 were invited to participate. Participants included mainly psychologists and psychiatrists with expertise in pediatric and/or adult OCD. In a first round, participants were presented with conceptual definitions of treatment response, remission, recovery and relapse adapted from the depression literature<sup>6</sup> and different ways to operationalize them, and were asked with which they agreed.

Analysis of the responses obtained in Round 1 (N=468) showed that there was broad consensus regarding the conceptual definitions (>88% for all), but disagreement regarding their operationalization. In Round 2, participants (N=326) received Round 1 results, and new questions were asked to facilitate consensus on the operational definitions. Analysis of the response showed continued consensus for all conceptual definitions (>95%), and acceptable consensus (>82%) for all oper-

ational definitions, with one exception that is noted below. The consensus definitions are the following:

- *Treatment response.* **Conceptual:** A clinically meaningful reduction in symptoms (time, distress and interference associated with obsessions, compulsions and avoidance) relative to baseline severity in an individual who meets diagnostic criteria for OCD. **Operational:** A  $\geq 35\%$  reduction in (Children’s) Yale-Brown Obsessive Compulsive Scale ((C)Y-BOCS) scores plus Clinical Global Impression – Improvement (CGI-I) rating of 1 (“very much improved”) or 2 (“much improved”), lasting for at least one week.
- *Partial response.* **Conceptual:** Defined as in *treatment response* above. **Operational:** A  $\geq 25\%$  but  $< 35\%$  reduction in (C)Y-BOCS scores plus CGI-I rating of at least 3 (“minimally improved”), lasting for at least one week.
- *Remission.* **Conceptual:** The patient no longer meets syndromal criteria for the disorder and has no more than minimal symptoms. Residual obsessions, compulsions and avoidance may be present, but are not time consuming and do not interfere with the person’s everyday life. **Operational:** If a structured diagnostic interview is feasible, the person no longer meets diagnostic criteria for OCD for at least one week. If a structured diagnostic interview is not feasible, a score of  $\leq 12$  on the (C)Y-BOCS plus Clinical Global Impression - Severity (CGI-S) rating of 1 (“normal, not at all ill”) or 2 (“borderline mentally ill”), lasting for at least one week.
- *Recovery.* **Conceptual:** The patient no longer meets syndromal criteria for the disorder and has had no more than minimal symptoms. Residual obsessions, compulsions and avoidance may be present and slightly fluctuate in severity over time but, overall, they are not time consuming and do not interfere with the person’s everyday life and therefore require no further treatment. The clinician may begin to consider discontinuation of treatment or, if the treatment continues, the aim is to prevent relapse. **Operational:** As in *remission* above, but lasting at least one year.
- *Relapse.* **Conceptual:** After response or remission or recovery was achieved, the patient experiences a return of symptoms. For patients who were in remission or recovered, obsessions, compulsions and avoidance are again sufficiently time consuming, distressing and impairing for the individual to meet diagnostic criteria for OCD. **Operational** (for responders who did not necessarily remit/recover): The person no longer meets the definition of  $\geq 35\%$  reduction on (C)Y-BOCS scores (relative to pre-treatment) plus CGI-I rating of 6 (“much worse”) or higher for at least one month. **Operational** (for remitters/recovered): OCD criteria are met

again, according to a structured interview (if feasible). Alternatively, the person no longer meets the definition of remission/recovery (i.e., the person again scores 13 or above on the (C)Y-BOCS plus CGI-I rating of 6 (“much worse”) or higher for at least one month, or needs to be withdrawn prematurely from the trial before one month has elapsed due to a severe worsening of OCD symptoms. Discontinuation of the trial due to reasons other than worsening in OCD symptoms (e.g. suicide risk) is not considered a relapse.

Two comments are worth adding. First, in Round 1, to consider a patient a treatment responder or remitter, many experts (56% and 58%, respectively) thought that sustained improvement should be present for at least one month. However, this proposed duration clashes with the (C)Y-BOCS, which asks about symptoms during the “previous week”. In addition, response has been defined in most prior OCD trials at the end of treatment. In Round 2, despite explicating this, only 64% and 46% of experts agreed with the proposal of “at least one week” for the duration of response and remission, respectively. To accommodate this disagreement in the field, the duration for response and remission above allows for “at least one week” and we recommend additional follow-up assessments where possible to assess whether response/remission status has been maintained over longer periods.

Second, to judge that a patient relapsed, many experts (Round 1: 48%; Round 2: 87%) thought that worsening of symptoms should be present for at least one month to protect against transient flares in symptoms. However, some patients acutely deteriorate and require immediate clinical intervention<sup>12</sup>. For this reason, the relapse definition above indicates that patients who need to be removed from treatment protocols before one month because of worsening of OCD symptoms should also be considered to have relapsed.

In summary, agreement was reached on how to define response, remission, recovery and relapse across a range of international professionals with expertise in OCD. We recommend that researchers report their results using these definitions whenever possible. As outlined by Frank et al<sup>6</sup>, doing so will lead to: a) improved design, interpretation and comparison of clinical trials of various modalities; b) improved communication of research findings between professionals and to the general public; c) improved guidelines for evaluation of clinical efficacy of various treatments by regulatory agencies; and d) development of improved treatment guidelines for clinical practice.

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## Sustaining Individual Placement and Support (IPS) services: the IPS Learning Community

Worldwide, the deficiencies in community mental health services are well known: despite the development of many evidence-based practices, few clients with severe mental illness actually receive effective, recovery-oriented services<sup>1</sup>. Evidence-based practices are often implemented poorly and rarely endure beyond initial enthusiasm and grant funding. We examined two-year sustainment rates for a network of programs implementing Individual Placement and Support (IPS), an evidence-based practice to help people achieve competitive employment<sup>2</sup>. IPS is spreading in the U.S. and internationally<sup>3</sup>, including in Europe, Australia, Asia, and North America. Yet, long-term continuation of these services has been uncertain.

Because multiple factors influence a program's long-term survival, a comprehensive international learning community

has been developed to ensure sustainability of IPS. Beginning in the U.S. in 2001, the Dartmouth Psychiatric Research Center and the Johnson & Johnson Office of Corporate Contributions partnered to develop a multifaceted program to strengthen state and local infrastructures to promote access to IPS through broad dissemination, high-quality implementation, and long-term sustainment. After starting as a small demonstration in three states, the program has evolved internationally into a network of 19 states and 3 European countries known as the IPS Learning Community<sup>4</sup>.

Historically, the term *learning collaborative* has been used to define a network of organizations with a shared goal of improving treatment for a specific medical condition, facilitated by regular communication and collection and dissemination of

objective information about procedures and outcomes, typically over a few months<sup>5</sup>. The IPS group adopted the term *learning community* to signify their long-term commitment to quality and intention to expand to other states and countries. The term differentiates our approach from time-limited quality-improvement learning collaboratives, such as those sponsored by the Institute for Healthcare Improvement<sup>6</sup>.

The IPS Learning Community has encompassed a two-tiered, decentralized approach. In the U.S., Dartmouth trainers and researchers bring together state leaders and help them to build a viable infrastructure for implementing and sustaining IPS services within their states<sup>4</sup>. For international partners, regional administrators are the counterparts to these state leaders. In each state, the leadership team establishes liaisons with the two key state agencies responsible for employment services (i.e., mental health and vocational rehabilitation) and one or more state trainers. State leaders create parallel learning communities consisting of IPS programs within their states.

As part of their participation in the learning community, state leaders collect and submit employment outcome data for IPS programs within their states; Dartmouth analyzes and distributes the data back to the states<sup>7</sup>. State trainers conduct periodic fidelity reviews of both new and established IPS programs, using a validated fidelity scale<sup>8</sup>. Fidelity reviews evaluate the quality of program implementation. IPS programs are considered active participants once they begin submitting outcome reports, typically about nine months after start-up.

Altogether 157 programs joined the IPS Learning Community in the U.S. from its inception until 2012. However, we had not systematically tracked how long programs continued to provide IPS services after joining the learning community, or the rate of discontinuing programs. We therefore conducted a prospective study to determine the two-year sustainment rate of participating sites in the U.S.. We operationally defined sustainment as follows: a program is *sustained* if it continues to employ staff, maintains an active client caseload, and provides direct services.

We identified all programs participating in the learning community in the U.S. as of January 2012. The sample, consisting of 129 sites in 13 states, had participated in the learning community on average for 4.5 years (SD = 2.7, median = 3.9). Two years later we contacted these sites to determine which were still providing IPS services. A total of 124 sites (96%) were sustained over the 2-year period. This sustainment rate is higher than the 80% rate over a two-year period after the termination of the formal implementation phase in a national study of 49 sites implementing a new evidence-based practice<sup>9</sup>, and also exceeds the 76% two-year rate in an evaluation of 33 demonstration projects<sup>10</sup>.

Statistics on sustainability of evidence-based practices are rarely published. Many studies make it clear, however, that enthusiasm for an innovative program model often fades over time<sup>11</sup>. Funding initiatives targeting specific program models often spawn growth, followed by rapid dissolution when a

state-sponsored funding ends. For example, over a span of less than a decade, one state experienced a cycle of rapid growth followed by a collapse of services for an evidence-based practice when the targeted funding for this program was abruptly curtailed<sup>12</sup>. To our knowledge, no one has examined the empirical literature on sustainment to establish benchmarks for target rates for sustaining programs over time.

Bolstering the case for sustainability in the IPS learning community, the 124 sustaining sites had been in existence for an average of 4.5 years at the inception of the study. In other words, taking into account the arbitrary start date for the 2012 interviews, the total length of time for sustaining IPS services was substantially longer, on average 6.5 years. The number of sites still active in 2014 represent 79% of the entire group of 157 programs joining the community over its 13 years of existence, further documenting the role of the learning community in helping to sustain a practice.

Throughout Europe, Australia, and the U.S., program leaders are developing regional and national learning communities of IPS programs. Another ambitious example, in an early stage of development, is an international network of advocates for IPS services in early intervention programs for first episode psychosis<sup>13</sup>. In the U.S., one state recently launched a state-wide IPS initiative modeled after the IPS Learning Community. This initiative includes a technical assistance center that provides training and monitors fidelity and employment outcomes. Its initial employment outcomes have been similar to those in the national learning community<sup>14</sup>. It also established a dedicated IPS funding mechanism, which has contributed to the rapid growth of IPS services. By the end of 2014, 59 (69%) of 86 eligible programs had joined the initiative.

Sustainability of evidence-based practices appears to be enhanced through the mechanism of a learning community. Originating in the U.S., the IPS Learning Community is now spreading internationally, with preliminary reports that the concepts transfer readily to other cultures and service systems. The learning community approach has been relatively untested with other evidence-based practices, but its basic concepts are promising. The field needs controlled studies of long-term learning communities in comparison with usual methods. Replications are needed before drawing firm conclusions.

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## Suicidal ideation and suicide attempts in Greece during the economic crisis: an update

The current financial crisis has exerted untoward effects on the mental health of the population worldwide, in the form of increasing prevalence rates of affective disorders and suicide<sup>1</sup>. Greece is among the countries most severely hit by the crisis and has thus attracted global attention with regard to the social and health-related repercussions of the economic downturn. In particular, throughout the years of recession, unemployment rates rocketed from 7.8% in 2008 to 9.6% in 2009, 12.7% in 2010, 17.9% in 2011, 24.5% in 2012, 27.5% in 2013 and 26.5% in 2014<sup>2</sup>. At the same time, the proportion of the population at risk of poverty or social exclusion rose from 28.1% in 2008 to 35.7% in 2013 and 36% in 2014<sup>3</sup>.

Nonetheless, the impact of the recession on suicides has been a highly contentious issue in the country. Recently, a 30-year interrupted time series analysis on the influence of austerity- and prosperity-related events on suicide rates in the period 1983-2012 found a rise in total suicides by 35.7% after the introduction of new austerity measures in June 2011<sup>4</sup>. In a similar vein, another ecological study reported an increase in suicides by 35% between 2010 and 2012, with unemployment bearing a strong correlation with suicide mortality especially among working age men<sup>5</sup>.

A series of nationwide surveys conducted by our research team has arrived at similar conclusions, confirming a significant rise in the one-month prevalence of suicidal ideation (from 5.2% in 2009 to 6.7% in 2011) as well as suicide attempt (from 1.1% in 2009 to 1.5% in 2011)<sup>6</sup>. In the same report, people suffering from major depression, married individuals, people experiencing financial strain, people with low levels of interpersonal trust and individuals with a history of suicide attempt were at elevated odds of manifesting suicidality symptoms<sup>6</sup>.

In this frame, another cross-sectional study was implemented in 2013 in order to monitor the impact of the recession on suicidality as well as to identify at-risk population subgroups. A random and representative sample of 2,188 people participated in the study. Information about the occurrence of major depression, suicidal ideation and suicidal attempt during the past month was assessed with the pertinent modules of the Structured Clinical Interview for DSM-IV Axis Disorders<sup>7</sup>. Participants' degree of economic hardship was measured by the Index of Personal Economic Distress<sup>8</sup>, while their levels of interpersonal trust was assessed by the germane questions of the European Social Survey<sup>9</sup>.

Comparative results from surveys demonstrate that one-month prevalence of suicidal ideation has declined in 2013: 2.4% in 2008, 5.2% in 2009, 6.7% in 2011 and 2.6% in 2013 ( $p < 0.05$ ). Similar findings were observed for one-month prevalence of suicidal attempt: 0.6% in 2008, 1.1% in 2009, 1.5% in 2011 and 0.9% in 2013 ( $p < 0.05$ ).

Regarding the risk and protective factors for suicidality, a different pattern of results emerges for suicidal ideation and suicidal attempt. The presence of major depression (adjusted OR = 12.35, 95% CI: 6.34-24.08,  $p < 0.01$ ), a previous suicide attempt (adjusted OR = 5.54, 95% CI: 2.19-14.00,  $p < 0.01$ ), unemployment (adjusted OR = 2.55, 95% CI: 1.04-4.34,  $p < 0.05$ ) and economic hardship (adjusted OR = 1.07, 95% CI: 1.01-1.14,  $p < 0.05$ ) were found to increase the odds of manifesting suicidal thoughts. With regard to suicide attempt, the presence of major depression remained the strongest risk factor (adjusted OR = 8.02, 95% CI: 2.67-24.14,  $p < 0.01$ ), followed by previous suicide attempt (adjusted OR = 5.22, 95% CI: 1.44-18.94,  $p < 0.05$ ) and low levels of interpersonal trust (adjusted OR = 3.84, 95% CI: 1.17-5.81,  $p < 0.05$ ).

From the above-mentioned results, it is clear that the prevalence of suicidal ideation and suicidal attempt has returned to pre-crisis levels in Greece. This is consistent with the view that suicidal acts may reflect an acute response to an economic crisis<sup>10</sup>, as evidenced by the surge in suicides after the outset of the recession in South Korea in 1998 and their subsequent decline<sup>11</sup>.

Concerning the risk factors for suicidal ideation and attempt, the differences illustrate the multifaceted nature of suicidality, which is better conceptualized as lying on a spectrum from ideation to act, with different factors playing a prominent role in each step of the spectrum. The presence of major depression and previous suicide attempt increase the odds of manifesting suicidality symptoms throughout the whole spectrum, in line with other studies corroborating their strength of association<sup>12</sup>, even amid recession.

Although suicidality rates have decreased in Greece, depression is still on the rise<sup>13</sup> and the socio-economic climate in the country remains unstable. There is imperative need for tailored public health interventions, including labour market and debt relief programmes, as well as for enhancing the social capital of the population<sup>14</sup>. From the clinical standpoint, timely screening of suicidal history and suicidal symptoms, effective

treatment of major depression, and capitalizing upon a patient's social networks should become a priority.

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## New analytic strategies help answer the controversial question of whether alliance is therapeutic in itself

The association between alliance (at a given point in time or aggregated across several sessions) and outcome is one of the most consistent findings in psychotherapy research<sup>1,2</sup>. However, the mechanism underlying this association is one of the most controversial. Some theorists and researchers believe that alliance is therapeutic in itself; others argue that it is a by-product of effective treatment or of a trait-like patient ability to benefit from treatment<sup>3,4</sup>. For many years, the debate has been confined mainly to the domain of theory. Recently, several studies have applied advanced analytic strategies to explore the mechanism behind the alliance-outcome association.

The argument that alliance is simply a by-product of successful treatment has been previously addressed by studies controlling for early symptomatic change when examining the ability of alliance to predict outcome. Some of these studies suggest that alliance is indeed a by-product of early symptomatic change, while others indicate that it can predict outcome even after controlling for that change<sup>1</sup>. However, previous studies treated alliance as a static variable, and ignored the fact it can change across treatment, which may have contributed to the mixed results. Recent studies used statistical methods such as autoregressive cross-lagged modeling to examine whether alliance levels precede symptomatic levels, session by session over the entire course of treatment. The findings show that alliance indeed precedes symptom reduction over the course of treatment in both psychotherapy<sup>5-7</sup> and psychopharmacotherapy<sup>8</sup>, suggesting that it is a true predictor of outcome.

The other challenge to the argument that alliance is therapeutic is the proposition that alliance is a by-product of a patient's general trait-like ability to benefit from treatment. Individuals who are more capable of forming strong and satisfying relationships with others may also have a better chance

of forming a strong and satisfying alliance with their therapist. Alliance cannot be said to be therapeutic in itself if it is a trait-like characteristic of the patient. Recently developed detrending and centering methods<sup>9</sup> have made it possible to explore empirically the theoretical distinction between the state-like and trait-like components of alliance and determine which of the two predicts outcome. Studies show that patients' pre-treatment interpersonal characteristics can predict alliance as it develops across treatment<sup>10</sup> and that the alliance trait-like component can significantly predict outcome<sup>7,11</sup>. However, studies also suggest that state-like changes in alliance over treatment can have a significant effect on outcome<sup>5,7,11</sup>.

If state-like changes in alliance can bring about therapeutic change, manipulating these characteristics is expected to influence outcome. One recent study has examined this question empirically, randomizing patients to either a feedback condition, in which therapists received feedback on the alliance to assist them in strengthening its state-like component, or to a control condition in which no feedback was provided. The study found a greater effect of the state-like component of alliance on outcome in the feedback condition<sup>7</sup>, suggesting that the effect of this component of alliance on outcome can indeed be manipulated. Furthermore, another recent study suggests that when therapists detect poor alliance with their patients, and have sufficient time to work on strengthening the state-like component of alliance, this component is associated with a better outcome<sup>12</sup>.

The groundbreaking methodologies recently applied in psychotherapy research bring new insights to our understanding of the question of whether alliance is therapeutic. These methodologies are poised to play a critical role in future research, focusing on diverse populations and therapeutic orientations,

and may lead to the development of even more advanced models of moderation-mediation analyses.

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## Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression

Though bipolar disorder is characterized by episodes of mania/hypomania, depressive episodes pose the most burden for patients suffering from the disorder. Regrettably, few proven treatments exist for bipolar depression, and many patients either do not respond to, or have difficulty tolerating these treatments. Hence, novel, safe and effective treatments are urgently needed.

The neuromodulatory approaches, such as repetitive transcranial magnetic stimulation (rTMS), have been demonstrated to be efficacious in randomized double-blind sham-controlled trials (RCTs) in treating depressive episodes in patients with major depressive disorder. However, it is unclear whether the antidepressant efficacy of rTMS extends to bipolar depression. Many RCTs of rTMS in major depression have included patients with bipolar depression. Therefore, our objective was to systematically review the rTMS literature to identify bipolar patients included in randomized trials in order to synthesize the data on clinical efficacy and safety of rTMS in bipolar depression.

We registered the literature review protocol with PROSPERO (CRD#42015017089), which involved considering systematic reviews of rTMS in major depression and searching English-language publications in MEDLINE, EMBASE, and CENTRAL until July 11, 2015. We included randomized, double-blind, sham-controlled trials of rTMS involving  $\geq 5$  sessions that randomized patients with bipolar depression to both active and sham rTMS arms. We excluded RCTs that did not include patients with bipolar disorder, and those for which rates of clinical response were not reported or could not be obtained in correspondence with the investigators. We synthesized the data using Comprehensive Meta-Analyses Version 2.0 (Biostat, Englewood, NJ, USA). We analyzed intention to treat data with random effects models. Efficacy was investigated by risk difference (RD) and the number needed to treat (NNT). Supporting materials, including detailed methods, tables and figures are available by contacting the authors ([alexander.mcgirr@alumni.ubc.ca](mailto:alexander.mcgirr@alumni.ubc.ca)).

In total, we retained 19 RCTs in our meta-analysis<sup>1-19</sup>, totaling 181 patients with bipolar disorder (type I, N=40; type II, N=20;

unspecified, N=121). The RCTs employed different stimulation targets: the left dorsolateral prefrontal cortex (DLPFC)<sup>1-6,9-11,13,16,17</sup>, the right DLPFC<sup>8,14,15,18</sup>, or bilateral DLPFC<sup>7,12,17,19</sup>. The majority of studies delivered high-frequency stimulation (HFS)<sup>1,3-6,9-13,16,18</sup>, while some delivered low-frequency stimulation (LFS)<sup>3,8,9,15,18</sup>, sequential LFS and HFS<sup>7,17,19</sup>, or theta burst stimulation (TBS)<sup>2,14,17</sup>.

Significantly more patients receiving active rTMS achieved clinical response at study end compared to patients receiving sham rTMS (47/106, 44.3%, vs. 19/75, 25.3%; RD=0.18, 95% CI: 0.06-0.30,  $p<0.01$ ). This represents a NNT of 6 (95% CI: 4-15). The fail-safe N was 29, suggesting that 29 missing or null studies are required to render this finding not statistically significant. Examination of the funnel plot revealed an asymmetrical distribution, with substantial loading at RD=0. Despite considerable methodological heterogeneity, there was no statistical evidence of heterogeneity ( $Q=19.99$ ,  $df=22$ ,  $I^2=0.00$ ,  $p=0.58$ ; Egger's intercept = -0.36,  $t(21)=0.42$ ,  $p=0.67$ ).

The optimal stimulation target and parameters are important considerations in rTMS due to differing physiological effects. We observed a trend towards differential target efficacy ( $Q=5.72$ ,  $df=2$ ,  $p=0.057$ ). Indeed, RCTs targeting the right DLPFC demonstrated superior efficacy, with 9/15 (60.0%) of active rTMS patients achieving clinical response compared to 1/15 (6.6%) of sham rTMS patients. This represents a RD of 0.48 (95% CI: 0.17-0.78,  $p<0.001$ ) and a NNT of 3 (95% CI: 2-6). RCTs targeting the left DLPFC also separated from placebo, with 33/68 (48.5%) of patients receiving active rTMS achieving clinical response compared to 15/50 (30.0%) of sham-treated patients (RD=0.16, 95% CI: 0.00-0.31,  $p<0.05$ ), for a NNT of 7 (95% CI: 4-112). We did not observe separation between active and sham rTMS in RCTs employing bilateral stimulation (5/23, 21.73% vs. 3/14, 21.42%,  $p=0.68$ ). We did not observe differential efficacy based on stimulation parameters.

The issue of treatment-emergent affective switches in managing bipolar depression is important and controversial, and extends to neuromodulatory treatments. We observed a very low rate of treatment-emergent affective switches, and we did

not observe an increased risk associated with active rTMS (1/106, 0.9% vs. 1/75, 1.3%,  $p=0.97$ ).

Though preliminary in nature, our analyses suggest that rTMS may be a safe and efficacious treatment option for acute bipolar depression. The degree of efficacy appears, on the surface, to be comparable to that observed among patients with major depressive disorder. Indeed, an overall NNT of 6 for clinical response is comparable to the NNTs reported in meta-analyses of rTMS in that disorder. Protocols targeting the right DLPFC with inhibitory LFS or TBS may be particularly efficacious; however, this is based on a small number of trials, influenced by a low sham-response rate, and requires additional investigation.

Unfortunately, two RCTs dedicated to bipolar depression, with a total of 25 patients, could not be included, as clinical response and/or treatment protocols were unavailable in published form or through correspondence with investigators. Other biases include methodological heterogeneity between RCTs, and the limited number of RCTs and patients. Moreover, obtaining bipolar depressed data relied in large part on correspondence with investigators, and any bias related to successfully accessing this data remains.

This is, to our knowledge, the first meta-analysis of RCTs of rTMS in the treatment of acute bipolar depression. We capitalized on the inclusion of patients with bipolar disorder in sham-controlled RCTs of rTMS in the treatment of major depression to identify 181 patients. Our analyses suggest that rTMS may be efficacious and safe in the treatment of acute bipolar depression and does not appear to be associated with treatment-emergent affective switches. Further, large sham-controlled RCTs are needed in bipolar depression to confirm the efficacy of rTMS.

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## WPA Position Statement on Spirituality and Religion in Psychiatry

The WPA and the World Health Organization (WHO) have worked hard to assure that comprehensive mental health promotion and care are scientifically based and, at the same time, compassionate and culturally sensitive<sup>1,2</sup>. In recent decades, there has been increasing public and academic awareness of the relevance of spirituality and religion to health issues. Systematic reviews of the academic literature have identified more than 3,000 empirical studies investigating the relationship between religion/spirituality (R/S) and health<sup>3,4</sup>.

In the field of mental disorders, it has been shown that R/S has significant implications for prevalence (especially depressive and substance use disorders), diagnosis (e.g., differentiation between spiritual experiences and mental disorders), treatment (e.g., help seeking behavior, compliance, mindfulness, complementary therapies), outcomes (e.g., recovering and suicide) and prevention, as well as for quality of life and wellbeing<sup>3,4</sup>. The WHO has now included R/S as a dimension of quality of life<sup>5</sup>. Although there is evidence to show that R/S is usually associated with better health outcomes, it may also cause harm (e.g., treatment refusal, intolerance, negative religious coping). Surveys have shown that R/S values, beliefs and practices remain relevant to most of the world population and that patients would like to have their R/S concerns addressed in health care<sup>6-8</sup>.

Psychiatrists need to take into account all factors impacting on mental health. Evidence shows that R/S should be included among these, irrespective of psychiatrists' spiritual, religious or philosophical orientation. However, few medical schools or specialist curricula provide any formal training for psychiatrists to learn about the evidence available, or how to properly address R/S in research and clinical practice<sup>7,9</sup>. In order to fill this gap, the WPA and several national psychiatric associations (e.g., Brazil, India, South Africa, UK, and USA) have created sections on R/S. WPA has included "religion and spiritu-

ality" as a part of the "Core Training Curriculum for Psychiatry"<sup>10</sup>.

Both terms, religion and spirituality, lack a universally agreed definition. Definitions of spirituality usually refer to a dimension of human experience related to the transcendent, the sacred, or to ultimate reality. Spirituality is closely related to values, meaning and purpose in life. Spirituality may develop individually or in communities and traditions. Religion is often seen as the institutional aspect of spirituality, usually defined more in terms of systems of beliefs and practices related to the sacred or divine, as held by a community or social group<sup>3,8</sup>.

Regardless of precise definitions, spirituality and religion are concerned with the core beliefs, values and experiences of human beings. A consideration of their relevance to the origins, understanding and treatment of psychiatric disorders and the patient's attitude toward illness should therefore be central to clinical and academic psychiatry. Spiritual and religious considerations also have important ethical implications for the clinical practice of psychiatry<sup>11</sup>. In particular, the WPA proposes that:

1. A tactful consideration of patients' religious beliefs and practices as well as their spirituality should routinely be considered and will sometimes be an essential component of psychiatric history taking.
2. An understanding of religion and spirituality and their relationship to the diagnosis, etiology and treatment of psychiatric disorders should be considered as essential components of both psychiatric training and continuing professional development.
3. There is a need for more research on both religion and spirituality in psychiatry, especially on their clinical applications. These studies should cover a wide diversity of cultural and geographical backgrounds.
4. The approach to religion and spirituality should be person-centered. Psychia-

trists should not use their professional position for proselytizing for spiritual or secular worldviews. Psychiatrists should be expected always to respect and be sensitive to the spiritual/religious beliefs and practices of their patients, and of the families and carers of their patients.

5. Psychiatrists, whatever their personal beliefs, should be willing to work with leaders/members of faith communities, chaplains and pastoral workers, and others in the community, in support of the well-being of their patients, and should encourage their multidisciplinary colleagues to do likewise.
6. Psychiatrists should demonstrate awareness, respect and sensitivity to the important part that spirituality and religion play for many staff and volunteers in forming a vocation to work in the field of mental health care.
7. Psychiatrists should be knowledgeable concerning the potential for both benefit and harm of religious, spiritual and secular worldviews and practices and be willing to share this information in a critical but impartial way with the wider community in support of the promotion of health and well-being.

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## Update on WPA scientific publications

The WPA continues to help support, mentor and encourage member societies and colleagues to use their considerable expertise to publish their work, in order to disseminate knowledge across the world.

To that end, President D. Bhugra has appointed a highly qualified and representative group of experts to lead the publications program through the Operating Council. They are: M. Riba and D. Lecic-Tosevski (co-chairs); P. Chandra, C. Szabo and R. Heun (members); P. Tyrer and A. Cia (consultants); and J. Castaldelli-Maia (observer). The Council brings together a diverse and balanced set of publication experiences that will help shape the future directions of the portfolio of WPA scientific publications. Future meetings of the Council will be held in conjunction with WPA International Congress in Istanbul, Turkey in July 2016 and at the World Congress in Berlin, Germany in September 2017.

The WPA official journal, *World Psychiatry*, has now reached an impact factor of 14.225, ranking no. 3 among psychiatric journals (only *Molecular Psychiatry* and the *Archives of General Psychiatry* have a slightly higher impact factor, 14.496 and 14.480 respectively). In addition to a variety of scholarly papers, the journal regularly publishes news about the WPA initiatives<sup>1-6</sup> as well as information relevant

to the WPA partnership with the World Health Organization<sup>7-18</sup>.

In addition, the WPA publication programme benefits from the important and significant work of WPA Scientific Sections, coordinated by Secretary A. Javed. An excellent example of publications emanating from the Sections is *World Child and Adolescent Psychiatry*, edited by N. Skokauskas, which is the official journal of the WPA Section on Child and Adolescent Psychiatry<sup>19</sup>. The journal features editorials, in-depth perspectives, interviews, conference summaries, updates, and provides information on programs from around the world, as well as including a trainees' forum. Prof. Skokauskas and the editorial board have noted their appreciation for contributors who have made the journal possible, and so successful.

Other initiatives underway include a series of books on Psychiatry and Primary Care, with D. Bhugra and M. Riba as editors, that will be published by Springer. Plans are underway to work with editors and authors on such topics as physician wellness and interaction between psychiatry and primary care. H. Herrman, P. Chandra and others are also working on a book related to women's mental health. We very much look forward to these contributions.

Finally, we are investigating ways to use the updated WPA website, developed

by WPA Secretary General R.A. Kallivayalil and colleagues, for disseminating and publishing materials such as course work and other educational tools that at some point may be collated into books, either in print or online. Secretary E. Belfort has led efforts for such materials to be available through a growing number of conferences and meetings with WPA support and investment.

### Michelle Riba

WPA Secretary for Publications

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