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EDITORIAL

The political mission of psychiatry

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What contributes to poor mental health is well known (1): adverse childhood conditions; experience of war, persecution and torture (2); social isolation; unemployment and social exclusion; poverty, poor education and low socio-economic status; and social inequality.

In this issue of the journal, K. Wahlbeck (1) calls for action and requests that the evidence is translated into practice. What should be done? Obviously, in order to achieve substantial improvements in public mental health, we require societies to change and implement all those factors that promote mental health: societies should provide safe and supportive upbringing conditions; secure peace within and between countries; eradicate poverty; guarantee good education; strive for full employment; promote social cohesion and functional communities; and have little social inequality. These requirements are clear and unequivocal, no more research needed. Accordingly, the Melbourne charter concluded that mental well-being is best achieved in equitable, just and non-violent societies (1).

Yet, there is little evidence that we are currently making much progress towards such societies. In most industrialized countries the difference between rich and poor has been increasing, making societies more rather than less unequal, and war activities have been increasing worldwide since 2011 (3).

How can this be changed and societies improved? Changing the rules and processes within societies is clearly a political task. Politicians get elected to take decisions about military activities, expenditure on education and social welfare, employment rules, taxation and other means of redistribution. Politicians are democratically legitimized and authorized, mental health experts are not. Perhaps, we should therefore just provide our expert view and leave it there? This appears to have been the dominating attitude of mental health professional bodies during the last three decades. One may conclude that such abstaining from political involvement has been a major mistake, both for people with mental disorders and the profession itself.

If there is a will to engage politically and call for societal change on the basis of the evidence for public mental health, there are likely to be various and potentially strong allies, calling for similar changes based on expertise from other fields of medicine and social sciences. For example, social inequality is bad not only for mental health, but also for physical health and other social phenomena such as crime rates (4). Consequently, a World Health Organization European review of social health determinants (5) calls for action in the wider social and economic spheres, with less deprivation and a more balanced social gradient. Linking with such calls from experts in other fields may strengthen the impact of a political voice from mental health.

Political engagement of mental health professionals – even if aligned with experts from other fields as well as patient and carer groups – might still not be successful. Other societal forces and interests might drive societies in opposite directions, e.g., towards military engagements and even greater social inequality. Politicians are unlikely to change the welfare system or stop wars just because they are told by experts that this would be better for public mental health.

Despite this, raising our professional voice in the political arena might still be important. How can we – as mental health academics or clinicians – know the central importance of societal factors for mental health and not call for the political action to improve them – loudly and clearly? Whether effective or not, political engagement appears a moral imperative for a credible profession with coherent values (6). As a minimum, it can underline the societal relevance of psychiatry and help to link psychiatry and other important societal groups.

There are two further aspects to the political mission of psychiatry. First, historically, when psychiatry and the wider society opened up towards each other with a mutual interest, major mental health reforms became possible and found wide public support. For instance, psychiatric reform legislation in the 1970s was passed by Italian and German parliaments practically unanimously. The case of people with mental disorders was important to parties from across the whole political spectrum, linked to values of liberalism, social religious teaching, emancipation and social inclusion. Second, political engagement for inclusive societies is essential to improve the situation for a core group of psychiatric patients, i.e., those with severe and chronic conditions. Even in rich countries, large numbers of such patients end up in prisons, get little appropriate care, or receive limited support in long-term protected housing arrangements (7). Increasingly, patients can get lost in fragmented care systems, that are driven by economic interests of provider organizations; and patients who are unlikely to be economically productive are of diminishing interest to health care funders. In more unequal societies, these patients are at risk of even further exclusion and disadvantage. They need a professional group to support them in everyday life and stand up for them – and as far as possible with them – on a political level.

Specific and individualized prevention programmes will have only limited effects, unless general societal factors are addressed. For example, providing people with job problems with cognitive behavior therapy (1) is less important than

ensuring that people have jobs in the first place and that contracts guarantee sufficient income and acceptable working conditions. Political engagement on a local, national and international level is required for credibility and realistic chances to improve public mental health.

What credibility and what societal relevance do we have as a profession, if we disseminate the evidence in scientific journals, but do not care about the political action required to implement it?

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EDITORIAL

Public mental health: science or politics?

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The history of public health intervention arguably began when the handle was removed from the pump supplying cholera-infected water to one side of a street in London in 1854. It was based on careful medical observation and hypothesis testing, it was effective and it was certainly timely. In relation to infection control, subsequent successful measures were the introduction of proper sewerage and the regulation of standards in food hygiene. Public health doctors continue to be specialists in exactly these areas, and their success has transformed life expectancy especially for babies and young children almost everywhere.

So, what is the equivalent of the pump handle and what will be the consequences of removing it in the field of mental health? Is the time really ripe for translation of evidence into practice in the field of public mental health, as K. Wahlbeck (1) suggests in this issue of the journal?

Clearly this requires that we already have interventions for immediate application to key public mental health improvement. A meta-analysis (2) cited by Wahlbeck implies that primary prevention of "mental illness" in children and young people at risk – a 40% reduction – is indeed possible. If true, this would be very good. However, that meta-analysis reported only 161 new episodes of illness in total across seven rather small psychotherapy trials. Given the increasingly recognized bias in the way such trials are conducted and analyzed (3), the reported effect is improbably high and anyway applies to short-term outcomes and minor illness. Such psychotherapy is also labour intensive and potentially expensive. It is difficult to see how current models of provision could ever provide a population level approach even if the therapy did work. Indeed, all the examples cited by Wahlbeck seem to me to highlight how weak our current evidence base is, how much more certain we need to be that our understanding of causes and treatments of illness is correct, and how impractical the proposed interventions are likely to be unless delivered electronically.

Wahlbeck goes a further step in emphasizing the importance of wellbeing and mental health promotion not only as an end in itself but also as a solution to mental illness. However, where the evidence base is developing (and allowing us the little confidence we do have in causes and solutions) is in research on mental illness, not mental health. Take the sociology of research funding: compared with other illnesses, spending remains low in proportion to the societal burden of mental illness. But we know that because we can measure the burden of mental illness. We do not infer it by measuring the population's average wellbeing. This is equally true of the evidence used to advocate "mental health promotion". Is it not simply an inversion of what we know causes mental illness/distress? Thus we know that "good enough" early experience is critical to the normal development of children because sexual and physical abuse, neglect and loss lead to mental illness in later life. We do not infer this from the good outcomes of people with exceptional parents or even the average outcomes of people with average parents. And how good is the evidence that we can improve societal outcomes by intervening in the normal parenting of average children? It is only in deprived settings that improving parenting skills is associated with better outcomes. This is irrelevant to the broader societal context in developed countries. It again depends on an inversion of the evidence to imply that everyone needs a government enforcer to improve their parenting skills. So there is no reason to believe that turning mental illness into a mental health question – a public health approach according to Wahlbeck – can improve our evidence base or promote better research.

What areas really do provide a current public mental health challenge where governments can intervene? Wahlbeck opines: "Substance abuse disorders can be prevented by universal policy actions aimed to reduce the availability of alcohol and drugs. Effective regulatory interventions include taxation, restrictions on availability and total bans on all forms of direct and indirect advertising". Really? So is this a pump handle issue, a no-brainer for public health campaigners? Well, no, actually. Prohibition of alcohol in the U.S. (the extreme of reduced availability) provides a worked historical example of what a disaster some universal policy actions can be. Make alcohol more expensive or ban it and you will immediately create an illegal market for its distribution (i.e., organized crime), risk poisonous contamination of the product and criminalize those in society who wish to be free to drink it. On the other hand, as currently being argued out (4), take a drug like cannabis which is currently criminalized and legalize it, as is happening in piecemeal fashion "for medical use", and you risk the business efficiency of legal private industry increasing availability, desirability and strength of effect. Big marijuana could be quite like big tobacco. A public health approach must engage with the risks and benefits and think them through; the failure to do so means the argument becomes at best frivolous, at worst fantasy.

Indeed, what of the whole thesis that mental health should necessarily concern itself not only with mental illness, but also health and wellbeing? The argument is that this is necessary to make mental health a matter "of interest to everybody". The burden of psychiatric illness and its under-resourcing should be de-emphasized to make this

alternative formulation. This is propaganda, not science. Mildly supportive research evidence may often be made to suffice in a transient political dispute, but it is regrettable when made the basis for a public mental health agenda. However, the primacy of the politics does explain why the argument ends up by moving so seamlessly to support for fashionable models of service provision, casual dismissal of the "medical model" and uncritical support for a "recovery-oriented system of balanced care".

In the UK, this kind of approach has held sway for at least 15 years. There have been consequences (5). We have seen a proliferation of managers and providers of specialist services all of whom spend immense amounts of time in meetings. The key expression is "clinical governance": managers not doctors lead services, in so far they are led at all. We have seen an irresponsible reduction in bed numbers, which makes inpatient care a routinely unpleasant experience. The role of diagnosis and specialist treatment is seen as something to be delegated and now divided. It tends to be replaced with something vacuous and imprecise. The role of the psychiatrists in this system is to be simultaneously marginalized, but they remain responsible when things go wrong. Recruitment into psychiatry has plummeted (6) and remains extremely problematic.

Read the following amazing piece of prose (7), which addresses a method (probably now discarded, I am not sure) for changing how psychiatrists work. For those of you who may adopt the "Birmingham model" or whatever our system is called in translation, you can expect a lot of this sort of thing: "New Ways of Working is what it says – new ways of working – rather than a single service model or structure that has to be adopted. It recognizes that services catering for the different types of needs of service users across their lifespan and differing demographics and geography will need different configurations to manage their task most effectively. However, the underlying principles relating to using the skills of the workforce in the most productive way are common. It is about achieving cultural change; a shift in the way teams think about themselves, the skills of the individuals within them, and the reasons they are there. However, cultural change is difficult to achieve and it is difficult to measure the extent to which it has been achieved".

It has the charm of a pamphlet extolling the virtues of a Soviet collective farm. When I get an outstanding medical student express an interest in psychiatry, would I be wise to have him read these inspiring words, ending as they do with a sentence that embodies exhaustion and futility?

So, is public mental health really about pump handle breakthroughs, or the construction of a convenient fig leaf of superficial data to hide the political nature of the arguments that have so often intruded into the diagnosis and treatment of mental illness? It will be obvious that I see it as the latter. I commend the public handle standard instead.

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SPECIAL ARTICLE

Social cognition and psychopathology: a critical overview

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The philosophical and interdisciplinary debate about the nature of social cognition, and the processes involved, has important implications for psychiatry. On one account, mindreading depends on making theoretical inferences about another person's mental states based on knowledge of folk psychology, the so-called "theory theory" (TT). On a different account, "simulation theory" (ST), mindreading depends on simulating the other's mental states within one's own mental or motor system. A third approach, "interaction theory" (IT), looks to embodied processes (involving movement, gesture, facial expression, vocal intonation, etc.) and the dynamics of intersubjective interactions (joint attention, joint action, and processes not confined to an individual system) in highly contextualized situations to explain social cognition, and disruptions of these processes in some psychopathological conditions. In this paper, we present a brief summary of these three theoretical frameworks (TT, ST, IT). We then focus on impaired social abilities in autism and schizophrenia from the perspective of the three approaches. We discuss the limitations of such approaches in the scientific studies of these and other pathologies, and we close with a short reflection on the future of the field. In this regard we argue that, to the extent that TT, ST and IT offer explanations that capture different (limited) aspects of social cognition, a pluralist approach might be best.

Key words: Social cognition, autism, schizophrenia, theory of mind, simulation theory, interaction theory

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The area of research dealing with how we make sense of the behavior of other human beings ("social cognition") has proved both productive and controversial, and has come to occupy an important position in contemporary debates in the philosophy of mind, psychology and neuroscience. The goal of this paper is to discuss the theoretical frameworks that connect social cognition and psychopathology, and that generate fruitful, philosophically well-grounded and empirically informed reflections that are relevant to psychiatric research.

The two leading approaches in this area are those called "theory theory" (TT) and "simulation theory" (ST). The TT claims that we make inferences about the mental states of others on the basis of a general and commonsense theory ("folk psychology") about the way in which mental states are usually connected to behavior. In contrast, the ST proposes that we mentally "step into the shoes" of the relevant person and model the mental states behind the behaviors by generating an internal simulation. Alternatively, a more recently developed approach, "interaction theory" (IT), highlights the (constitutive) role of social interaction, and maintains that in many cases we do not need to theorize nor to run a simulation in order to make sense of others.

To understand the concept of "theorizing" in contemporary discussions in the field of social cognition, it is useful to point to Premack and Woodruff's (1) famous experiments that led to reflections about whether chimpanzees might possess a "theory of mind". The idea that the "folk" understanding of psychology is underpinned by some kind of "theory" was not unknown in philosophy. But since Premack and Woodruff's paper it has become common to discuss processes in which we make sense of the mental states of others under the label "theory of mind" (ToM) (2). In this context, "theory" is defined as a system of inferences that can be used to "mindread", i.e., to attribute mental states in order to explain or make predictions about the other's behavior.

Having a ToM requires one to have a concept of belief, and one way to show that an animal or a human possesses the concept of belief is to show that it is able to impute a "false belief" to another. Wimmer and Perner (3) designed experiments to determine when, developmentally, children are able to impute false beliefs to others. The results showed that, on average, 3-year-old children fail on "false-belief tasks", but they acquire the concept of false belief by the age of 4 or 5.

On some accounts of TT, the theory or theory mechanism is innate and activated at a certain stage of development (4-6); on other accounts, the theory ("folk psychology") is acquired gradually: children, somewhat like scientists, revise their theories in light of new evidence (7,8).

Already by the mid 1980s, ST was put forth as an alternative to TT (9-11). ST denies that social cognition proceeds by deploying theories, and argues instead that "mindreaders capitalize on the fact that they themselves are decision makers, hence possessors of decision-making capacities; to read the minds of others, they need not consult a special chapter on human psychology, containing a theory about the human decision-making mechanism; because they have one of those mechanisms themselves, they can simply run their mechanism on the pretend input appropriate to the target's initial position" (2).

Instead of relying on a theory, ST maintains that mindreaders use their own minds to make sense of others. Of

course, this view has to be rendered more precise to avoid the obvious charge that ST is only a particular form of TT, since, in order to get the simulation process going, it may seem that one requires the inference that the person to be simulated is relevantly like the person who simulates (12). Also, the view that simulation and theorizing processes might not be mutually exclusive has given rise to hybrid theories (13).

While TT and ST have largely dominated the discussions over the past decade or so, some philosophers have argued that one other possibility is to construct hybrid accounts combining ST and TT processes on different levels. The idea is that theory or simulation might have different functions that together enable social cognition. One difficulty that such accounts have to overcome is to specify the roles that theory and simulation procedures are meant to play (14), while securing that the hybrid account is not vulnerable to the objections that ST or TT face.

Although there is much more to be said about hybrid theories, the very fact that ST and TT can be combined demonstrates to some extent that they share some common commitments. One of these commitments is that social cognition, which both theories conceive of as the prediction and explanation of behavior, proceeds by the inferential or projective attribution of causally efficacious mental states. The closely related common assumption that often finds expression in the literature is that we can only know of mental states indirectly, as we only have access to outward behavior, but not to the mental states themselves.

In recent years, IT has been proposed as an alternative to TT and ST. IT puts more emphasis on social interaction and the direct perception of at least some mental states (15-20) and draws on embodied, embedded, and especially enactivist theories of perception and cognition (e.g., 17,21,22), which are currently gaining ground in cognitive science. Enactivists in general maintain that the mind is embodied, that perception and action are closely related (perception is "for action"), and that cognition is not mediated by internal representations (21,23,24). IT claims that social cognition is embodied, that perception is for *inter*action, and that, for most of our ordinary everyday interactions, mindreading (including meta-representational versions of mindreading) is not necessary.

To make this case IT appeals to ongoing research in developmental psychology. Psychologists like Trevarthen (25), Hobson (26), Reddy (27) and Rochat (28) have provided convincing evidence that sensory-motor processes of perception and action, as well as emotional aspects of dyadic encounters, are central to the early development (in the first year of life) of social interaction (this is termed "primary intersubjectivity").

By the end of the first year of life, primary intersubjective processes allow the child to gain a basic perception- and interaction-based embodied understanding of the intentions and emotions of others. For example, given that intentions are perceptible as intrinsic features of actions (different intentions involve different kinematic properties) (e.g., 29), infants gain a perception-based understanding of other people's intentions by 10 months (30,31). They also interact through embodied responses in line with their caregivers' dynamically expressed emotions.

Importantly, such primary intersubjective processes are not merely developmental stages that disappear in adulthood. Rather, they continue operating and progressively become more refined, to the extent that in many everyday interactions we immediately understand the intentions, emotions and actions of others in their movements, gestures, facial expressions, vocalizations, and in the particular pragmatic and social contexts in which they act, without having to infer or simulate what is going on inside their heads.

The developmental literature also specifies that "secondary intersubjective" processes, starting with joint attention in the first year of life, allow for a contextualized understanding of others as we engage with them in pragmatic and social contexts. We begin to understand others by seeing them act in specific circumstances, and by interacting with them in such circumstances.

Later in development, according to IT, communicative and narrative competencies are built on primary and secondary intersubjective processes. Developmental studies of 2-4 year-olds and older children show the importance of communicative interactions and the ability for framing the actions of others in narrative terms (e.g., 32-35). Understanding others along these lines limits the need for mindreading, understood as focused on explaining and predicting behavior based on mental state attribution, as in ToM.

These three approaches – TT, ST and IT – form the basis for ongoing theoretical debates concerning core aspects of social cognition, cutting across philosophy, psychology and neuroscience. Within such debates, questions about psychopathology have been consistently raised. There has been a special focus on autism, because it involves clear deficits in social cognition. Such deficits, however, are also found in schizophrenia (36-38), depression (39), bipolar disorder (40), and other disorders.

AUTISM

First identified by Kanner and Asperger in the 1940s as a distinct clinical entity, autism has presented many enigmas to researchers. One of the most crucial observations was that, while children with autism demonstrated sustained interest in engaging with a variety of objects, they exhibited very little interest in engaging in interaction with the persons in their respective environments.

Kanner reported that individuals with autism engage in repetitive, monotonous activities with numbers or objects. Concerning one individual with autism, he noted that "when taken into a room, he completely disregarded the people and instantly went for objects, preferably those

that could be spun" (41). In more recent research, it is common to speak about a triad of problems, involving socialization, communication, and imagination, as central to autism (42).

Autism and TT

The general theoretical approach that many researchers since the 1980s have adopted concerning autism is one that links the impairments to deficiencies in fundamental "mindreading" abilities. In autism, as noticed by Baron-Cohen (43), mindreading and joint attention deficits appear early at the end of the first year of life and are universal for the whole spectrum of the disorder. It is due to such considerations, and to the fact that this particular approach has been able to successfully explain some of the features in all three previously mentioned areas, that autism is often described as "mindblindness" (44).

Crucial findings by U. Frith, Leslie and Baron-Cohen influenced the way in which the TT approach developed. A false-belief task experiment involving a group of typically developing children, one of children with autism and one of children with Down syndrome successfully established a very solid connection between autism and deficits in social cognition. A large majority of autistic children, in contrast to the typically developing and the Down syndrome groups, failed the false-belief task. Together with the finding that autistic children fail to understand mentalistic stories (45), this led to the conclusion that autism impairs a domain-specific capacity.

The ToM explanation of autism expounded by these researchers suggested that typically developing children from the age of 4 years have an implicit understanding of people as entertaining beliefs and desires that causally influence their behavior. The ability to implicitly or explicitly theorize about mental states in others is lacking or is impaired in children with autism, and the impairments include the inability to attribute true and false beliefs to others (45-48).

In addition, the fact that autistic children do not exhibit cognitive-inferential shortcomings led researchers to infer the existence of a particular, likely modular, "ToM mechanism" for creating and handling meta-representations (47), which some believed was additionally supported by evolutionary psychology (44). Leslie (6) argued that the "ToM mechanism" is domain specific, employs a proprietary representational system, and forms the basis for acquiring a ToM. In cases of childhood autism, the mechanism is damaged, resulting in difficulties acquiring a full-fledged ToM, a form of "mindblindness" which is "the core and possibly universal abnormality of autistic individuals" (43).

Leslie (49) further suggested that individuals with autism have a meta-representational deficit, and that the capacity for pretending (also problematic in autism) draws on the same cognitive mechanism involved in understanding others. Symbolic-pretend play requires "double knowledge" of the situation, otherwise confusion would occur in regard to distinguishing real from pretend (50,51). For example, the child pretends that the banana is a telephone, while keeping in mind that inferences made from this pretense are not valid in real-world belief contexts (52). Leslie's point was that the same de-coupler mechanism is a central component employed in both pretend play and mindreading, in which the child forms a meta-representation of the mental states of others (5). On this view, pretend play provides early evidence of a "ToM mechanism" (53,54), which enables mental representation of another's mental representation (55).

While the connection of deficits in pretend play with deficits in the operation of the meta-representational aspect of the "ToM mechanism" appears productive, a range of theorists have criticized the view. For instance, it has been documented that some high-functioning autistic individuals and children with higher verbal mental ages are able to produce limited symbolic-pretend play. In other words, they show the ability to meta-represent, even if their pretend behaviors are frequently stereotyped. Although they do not engage in pretense spontaneously, when receiving guidance and appropriate prompts, many children with autism are able to engage in symbolic-pretend play (56-59). In addition, it is not entirely clear that pretense necessitates meta-representation (60). Clearly, the child has to be able to distinguish a pretense situation from a real one, but it is not clear to what extent the child has to know exactly how the real situation differs from the imagined one. One could argue that, in order to understand the pretend situation, all one needs to know is what we could call the implied referential ambiguity of pretense: that the pretend situation somehow differs from the real one. Nor is it clear that the child needs to possess knowledge of the real situation in order to evaluate the truth of psychological predicates (60-62).

There are further reasons to doubt that the TT explanation is wholly satisfactory. Some of the criticism is motivated by the fact that between 15 and 60% of individuals with autism actually manage to pass false-belief tasks (42,63). Others have maintained that the ToM deficit may not be primary for every case of autism, but rather a correlated deficit (64). More recently, Apperly (65) concluded that "research on autism does not provide support for the hypothesis that mindreading has a strongly domain-specific cognitive or neural substrate, nor does it provide clear evidence on the causal dependence of mindreading on language and executive function; and, the fact that a significant sub-set of people with autism – who have clinical levels of social impairment – nonetheless pass many standard mindreading tasks should make us cautious about claims that autism is due to a lack of mindreading concepts, or that the presence or absence of these concepts can be straightforwardly diagnosed with laboratory tasks".

But the TT explanation of autism has also been criticized on different grounds. Hobson (26,66) maintains that Kanner's (41,67) original emphasis on the emotional nature of the disorder, and the failure of individuals with autism to

engage in affectively charged interactions, have been neglected. The crucial point in Hobson's work is that autism involves a diminished or lack of capacity to perceive other people as creatures intentionally directed to the world – a capacity that develops in the interactional context of caregiving. Among other sources, Hobson (26) points to the case of severely abandoned and socially deprived children in Romanian orphanages. While social deprivation resulted in profound emotional difficulties and delayed cognitive development, a significant minority also exhibited severe autistic-like behaviors. Roughly put, Hobson argued that the autistic-like behaviors could be explained through the lack of affectively saturated interactions with caregivers. Of course, the conclusion is not that autism is caused by social deprivation, but that any explanation of autism should be more sensitive to affective-interpersonal factors.

Another objection is that there is a risk in the relevant research of equating the possession of a ToM to the capacity to pass false-belief tasks (68). When we take seriously the amazing complexity of the ways in which we understand other human beings, it seems improbable that an explanation of its delayed or impaired development could be achieved by recourse to one particular construct. As Bowler (68) argues, "precisely because the term 'theory of mind' can now only be used descriptively, and precisely because the tests used to demonstrate autistic social impairment at different ages and different levels of ability vary radically in terms of their underlying theoretical constructs, we must look elsewhere for an explanation of what confronts the observer as impairment in the social domain".

Autism and ST

Proponents of ST have offered their own accounts of autism. For example, although Goldman maintains that autism is so complex that it is unlikely that one single theory will explain everything, he also thinks that ST may provide a good explanation (2). In particular, he takes the "extreme-male-brain theory of autism" as elaborated by Baron-Cohen (69) to support ST.

The core of Baron-Cohen's thesis is the existence of two kinds of cognitive activity in normal humans: empathizing and systemizing. Crudely put, autistic individuals exhibit severe deficiencies in empathizing, but not in systemizing. This "would provide strong evidence for ST, because it would show that a major clinical population known to be deficient in mindreading is also deficient in the use of simulation for mindreading" (2). Goldman, and others, equate empathy, mindreading and simulation, and link these capacities to the proper function of mirror neurons. Indeed, Goldman argues that "it is precisely a deficit in interpersonal mental simulation, also called empathizing, that seems to characterize autistic individuals" (2), and he thinks that the link between autism and mirror-neuron dysfunction, suggested by some studies, lends further credibility to an ST account of autism.

But the nature of the link is not entirely clear. It is indeed true that some researchers believe there is a connection between autism and dysfunction of mirror neurons (70,71), but the evidence is indirect (72) and does not clearly establish that autistic subjects are not capable of low-level, automatic simulation. There is also some theoretical resistance to the idea that mirror neurons should be construed as *simulating* in the manner suggested by Goldman (73), and several empirical studies challenge the idea of automatic mirroring, understood as intersubjective matching or simulating (74-76).

Indeed, neither the conventional conception of simulation that involves pretense, nor a redefinition of simulation in terms of matching seems to work as a model for mirror neuron activation (77). For this reason some theorists have proposed a redefinition of simulation in terms of neuronal reuse (78-81). On the latter view, we (re)use motor control mechanisms (the so-called forward model, which allows us to correct our actions as they are in process), to simulate the actions we see others do. One question, however, is how redeployment of such mechanisms, which remain on a low level of effector-related basic movement (reaching and grasping with hand, for example), can deliver an unambiguous understanding of the other's intention or goal in the social cognition context. That is, a motor control model based on reuse of efferent signals may be too low level (too closely tied to effectors) to give us an understanding of anything close to the goal-related meaning of even a simple intentional action (see 82). Furthermore, the neural reuse account of simulation offers an explanation of how simulation mechanisms evolved, but does not offer an alternative account of how those mechanisms work that would differ from the concept of simulation as matching. To be clear, mirror neurons may very well be activated in normal everyday intersubjective interactions, and may be dysfunctional in autistic subjects; what is in question is whether the simulationist interpretation of the mirror system, in terms of pretense, matching or reuse, is accurate or sufficient.

Autism and IT

IT theorists have also attempted to account for some of the puzzling characteristics of autism, providing an alternative to the existing TT and ST approaches. These theorists focus on the fact that children with autism display problems on the level of primary intersubjectivity, at a developmental stage before anything like ToM impairments appear (83).

Sensory-motor impairments affecting primary intersubjective functions related to social interaction appear early (during the first year) in infants later diagnosed with autism. Studies that show basic sensory-motor problems in autistic children during the first year (84), as well as between 3 and 10 years (see 85,86), support this general idea. This research

has been recently and dramatically reinforced in studies by Torres and colleagues (87). These studies show, in great detail and across the entire autistic spectrum, disrupted patterns in re-entrant (afferent, proprioceptive) sensory feedback that usually contributes to the autonomous regulation and coordination of motor output. Such feedback supports volitional control and fluid, flexible transitions between intentional and spontaneous behaviors. In autism, there is a disruption in the maturation of this form of proprioception, and this is accompanied by behavioral variability in motor control. In contrast to typically developing individuals, the normalized peak (micro-movement) velocity and noise-to-signal ratios in the movement of all participants with autism, across different ages and across different verbal or non-verbal status, remained in a region corresponding to younger (3-year-old) typically developing children. Noise overpowers signal in the motor systems of individuals with autism. Proprioceptive input is random (unpredictable), noisy (unreliable), and non-diversified. Subjects with autism had difficulty distinguishing goal-directed from goal-less motions in most tasks (87). In effect, central aspects of primary intersubjectivity, a pervasive and basic component of social interaction, were disrupted.

Because sensory-motor processes are random, noisy and restricted, it is unlikely that individuals with autism can anticipate the consequences of their own impending movements in a timely fashion. It also makes it difficult if not impossible to apply fine-tuned discriminations to the actions and emotional facial expressions of others during real-time social interactions. The use of ToM strategies in high-functioning autistic subjects, then, would be compensatory for the loss of the more primary processes.

Such sensory-motor problems can also explain other aspects of autism. Donnelan et al (88) note that "some people [with autism] rock, repeatedly touch an object, jump, and finger posture while other people come to a standstill in a doorway, sit until cued to move or turn away when someone beckons". Whereas such patterns are usually interpreted as meaningless and explained away reductively, Donnelan et al argue that they should be taken very seriously. Further, a meta-analysis by Fournier et al (89) confirms such sensory-motor problems in autism and suggests that they constitute a "core element", which should be reflected in interventions (see also 90,91). Savarese (92) notes that "the tide has clearly shifted with respect to the sensorimotor hypothesis; what was once dismissed out of hand by an earlier generation of autism researchers is now increasingly being taken up for its superior explanatory power".

SCHIZOPHRENIA

Autism has attracted an increasing interest of researchers involved in both philosophical and psychiatric inquiry on social cognition over the past 20 years, and there are clear positions staked out on the issues involved in this condition. This is not the case with schizophrenia, although a great number of studies have confirmed ToM impairments (and a reduced capacity to engage in communication) in individuals with this disorder.

Schizophrenia and TT

Neither the TT nor the ST has been fully explored to link them to the behaviors of patients with schizophrenia (93). This situation is the result of several factors, but one of them is surely that is has been difficult to establish whether the empirical results do indicate a specific ToM deficit in this disorder. On the one hand, there is some evidence that ToM deficits in schizophrenia are domain specific rather than the result of general cognitive impairments (37,94,95). On the other, there are some doubts as to whether the tests used to assess ToM (false-belief task, story comprehension, etc.) in fact clearly demonstrate this. Park et al (93) argue that the tasks "are not specific to tapping mental state attributions and instead, recruit an assortment of cognitive functions, ranging from working memory and selective attention to semantic memory and pragmatics". In a somewhat similar way, some suggest that executive and planning deficits may be responsible for some of the ToM disturbances (e.g., 96,97).

C. Frith (98) argued that symptoms associated with schizophrenia could be explained by impairment in mindreading abilities. In particular, he emphasized failures in self-monitoring and recognizing mental states and behavior; accordingly, he proposed to understand schizophrenic symptoms as linked to impaired meta-representation. As to the positive symptoms of schizophrenia, two specific deficits, delusions of control and thought insertion, were highlighted (98-100). The failure to successfully monitor one's own mental states might lead to such symptoms, while the failure to keep track of the mental states of others could result in a variety of paranoid delusions.

The idea that ToM deficits can explain some psychotic symptoms, however, does not sit well with the dominant models of autism, which link those deficits to autistic symptoms. Frith (98) distinguished between deficits in early-onset and late-onset mentalizing/mindreading. He maintained that in autism the ToM is not operative early in life, which hinders normal development of social skills. In patients with schizophrenia, instead, the ToM is operative early in life, allowing normal development and mastery of deploying mental state concepts to make sense of behavior. Nevertheless, with the onset of the disease, ToM impairments lead to unwarranted inferences about other people's mental states.

The evidence that patients with schizophrenia fail modified ToM tasks previously used to assess mindreading capacities in autism is consistent with this distinction (94). Patients with schizophrenia demonstrate reduced understanding of false beliefs and have problems inferring intentions of speakers from indirect hints (99,101). Moreover,

individuals with schizophrenia have difficulties comprehending jokes when they require reflection on mental states (101).

Nevertheless, some problems remain for the TT account. If meta-representations are conceptualized as non-modular, then the challenge is to explain why adults with schizophrenia fail the ToM tasks, although they possess conceptual knowledge about the nature of mental states. As Langdon et al (94) note, "many deluded patients with schizophrenia clearly know that beliefs can be false and that other people's beliefs differ from their own: they simply hold that their own beliefs are true". Put differently, one problem for TT is that schizophrenia patients do not necessarily lack basic knowledge about mental states, which suggests that they are able to use meta-representation.

Schizophrenia and ST

Those who favor ST start by taking seriously the fact that schizophrenic patients with severely disorganized cognitive, planning and communicative abilities usually perform poorly on ToM tasks, while patients without disorganization symptoms often have preserved ToM skills. Patients with cognitive disorganization are unable to monitor their own thought processes and therefore unable to use their own mental states as a model for simulating others (37,97).

Park et al (93) studied the ability of patients with schizophrenia to imitate behaviors, and found a "fundamental" impairment in imitation skills. The patients exhibited deficits even in imitating simple meaningless manual and oral gestures as well as facial emotional expressions, which has been confirmed in other studies (102). Regardless of the complexity of the task, the patients were less accurate than controls. Although the study did not directly address the relationship between simulation and social cognition, it suggests that a basic deficit in the imitation ability may lead to difficulties in simulation.

Both TT and ST suggest some differentiation among patient groups. Patients with negative symptoms and cognitive disorganization would be most ToM impaired (similar to autistic individuals), and may have difficulty representing mental states at all. Those with paranoid symptoms also have trouble with ToM, overly monitoring the intentions of others, and doing so inaccurately (103-105). Patients with passivity symptoms, however, perform closer to normal on ToM tasks (37,95,106).

A number of factors, however, have complicated empirical studies of ToM performance in schizophrenia. Consider that brain areas involved in ToM (including prefrontal cortex, paracingulate cortex, amygdala and temporal cortex) are frequently abnormal in schizophrenia, although not always, and not exclusively. Cortical connectivity is also an issue (e.g., 107-109). Furthermore, the results of false-belief tests may be complicated by the more general loss of contact with reality characteristic of some schizophrenic processes. Patients with schizophrenia, for example, not only fail to attribute the correct mental states to others, but also often fail to correctly respond to the reality questions used as a control – e.g., in the Sally-Anne test, "Where is the toy *really* located?" (100,110).

Schizophrenia and IT

From a critical perspective, IT points to some important limitations involved in the ToM approaches for understanding social cognition in schizophrenia. For example, a study by McCabe et al (111) suggests that, in contrast to the difficulties shown by schizophrenic patients with ToM tasks in the various experimental studies, these patients show no such problems in clinical conversations and interviews. They respond to the clinician on the basis of what the clinician needs to know. They acknowledge and take account of the fact that the clinician can have different beliefs from their own. This points to an important difference between the experimental ToM task and a clinical conversation. In the latter case the patient is *interacting* with the clinician, whereas, in the typical ToM task, the patient is asked to make observational or third-person judgments about another person's beliefs.

Frith (106) rightly notes that there is a fundamental difference between the use of mentalizing in discourse and in ToM tasks. In other domains this difference has been characterized as "on-line" versus "off-line" processing (e.g., 112). During discourse, mentalizing is used implicitly and automatically in the service of communicating; in this sense, it is used on-line. In most ToM tasks mentalizing is carried out off-line: the patient is not taking part in the interaction, but must make explicit use of mentalizing to answer questions about an interaction that has been described. This requirement puts more weight on working memory and on meta-cognitive processes (i.e., reflecting on mentalizing).

The typical false-belief test performed with children explores mindreading from an observational rather than interactional perspective. Even in such testing situations, however, the 3-year old child who fails the false-belief test shows no problem in understanding the experimenter, or what the experimenter wants. That is because the child is in a second-person, interactive relation with the experimenter. This is an important difference from the perspective of IT. For IT, the primary process in everyday social encounters is interaction. Taking a reflective, third-person, observational stance is a more sophisticated and derived accomplishment. In this regard, if schizophrenic patients do better in some cases of second-person interaction (as in the clinical setting) than in third-person ToM experiments, this suggests that at the very least the ToM explanations are not giving us the best accounts of their problems.

Given the various problems that people with schizophrenia have with contextual cues, IT suggests that disruptions in abilities associated with secondary intersubjectivity are

involved. Secondary intersubjectivity involves engaging in contextualized activities with others and relying on contextual differences for understanding the meaning of the other's actions. Schizophrenic patients show impairment in using contextual information in intersubjective situations (94,98). Such problems with contextual perspective are reflected in problems with language (97,113), including problems with communicative pragmatics and narrative competency.

Schizophrenia patients have a tendency to interpret metaphorical speech literally (37,114), show impaired pragmatics (115), and impaired use of context-dependent information when presented with ambiguous verbal material (116). They also show problems in understanding and generating narratives (117-120), which likely interfere with narrative-based false-belief tests (see 99,121). Additional problems with autobiographical memory in schizophrenia (122) are disruptive for the formation of self-narrative. Related to this, Bruner (123) points out that "dysnarrativia" (encountered for example in Korsakoff's syndrome or Alzheimer's disease) is destructive not only for self understanding generated in narrative (see 124), but also for the ability to understand others' behavior and their emotional experiences.

OTHER MENTAL DISORDERS

Deficits in social cognition have been reported in many other mental disorders, including depression (39), bipolar disorder (40,125), Alzheimer's disease (126), and frontotemporal dementia (127). The literature on these disorders is very limited, however.

In a study of Alzheimer's disease involving mild dementia, 65% of patients failed to understand false-beliefs presented in short stories (127). The same group also had severe deficits on tests of verbal anterograde memory, verbal comprehension, abstract thinking, and naming, compared to patients who passed the test. Further testing would be required to determine whether these are problems that involve a ToM mechanism or problems with narrative competency, and to explore to what extent these are problems encountered in everyday circumstances of "on-line" interactions, rather than simply in the experimental setting.

Similar questions are relevant to studies of ToM which indicate problems in frontal and temporal cortical areas in bipolar disorder (40,125), and the various studies reviewed by Adenzato et al (127) where traditional ToM/false-belief tests were used to test patients with the behavioral variant of frontotemporal dementia. Neuroscientific interpretation framed in terms of TT or ST can complicate the results. Cortical areas involved in studies of frontotemporal dementia – medial prefrontal cortex especially, but also temporoparietal junction, and temporal poles – are associated with ToM functioning, but not exclusively so. Such areas are not specific for intersubjective understanding, since they also serve future planning, abstract representations, evaluation, as well as default mode functions that may or may not involve self-monitoring, self-referential process and self-generated thoughts. In effect, these areas may serve a general evaluative performance over a wide scope of functions (128). The design of mindreading or false-belief experiments may call upon these brain areas only because the tasks are all "off-line" and call for a reflective evaluative rather than on-line social interaction.

One might expect to find problems with intersubjective relations in antisocial personality disorders. Studies designed on the ToM model, however, show that subjects with these disorders do not perform worse than controls on most of the standard ToM tests (129,130). As Frith (106) has noted, however, ToM should not be equated with social cognition more generally. Studies that focus on strict mindreading abilities will only reveal to us a part of the nature of intersubjectivity. Studying intersubjectivity in psychopathologies, therefore, requires going beyond ToM functions and investigating on-line, second-person, social interactions, as well as more general issues about how patients are able to relate to and communicate with others, and the various social problems they may experience.

CONCLUDING REMARKS

The philosophical interest in psychopathology is propelled by the hope of providing a profound understanding of the dimensions of the impairments involved, but also by expectations that studies of psychopathology will help to reveal crucial aspects about the social cognitive processes at stake in non-disordered cases. To the extent that philosophical debates about social cognition can have relevance to psychiatry, then one point to take home is that empirically informed discussions that aim to integrate findings from research on psychopathology cannot afford to ignore the recent research on basic sensory-motor issues and embodied interaction.

More generally, to the extent that TT, ST, and IT offer explanations that capture different aspects, while no one of the theories captures all aspects of social cognition, one good option is to defend a pluralist approach (e.g., 131). Depending on circumstances, we may rely entirely on embodied interactive processes in richly contextualized settings, or fall back on narrative competencies, or we may be required to use theoretical inference or to run simulations. It may also be the case that a person's social cognitive competencies are disrupted by different psychopathological problems in a number of different ways. That is, some disorders may knock out capabilities for interaction associated with primary intersubjectivity, which can lead to more general social-cognitive problems; other disorders may affect very circumscribed ToM or narrative capabilities, leaving most embodied and interactive processes untouched.

While it is evident that understanding the underlying cognitive and emotional features of social cognition in a range of psychopathologies has important implications for

psychiatry, it is also true that the philosophical and interdisciplinary discussion on social cognition is helpful for achieving explanatory goals. It is likely that whatever form a successful explanatory strategy will take, it will be a "super-hybrid", one that combines ideas from TT, ST and IT. However, for this to be possible, there are a range of issues that have to be clarified, a number of which we have reviewed in this paper.

We end, however, by noting one central issue that defines a major difference between TT and ST, on one side, and IT on the other. Both TT and ST search for an internalist or individualist solution to problems of social cognition that would identify the proper functioning or, in the case of pathology, a disrupted functioning of a specific mechanism (ToM mechanism, mirror neurons, etc.) located within the individual. In contrast, IT focuses attention on social interaction itself, and it opens the door to the possibility that problems in social cognition may involve more than individual-bound mechanisms. If, as IT argues, social interaction may itself be constitutive of social cognition in some cases (e.g., 15), then some problems with intersubjectivity in psychopathology may involve social and cultural factors, and not just individual ones.

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Novel psychoactive substances of interest for psychiatry

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Novel psychoactive substances include synthetic cannabinoids, cathinone derivatives, psychedelic phenethylamines, novel stimulants, synthetic opioids, tryptamine derivatives, phencyclidine-like dissociatives, piperazines, GABA-A/B receptor agonists, a range of prescribed medications, psychoactive plants/herbs, and a large series of performance and image enhancing drugs. Users are typically attracted by these substances due to their intense psychoactive effects and likely lack of detection in routine drug screenings. This paper aims at providing psychiatrists with updated knowledge of the clinical pharmacology and psychopathological consequences of the use of these substances. Indeed, these drugs act on a range of neurotransmitter pathways/receptors whose imbalance has been associated with psychopathological conditions, including dopamine, cannabinoid CB1, GABA-A/B, 5-HT2A, glutamate, and k opioid receptors. An overall approach in terms of clinical management is briefly discussed.

Key words: Novel psychoactive substances, legal highs, smart drugs, research chemicals, substance abuse, dual diagnosis, psychedelic phenethylamines, synthetic cannabimimetics, phencyclidine-like drugs, cathinones, tryptamines

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In parallel with a decrease/stabilization of the use of internationally controlled drugs (1), the market of novel psychoactive substances is on the rise year on year. The diffusion of these substances has been identified in 94 countries/territories (2), with some 5% of 19-24 years old European people having already experimented with them. The web plays a major role in shaping this unregulated market (3), with users being attracted by these substances due to both their intense psychoactive effects and likely lack of detection in routine drug screenings (4).

Overall, novel psychoactive substances are defined as new narcotic/psychotropic drugs which are not controlled by the United Nations' 1961 Narcotic Drugs/1971 Psychotropic Substances Conventions, but which may pose a public health threat (5). However, "novel" will not necessarily mean here a new development, but will refer to substances that have recently become popular/available, constituting a reason of current/potential public health concern.

In particular, there are increasing levels of concern about the onset of acute/chronic psychopathological manifestations associated with the intake of a range of novel psychoactive substances (3,6,7). Here we provide an overview of the clinical pharmacology of the few hundred substances available (4,8,9) and the psychopathological disturbances they can produce.

We searched Medline/PubMed for studies using the terms "new psychoactive substances", "novel psychoactive substances", "legal highs", "designer drugs", "research chemicals", "smart drugs", and "emerging drugs of abuse". A similar search was carried out for the main groups of substances and associated psychiatric manifestations. Where no information relating to the index substances was available from the peer reviewed literature, specific websites were identified by typing the index substance keywords on Google, with selection and analysis of fora posts/threads.

SYNTHETIC CANNABIMIMETICS

Synthetic cannabimimetic (SC) preparations are composed by a dried plant, marijuana-like, base and a sprayed mixture of SCs. Oral/e-liquid/injectable SC formulations are also available (10-12). Within any given "Spice" package, usually a range of different SC molecules (13) and/or further psychoactives (14-20) can be identified. Batches of the same brand may possess highly variable SC concentrations (21).

It is likely that a few hundreds of SC molecules are currently available (8,9). SCs possess high/very high cannabinoid receptor binding affinity levels, with a significantly higher dose-response efficacy than tetrahydrocannabinol itself (22,23). In addition to this, some SCs show further pharmacodynamic actions (24) which may *per se* be a reason of clinical concern, such as N-methyl-D-aspartate (NMDA) receptor antagonism (25) and/or monoamine oxidase (MAO) inhibitory properties (26). Furthermore, almost all SCs possess indole-derived structures, which may in itself facilitate 5-HT2A receptor dysfunction, typically associated with both hallucinations/psychosis (27-30) and the serotonin syndrome (31). Further, the recent trend of SC fluorination may increase the compounds' lipophilicity, hence enhancing the absorption through biological membranes/blood brain barrier (32,33).

Acute SC intoxication is characterized by agitation/anxiety and visual/auditory hallucinations (34-36), together with tachycardia, hypertension, mydriasis, hyperglycaemia, dyspnoea, vomiting and seizures. Further SC-related medical complications may include stroke, encephalopathy, myocardial infarction and acute kidney injuries (37-40).

A number of analytically confirmed accidental deaths/suicides have been related to SC ingestion, either on their own or in combination with other compounds (41-51).

Long-term SC misuse may be associated with both tolerance/dependence (35,52) and a severe/prolonged withdrawal syndrome (53-56). A risk of developing psychosis in chronic marijuana users has repeatedly been described, and a correlation with the dosage ingested has been reported (57). Similarly, SC intake has been associated with the occurrence of florid/acute transient psychosis, relapse/worsening of a pre-existing psychosis, persisting psychotic disorders/"spiceophrenia" (6), and manic-like symptoms or relapse of pre-existing bipolar disorder (58,59).

SYNTHETIC CATHINONES

Synthetic cathinones have been first detected by our web-mapping research group in 2008 (4). They are beta-ketophenethylamines structurally similar to amphetamines/catecholamines, with subtle variations that alter their chemical properties, potency, pharmacokinetics and pharmacodynamics. Their popularity was driven by the lack of availability or the poor purity of cocaine or 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy"), combined with little, if any, legal restrictions (3).

Typically, synthetic cathinones are snorted or ingested orally or injected. For mephedrone, the half-life is as short as one hour, hence the re-dosing risk (60). Each synthetic cathinone has variable effects and potency levels on serotonin, dopamine and noradrenaline pathways, but all typically possess sympathomimetic/amphetamine-like effects (8,9).

Cathinone-related psychoactive effects include increased alertness, euphoria, excited delirium, hallucinations, agitation and aggression, associated with tachycardia, hypertension and dilated pupils. Abdominal pain, flushing, sweating, chills, restlessness and anxiety can be observed as well (8,9,61). Mood disturbances and paranoid ideation have been observed in chronic users (61-64). Additional reported mephedrone serious effects include hyperthermia, rhabdomyolysis, renal failure and seizures.

Fatalities have been associated with mephedrone (47,61,62), methylone and butylone (65). A significant proportion of synthetic cathinones' users report tolerance, dependence or withdrawal symptoms (66). Abstinent methcathinone users may present with decreased striatal dopamine transporter density on positron emission tomography scans, suggesting the potential risk for long-term psychiatric problems (67).

NOVEL DERIVATIVES OF "CLASSICAL" PSYCHEDELIC PHENETHYLAMINES/ MDMA-LIKE DRUGS

MDMA ("Ecstasy") is only one of the psychedelic phenethylamine products. Recent and popular appearances into the drug scenario include a few 2C molecules, such as 2,5-dimethoxy-4-bromophenethylamine (2-CB, "Nexus") (68), 2,5-dimethoxy-4-iodophenethylamine (2C-I) (69), and 2,5-dimethoxy-4-ethylphenethylamine (2C-E) (70). Most 2C drugs show affinity for 5-HT2A receptors, whilst some of them inhibit the dopamine/noradrenaline/serotonin reuptake as well (3). They may be purposefully or unintentionally ingested as MDMA substitutes.

With MDMA-like drugs, enhanced mood, increased energy, openness and perceptual alterations are typically reported, together with a range of serotonergic and sympathomimetic toxicity effects, including tachycardia, hypertension, metabolic acidosis, convulsions, rhabdomyolysis, mydriasis, vomiting, diarrhoea and thrombocytopenia. Acute renal failure and hyperthermia are a reason of particular concern (3,7,71,72).

3C-bromo-Dragonfly ("B-Fly") has been described as a powerful/long lasting (up to 3 days of psychoactive effects) drug, associated with long-standing hallucinations, mood elevation, paranoid ideation, confusion, anxiety and flashbacks (73).

25C-NBOMe ("N-bomb", "Pandora") (74) is one of the most popular NBOMe compounds, a group of high potency drugs which are currently a reason of public health concern (8,9). Sold online as legal lysergic acid and typically ingested orally or sublingually, "N-bomb" is a partial agonist of 5-HT2A receptors. Its effects include stimulation, hallucinations, dissociation, anxiety, aggression and unpredictable violent episodes (74).

"B-Fly", "N-bomb", para-methoxyamphetamine (PMA, "Dr. Death"), 4-methyltioamphetamine (4-MTA, "flatliners") and 6-(2-aminopropyl) benzofuran (6-APB, "Benzofury") have all been implicated in a number of acute toxicity events and fatalities (47,73,74).

NOVEL STIMULANTS

4,4'-dimethylaminorex (4,4'-DMAR, "Serotoni") is a derivative of aminorex (75,76) which has been associated in 2013/2014 with some 30 deaths in Europe (77). Similar to amphetamine-type stimulants (71), "Serotoni" is a potent dopamine/noradrenaline releaser whilst inhibiting the serotonin transporter as well (78). It may be snorted or ingested (79-81). It produces euphoria, alertness and agitation lasting several hours (80). Hyperthermia and cardiorespiratory problems have also been described (82).

Although synthesized some 70 years ago, methiopropamine (MPA, "Blow"), a methamphetamine analogue, started to be recently advertised online as a "research chemical" (83-85) to be smoked, ingested or snorted. Being a selective noradrenaline/dopamine reuptake inhibitor (86), it produces euphoria, hallucinations, alertness and sexual arousal. This may be associated with loss of appetite, tachycardia, anxiety, nausea, headache, dizziness, skin irritation, difficulty urinating and hangover effects (87).

SYNTHETIC OPIOIDS

These compounds share with morphine most of their clinical pharmacological effects, including analgesia, sedation, euphoria and risk of respiratory depression.

AH-7921 ("doxylam") is equipotent to morphine (88). Although first synthesized some 45 years ago, it is now available online in powder form to be snorted or ingested. A few related fatalities have recently been identified (82).

Although never marketed as such, MT-45 was developed in the early 1970s as a potential analogue of the analgesic lefetamine (89). Being a mu/delta/sigma opioid receptor agonist (90), it is currently a popular compound, either on its own or in combination with synthetic cathinones ("Wow") (82). MT-45 intake has been associated with respiratory depression, loss of consciousness and ototoxicity (91) and a number of fatalities as well (82).

Further popular drugs include nortilidine, which is an NMDA receptor antagonist and dopamine reuptake inhibitor equipotent to morphine (92); the high potency mu-opioid agonists W15 and W18 (93); 4-fluoro-butyrfentanyl ("4FBF") and IC-26 ("methiodone"), a methadone analogue.

SYNTHETIC COCAINE SUBSTITUTES

RTI-111 is a potent stimulant acting as an inhibitor of serotonin, dopamine and noradrenaline reuptake (94). RTI-121, developed in the 1990s, is a potent/long-lasting stimulant acting as selective dopamine reuptake inhibitor (95). RTI-126 (96) may present with a potency 5-fold higher than cocaine (97). When snorted, these compounds are associated with alertness, euphoria, talkativeness, insomnia and prolonged residual tension/anxiety (87).

NOVEL TRYPTAMINE DERIVATIVES

Synthetic tryptamines appeared on illicit drug markets throughout the 1990s (98), to be replaced over the last few years by cathinones, phenethylalamines and piperazines (82,99).

Nevertheless, novel tryptamines (e.g., N-diallyl-5-methoxytryptamine, 5-MeO-DALT; alpha-methyltryptamine, AMT; 5-methoxy-alpha-methyltryptamine, 5-MeO-AMT; N,N-diallyl-4-hydroxytryptamine, 4-HO-DALT; 5-methoxy-diisopropyltryptamine, 5-MeO-DIPT; 5-methoxy-N,N-dimethyltryptamine, 5-MeO-DMT; N,N-diethyltryptamine, DET; 5-(2-aminopropyl)indole, 5-IT) continue to appear on the online drug scenario (2,82,100,101).

Most exogenous tryptamines are psychoactive hallucinogens found naturally (102-106), notably in Delosperma species plants (dimethyltryptamine, DMT; 5-MeO-DMT), hallucinogenic fungi (psilocin; 4-OH-DMT), and amphibians (bufotenin). Endogenous bufotenin and DMT have been detected in humans as well (107-109), even though their biological functions remain unclear.

The predominant clinical effects of tryptamines, associated with both agonist activities at 5-HT2A receptors and serotonin transporter inhibition (110-117), consist in visual hallucinations, alterations in sensory perception, distortion of body image, depersonalization, marked mood lability and anxiety/panic (98,118). Untoward effects include agitation, tachyarrhythmia and hyperpyrexia (111). There are small numbers of confirmed post-mortem toxicology reports on tryptamines, mainly relating to AMT (47).

Bufotenin (119) is found on the skin of various species of the toad Bufo genus, in Amanita mushrooms, and in Anadenanthera peregrina/Piptoderma peregrina plants (120). Its psychoactive effects are mainly due to its enzymatic conversion to 5-MeO-DMT. Typically, consumers smoke the crystals obtained by drying the liquid taken from the frogs, but both oral and intravenous use have been recently reported as well.

AMT is available mainly from the web, in tablet and liquid formulations. Visual illusions and euphoria have been reported (121). 5-MeO-AMT and 5-MeO-DMT have a structure similar to amphetamine, hence explaining their sympathomimetic effects (98,99). 5-IT, a positional AMT isomer and a substituted phenethylamine, has been made available since 2012. It possesses both hallucinogenic and stimulant effects (98,99).

GABA-A/B RECEPTOR AGONISTS

Currently used in some countries to treat narcolepsy and alcohol withdrawal (122), gamma-hydroxybutyric acid (GHB, "liquid Ecstasy") was developed as an anaesthetic some 50 years ago. It can be produced in clandestine laboratories using a relatively simple synthesis with readily available and inexpensive source materials. It is typically ingested orally. Gamma-butyrolactone (GBL) and 1,4-butanediol, both industrial chemicals, are also currently used for their GHB-like effects, with GBL being a high lipophilicity/high potency GHB pro-drug.

GHB intake is associated with both increased central dopamine levels and activation of GABA-A/B receptors (123). GHB elimination half-life is 27 minutes, hence the re-dosing risk (124). Euphoria and calmness are initially observed after ingestion. A low/moderate oral dose of 10 mg/kg (0.75 g) can produce short-term amnesia, hypotonia, lowering of inhibitions and libido increase. Higher dosages lead to drowsiness, nausea, vomiting, muscle stiffness, dizziness, confusion, delirium, hallucinations, convulsions and cardiopulmonary depression.

GHB is highly addictive (125), with its withdrawal syndrome being characterized by insomnia, muscular cramping, tremor and anxiety (126). Initial UK data indicate that there have been 159 GHB/GBL-associated fatalities reported over the last two decades. Most deaths (79%) were accidental and GHB/GBL alone was implicated in 37% of cases (127).

Baclofen is a GABA-B agonist (128) showing both anxiolytic and analgesic properties whilst exerting some beneficial alcohol, cocaine and nicotine anti-craving effects (129-132). It can also be used for GHB/GBL withdrawal/detoxification (133). Most typically, misusers present with a history of substance abuse/self-medication with other substances and start taking large dosages after being regularly prescribed with baclofen for medical reasons (134).

Although signs of toxicity may be identified with as little as 100 mg of baclofen (135), misusers report the intake of higher dosages in order to achieve the desired effects, including euphoria, relaxation and anxiety obliterating/antidepressant-like effects, similar to those reported after GHB and pregabalin intake (80,136).

Several deaths after baclofen overdose have occurred (137). The acute intoxication is characterized by severe hypotonia, delirium, sedation, respiratory depression, cardiac conduction abnormalities, and possibly coma. Baclofen should always be withdrawn gradually (138). Common presenting withdrawal features are muscular hyperactivity, hyperthermia, metabolic derangements, rhabdomyolysis, convulsions and delirium, with issues similar to the serotonin syndrome (139).

Phenibut ("PB") is being used in Russia and Latvia for the treatment of anxiety/alcohol withdrawal symptoms and as a nootropic (140). As a dietary supplement, it is freely available online. When misused, it is typically taken orally in dosages (e.g., 1-3 g) notably superior to the therapeutic ones, thus leading to a risk for overdose. At these dosages, it acts as agonist at GABA-A/B receptors, whilst stimulating dopamine/serotonin neurotransmission as well (141,142).

Its use may rapidly lead to dependence/tolerance (143), with related withdrawal symptoms being managed with baclofen (144). Withdrawal signs/symptoms may include visual and auditory hallucinations, psychomotor agitation, derealization, depersonalization, increased light and sound sensitivity, muscle pain/twitches, tachycardia, nausea, tremor and insomnia (145). Acute intoxication is characterized by tachycardia, visual hallucinations, tremor, nausea and vomiting, with the possible occurrence of the serotonin syndrome (146,147).

PHENCYCLIDINE-LIKE DISSOCIATIVE DRUGS

Dissociative drugs are both popular and a cause of clinical concern (148-150). Ketamine hydrochloride ("special K") is of widespread use worldwide.

Ketamine is usually diverted from veterinary clinics, where it is used for surgical interventions. Its hallucinogenic effects are related to central 5-HT2A agonism (151), NMDA receptor antagonism (152), and high affinity for mu/delta/sigma opioid receptors (153).

When misused, ketamine can be injected or snorted or smoked or administered rectally, in a dosage range of 25-300 mg. Its psychotropic effects include referential thinking, dissociation, depersonalization, psychotic experiences and out-of-body/near death experiences (e.g., the "K-hole", 150). In the long term, tolerance, dependence, withdrawal signs and flashbacks are described, with schizotypal symptoms and perceptual distortions possibly persisting after cessation (154).

Approximately one third of patients with long-term recreational ketamine use present with both urological ("k bladder", e.g., dysuria, suprapubic pain, haematuria, decreased bladder capacitance, abnormal bladder histology, hydronephrosis) (155) and intestinal ("k cramps") (153) problems. High dosage self-administration may be associated with both cardiovascular and respiratory toxicity. Numbness, muscle weakness and impaired perception can result in falls, trauma or burns. Risks have also included drowning, death from hypothermia due to lying outside in winter, traffic accidents and becoming a crime victim (47,150).

Methoxetamine (MXE, "Special M") has recently entered the market as a structural analogue of ketamine in order to elude legislative sanctions (149). It may be swallowed or insufflated or injected or used rectally or sublingually at a dosage range of 5-100 mg (9,80,87,136).

MXE possesses NMDA receptor antagonism, dopamine releasing and serotonin transporter inhibiting activities (153). Most users report long-lasting dissociative effects (e.g., the "M-hole", 156). Although having been marketed as "bladder friendly", initial preclinical studies are a reason of clear concern (157), with cerebellar features and seizures being unique to "special M" intoxications (158). A number of analytically confirmed MXE-related fatalities have been described (148).

Diphenidine (DND) and methoxphenidine (MXP) are novel lefetamine derivatives acting as NMDA receptor antagonists (159), serotonin transporter inhibitors, dopamine agonists, and opioid agonists (87). They can be ingested or insufflated or injected at a dosage range of 50-150 mg, with a duration of effects of 8-12 hours (87). Interestingly, a range of serotonin syndrome signs/symptoms have been associated with DND/MXP high dosage ingestion (80,87,136).

Dextromethorphan (DXM) is an over-the-counter antitussive lacking strong mu-opioid agonist properties but acting as an NMDA receptor antagonist (159) whilst possessing serotonin transporter inhibiting activities (160). With long-term DXM abuse, psychotic disturbances can be observed (8,9). Abrupt DXM cessation has been associated with withdrawal symptoms (e.g., vomiting, diarrhoea, myalgias, restlessness, night sweats, insomnia, anxiety, but also hallucinations and flashbacks) (161). DXM high dosage ingestion may be associated with occurrence of the serotonin syndrome (160).

PIPERAZINES

Benzylpiperazine (BZP) was initially trialled as an antidepressant some 40 years ago, but never entered the market.

Especially in the past, it was included in "fake" Ecstasy tablets. It is an 5-HT2A receptor agonist, which explains its hallucinogenic effects at higher doses.

Piperazines have become popular to mimic Ecstasy effects, with the recently introduced "Molly" being typically an MDMA/piperazine combination (162). Their effects are similar to those of amphetamine, but less intense (8,9,162). Their ingestion is typically associated with stimulant effects, but at higher dosages hallucinations can be reported as well. Seizures can occur in as many as one in five patients presenting with piperazine toxicity, with hyponatremia, serotonin syndrome and renal failure having been described as well (162).

Meta-chlorophenylpiperazine (mCPP) is the main trazodone/nefazodone metabolite. Its high dosage ingestion can produce euphoria, hypertension and tachycardia.

HERBS/PLANTS

Salvia divinorum ("Sally-D") has a long history as a divinatory psychedelic. Its current use includes smoking or chewing the dried leaves containing salvinorin A and B, both k-opioid receptor agonists (163). At high dosages, time distortion, vivid imagery and empathogenic effects have been anecdotally reported (80,87,136). When smoked, its clinical effects occur within 20-60 seconds and last 5-15 minutes. Its intake may be associated with perceptual disturbances, psychosis, headache, irritability and anxiety (80,87,136). Dependence and tolerance have not been reported.

Sceletium tortuosum ("Kanna") is a traditional Southern Africa entheogen (164) currently available as extract, dried-powdered herb, tincture, tea bags and seeds. It may be snorted, smoked, chewed or swallowed (80,87,136). Desired effects include euphoria, reduction of tension, libido enhancement and appetite suppression. The mood-elevating action is due to the serotoninergic activity of its alkaloids (165), e.g., mesembrine, mesembrenone, mesembrenol and tortuosamine. Common side effects reported are hypertension, headache and nausea, associated with anxiety, irritability and insomnia. A serotonin syndrome can occur if Kanna is associated with selective serotonin reuptake inhibitors (SSRIs) or MAO inhibitors (MAOIs) (80,87,136).

Mitragyna speciosa ("Kratom") is a tree native to some Asian countries whose leaves contain mitragynine, mitraphylline, 7-hydroxymitragynine and O-desmethyltramadol. Mitragynine ("biak-biak") is a partial agonist of the mu/delta opioid receptors. 7-hydroxymitragynine is a mu-opioid agonist 30-fold more potent than mitragynine. Mitraphylline acts both on mu/delta opiate receptors and as an NMDA receptor antagonist (119). Kratom may be smoked or brewed or ingested as an extract. Users report either an opiate-like sedation, particularly at higher dosages, or a cocaine-like stimulation at lower dosages (80,87,136). Other clinical effects include severe nausea and vomiting associated with visual disturbances. Regular use may lead to dependence and opioid-like withdrawal symptoms upon discontinuation. A few related fatalities have been reported (47).

Piper methysticum ("Kava Kava") is a social/ceremonial drink in many South Pacific Islands, with kavalactones and kavapyrones being its active constituents (8,9,119). Out of these, desmethoxy-yangonin is a reversible MAOI-B, able to increase as well dopamine levels in the nucleus accumbens (166). Kavain is a N-terminal acetyltransferase (NAT) inhibitor, supposedly with serotonin reuptake inhibition and NMDA receptor activation properties (167). Yangonin acts as a cannabinoid CB1 agonist (168). Kava roots are also available in liquid form, tinctures, extracts and tablets. Kava confers a rapid onset, long-term sedation (119). There are several reports of associated liver damage or failure (169).

Ayahuasca is a psychedelic South American brew, traditionally made from Banisteriopsis caapi vine (containing beta-carboline harmala alkaloids, possessing reversible MAOI-A properties) and Psychotria viridis, a DMT-containing plant (8,9,119). Being metabolized by the digestive MAO, DMT is practically inactive if taken orally, unless combined with a MAOI. Effects may last 2-6 hours, and include intense visual hallucinations, euphoria, paranoid ideation and entheogenic sensations, associated with vomiting and/or diarrhoea (8,9,119).

Ibogaine is a hallucinogenic alkaloid extracted from the root bark of the Western African shrub Tabernanthe iboga, traditionally used as a sacrament (8,9,119). It is an 5-HT2A agonist, dopamine agonist, NMDA receptor antagonist and k-opioid receptor agonist (170). Its ingestion is associated with visual hallucinations and entheogenic effects, possibly associated with ataxia, nausea, vomiting and arrhythmias (171).

A recent increase in online discussions relating to the possible misuse of magnolols has been identified by our research group (172). The bark extract of Magnolia officinalis is typically used in traditional oriental medicine for the treatment of insomnia, anxiety and allergies (173). Honokiol and magnolol, the main constituents of its extracts, are both weak cannabinoid CB2 and GABA-A receptor agonists (174). Magnolol is then metabolized into its 20-fold more potent metabolite tetrahydromagnolol, active at cannabinoid CB1/CB2 receptors (174). Cannabis- and benzodiazepine-like effects (e.g., sedation, reduced attention and concentration, headache) are being reported (80,87,172).

Hydrangea paniculata/Hortensia is a common ornamental plant. Its misuse may be associated with a range of cannabis-like effects, e.g., euphoria, sedation, confusion, dizziness and headache (80,87,136). It may be smoked, or ingested in capsules, extracts, teas or sugar syrup.

Datura stramonium is another common plant well known for its mind-altering properties (e.g., hallucinations, delusions, bizarre behavior and euphoria) associated with xerostomia, severe mydriasis/photophobia, confusion, disorientation, tachycardia, and amnesia (8,9,80,87,119). Related fatal medullary paralysis, arrhythmias and cardiovascular collapse events have been reported (47).

Nauclea latifolia is a flowering, tramadol-containing, sub-Saharan plant (175), used recreationally to obtain pain relief, sedation and anxiolytic effects (80,87).

PRESCRIBED PRODUCTS

Pregabalin is approved in Europe for the treatment of epilepsy/partial seizures, neuropathic pain and generalized anxiety disorder. The molecule is however also often prescribed off-label for a range of psychiatric conditions, including bipolar disorder, alcohol/narcotic withdrawal states and attention-deficit/hyperactivity disorder. In parallel with increasing prescribing levels, a growing black market is currently being observed (8,9,176,177).

Potent binding of pregabalin and gabapentin at the calcium channel results in a reduction in the release of excitatory molecules. Furthermore, they are thought to possess GABA-mimetic properties and direct/indirect effects on the dopaminergic "reward" system (177). Overall, pregabalin is characterized by higher potency, quicker absorption rates and greater bioavailability than gabapentin (176).

Typical misusers of these compounds are individuals with a history of recreational polydrug use. A range of experiences may be associated with gabapentin abuse, including euphoria, improved sociability, opiate-like sedation and psychedelic effects (176). Similarly, pregabalin is considered an "ideal psychotropic drug" to achieve specific mindsets, including sedative effects mixed with euphoria and dissociation.

Misuse of pregabalin, at dosages up to 3-20 times higher than the maximal dosage indicated (176), mostly seems to occur orally, but intravenous use, rectal "plugging" and smoking have been reported as well. A few drugs are reportedly misused in combination with pregabalin or gabapentin, including cannabis, alcohol, lysergic acid, amphetamine and GHB (176,177).

Phenazepam ("Zinnie") is an old benzodiazepine, currently prescribed in the Russian Federation for the treatment of a range of neurological disorders as well as for alcohol withdrawal/anxiety, and as a surgery premedication (178). Easily accessible online at low prices, it is considered five times more powerful than diazepam (179). It can be ingested, snorted or injected, either on its own or in combination with other substances, with euphoric effects having been described (8,9). Reported side effects include amnesia, dizziness, loss of coordination, drowsiness, blurred vision, slurred speech and ataxia. Deaths by respiratory arrest due to its misuse in combination with other sedatives have been reported (180).

Olanzapine is being anecdotally advised online as the "ideal trip terminator" after a psychedelic drug binge (181). The molecule is self-prescribed, and for a few days only, at daily dosages up to 50 mg/die.

Quetiapine ("Q ball") is similarly anecdotally considered to "come off the psychedelic trip" (181), with typical misusers being clients with a previous substance abuse history. Vulnerable subjects (e.g., adolescents, inmates) may be particularly at risk (182). Reasons for abuse of atypical antipsychotics may include the desire of "feeling mellow" (183).

There are anecdotal reports of misuse of venlafaxine, particularly in combination with other substances (80,87,136), possibly related to the increase it produces in dopamine neurotransmission (184,185), particularly at the level of the prefrontal cortex (186).

Recent concerns relating to orphenadrine (an anticholinergic drug) misuse have been reported (187). Similarly, misuse of tropicamide (an ophthalmic anticholinergic compound producing short-acting mydriasis and cycloplegia) has been recently described (188). When misused, tropicamide is typically injected intravenously, often in combination with other psychoactives. Tropicamide-related psychoactive effects include hallucinations, "open eye dreams" and dysphoria, associated with slurred speech, persistent mydriasis, hyperthermia, tremor, convulsions, psychomotor agitation, tachycardia and suicidal ideation (188).

PERFORMANCE AND IMAGE ENHANCING DRUGS

Increasing consumption levels of substances known as performance and image enhancing drugs (PIEDs) have been recorded (8,9,189). PIEDs are drugs, nutrients, drinks, vegetable extracts or potions from a range of different sources.

Among image enhancers, there are increasing levels of concern regarding the misuse of the slimming aid dinitrophenol (DNP), whose intake has been implicated in a number of UK fatalities (47,190). DNP is offered online as a metabolism booster to bodybuilders and dieters. Its ingestion may be associated with euphoria, energy increase, nausea and headache (8,9).

Typically identified in dietary supplements, 1,3-dimethylamylamine (DMAA) intake is associated with euphoria and mild stimulant effects, together with hypertension, headache, nausea, and vomiting (80,87,111). In parallel with concerns about DMAA's health risks, including deaths (191), new synthetic stimulants, including beta-methylphenylethylamine (BMPEA), N,alpha-diethylphenylethylamine (DEPEA) and more recently 1,3-dimethylbutylamine (DMBA) have been offered to online customers looking for alternative "natural" dietary supplements. With DMBA, effects such as restlessness, mood enhancement, increased focus, nausea, flushing and tachycardia have been reported (80,87,192).

Melanotan synthetic tanning agents are largely available online, aiming at promoting melanogenesis and hair-skin pigmentation. Melanotan user groups include aesthetically driven women, body dysmorphics and male bodybuilders. Sexual arousal, flushing, nausea, weight loss and immune response alterations have been reported (193,194).

A range of natural products available online, such as those containing Tribulus terrestris, are becoming popular

because of their alleged powerful pro-testosterone, muscular strength enhancer formula. Both increased sexual arousal (80,87) and psychotic episodes (associated with long-term ingestion) (189) have been described.

Among cognitive enhancers, piracetam, aniracetam and centrophenoxine have been reported to be abused by healthy individuals with the hope to improve their performance in study and work-related activities (195). Piracetam is a GABA derivative, originally marketed in 1971 as a nootropic (196), due to restored neurotransmission and increased brain oxygen consumption (197). With the ingestion of high dosages of these substances, hallucinations and mood alterations have been reported (80,136,196).

"Natural" sexual performance enhancers are advertised online as "safer" alternatives to pharmaceutical phosphodiesterase type 5 inhibitors. The most popular compounds include yohimbine, Maca, Epimedium and Ginkgo Biloba. Their ingestion has been associated with anxiety, irritability, hypomanic reactions and inappropriate behaviour (80,87, 136,198).

DISCUSSION

The ever-increasing number of novel psychoactive substances emerging worldwide (2,8,9,101) and the parallel changes in drug scenarios represent a challenge for psychiatry. In fact, the intake of these substances is typically associated with the imbalance of a range of neurotransmitter pathways/receptors, and consequently with the risk of psychopathological disturbances.

The occurrence of psychosis has been related to: a) increased central dopamine levels (199), associated with the intake of most of these substances, including novel psychedelic phenethylamines, synthetic cathinones and 4,4'-DMAR; b) cannabinoid CB1 receptor activation (200), achieved with synthetic cannabimimetics; c) 5-HT2A receptor activation (201), reported with NBOMe compounds, latest tryptamine derivatives, lefetamine derivatives, DXM and hallucinogenic plants; d) antagonist activity at NMDA receptors (202), described with phencyclidine-like dissociatives; and e) k-opioid receptor activation (203), typically associated with Salvia divinorum intake.

Vulnerable subjects, including both children/adolescents and psychiatric patients, may be exposed to a plethora of "pro drug" web pages, which provide direct drug purchase opportunities and/or drug information (e.g., description of the drug effects, dose, chemistry and intake experiences). Advanced levels of knowledge related to novel psychoactive substances are typically provided by drug fora/blog communities' members (e.g., the "e-psychonauts", 4).

It is arguably inappropriate to trust information obtained online without independent verification, and only large scale, adequately controlled clinical studies can give a clear indication of drug characteristics and adverse effects. However, previous studies from our group (4,176) have clearly suggested that an increase in online trafficking/debate about a specific psychoactive drug typically precedes the occurrence of clinical incidents at the population level.

Consumers of novel psychoactive substances may self-refer overnight to accident and emergency departments, when concerned with acute medical or psychiatric problems, without disclosing their substance intake and showing negative results at the standard drug tests (8,9). It is clearly difficult to draw a detailed and universal management plan to cope with the behavioural and psychopathological disturbances related to the intake of the virtually few hundreds of substances currently available (8,9,162).

Given the complex or unknown pharmacology of the substances possibly ingested by the client, benzodiazepines may be agents of choice (3). They may, however, need frequent re-dosing/high dosages to achieve adequate sedative effect, and this may be a problem if clients have co-ingested alcohol (3). Where patients cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics may be considered (8,9,162), although this may further contribute to the acute toxicity effects of the abused substances.

Treatment of hyperthermia needs to be aggressively planned, and this typically involves cooling measures and intravenous fluid administration for rhabdomyolysis concern (3). Serotonin syndrome is managed using benzodiazepines and cyproheptadine (204). Inpatient admission, possibly to intensive care units, may at times be needed (8,9,162).

The increasing levels of misuse of a range of medicinal products, otherwise representing a valuable asset in the pharmacological repertoire of psychiatry/addiction medicine (177), are a reason of further concern. Possible sources of this acquisition may either be diversion of regularly prescribed medicines or online/"rogue" pharmacies (205).

Psychiatrists/physicians who consider prescribing a psychoactive molecule possessing a potential for misuse (e.g., pregabalin or gabapentin for neurological/psychiatric disorders) should carefully evaluate a possible previous history of drug abuse. Furthermore, they should be able to promptly identify signs of misuse, and provide assistance in tapering off the index medication (177).

The online market of novel psychoactive substances is unfortunately developing far more rapidly than academic research (4). We believe that mental health professionals need to be aware of the psychopathological effects of these substances. We hope that the present paper may represent a useful contribution in this respect.

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Transdiagnostic factors of mental disorders

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Official nosological systems, such as the DSM-5 and ICD-10, define psychopathology and substance use disorders as distinct, independent, and categorical constructs. In other words, the classification systems imply that a patient either meets the diagnostic threshold for a particular mental disorder or does not (categorical), the disorder does not overlap with other disorders (distinct), and therefore presence of the disorder should not necessarily be associated with a higher probability of having another disorder (independent).

Both clinical experience and empirical research indicate that these assumptions are not justified, however. First, subthreshold disorder manifestations can be associated with significant distress and dysfunction; moreover, there are important severity differences among individuals receiving the same diagnosis. This suggests an underlying dimensionality to mental disorders not captured by categorical diagnoses and highlights the information lost when reducing a complex constellation of signs and symptoms to a present-absent dichotomy. Second, comorbidity is the rule, rather than the exception. Individuals who have one disorder are likely to meet criteria for additional disorders at rates far exceeding what would be predicted from disorder prevalence rates.

Research on disorder dimensionality and comorbidity suggests that many mental disorders are manifestations of relatively few core underlying dimensions. Beginning several decades ago, investigations of common symptoms and behaviors in children, and diagnoses in adults, have repeatedly replicated such an underlying cross-cutting transdiagnostic structure: the internalizing-externalizing model. *Internalizing* accounts for comorbidity among major depression, generalized anxiety disorder, dysthymia, panic disorder, social and specific phobias, post-traumatic stress disorder, and so on, while *externalizing* accounts for comorbidity among substance use disorders and antisociality-, behavioral-, and impulsivity-related disorders.

Unlike the organizations of many official nosologies (e.g., "mood disorders" as separate from "anxiety disorders"), this internalizing-externalizing model provides excellent fit to the data and has been replicated in various populations, from around the world (1,2). This report highlights recent advances and contemporary directions in transdiagnostic comorbidity research.

THE NATURE OF INTERNALIZING AND EXTERNALIZING

Disorder persistence

Studies have shown that internalizing and externalizing are quite stable over time, which has marked implications for understanding successful psychological aging as well as disorder persistence. Indeed, research on this question illustrates that these two transdiagnostic factors are key to understanding disorder continuity. The transdiagnostic variance that related disorders share (captured by the factors) appears to drive disorder persistence. On the other hand, the unique variance of disorders – disorder-specific variance that makes each disorder different from its related disorders – tends to show comparatively low, often negligible, stability. In other words, internalizing and externalizing appear to serve as the primary pathway for homotypic disorder persistence over time. Generalized anxiety disorder, for instance, appears to persist because the internalizing factor variance saturates the diagnosis, and it is this transdiagnostic variance that is stable, not the disorder-specific variance (3,4).

Disorder onset

Since the factors account for the majority of homotypic continuity over time, investigations of their role in heterotypic continuity and disorder onset are crucial. For instance, one can conceptualize lifetime transdiagnostic factor levels as a liability for subsequent disorder onset and thus as the key drivers of the development of sequential comorbidity. In longitudinal onset data on eighteen disorders, Kessler et al (4) applied a novel time-lagged latent comorbidity survival model, and found that internalizing and externalizing at time 1 accounted well for subsequent onset of new disorders. This highlights the need for latent structure modeling to move beyond cross-sectional data into well-characterized longitudinal datasets.

Factor characteristics

Researchers have recently addressed three important questions about transdiagnostic factors' characteristics. First, how is the distribution of these factors best conceptualized? This distributional question is important in that it allows for a better understanding of latent internalizing and externalizing generally, and it thus helps us understand the dispersion of these factors in the population. Multiple studies now indicate that these factors are continuously distributed dimensions (vs. liability classes, or dimension-class hybrids) (3).

Second, how similar (invariant) are these factors across different groups? Studies of internalizing-externalizing across several populations – comparing individuals by gender, race/ethnicity, age, and sexual orientation – have repeatedly

replicated the finding that internalizing and externalizing are invariant (3,5,6). This indicates that the reason mental health disparities are observed in particular disorders is because groups differ in their average transdiagnostic factor levels. Women thus report higher rates of major depression than men because women, on average, have higher levels of internalizing than men.

Third, are these factors best thought of as single factors or as subsuming sub-factors? The answer to this question points to a hierarchical account. Investigations of externalizing typically suggest a single factor in adulthood; however, correlated sub-factors (e.g., substance use) can also emerge. Regarding the higher-order structure of internalizing, some studies support a single internalizing factor and others find that internalizing subsumes two lower-order factors: *distress* (major depression, generalized anxiety, dysthymia) and *fear* (agoraphobia, social phobia, specific phobia).

DISORDER RELATIONS WITH OUTCOME AND EXPOSURE

Internalizing and externalizing, unlike disorder-specific variance, predict subsequent disorders, but what role do they play in linking disorders with other important variables? A growing number of studies indicate that disorders' associations with important outcomes are driven by transdiagnostic variance rather than disorder-specific variance. For instance, the association between major depression and suicidal behavior largely seems to reflect depression's association with internalizing, not something particular about depression (3).

In terms of the links between environmental exposures and disorders, studies suggest that transdiagnostic factors largely mediate these associations, meaning that an exposure (e.g., discrimination, adverse childhood experiences) likely raises transdiagnostic factor levels, which manifest as higher rates of multiple observed disorders (5). These findings clarify the diffuse impact of individual exposures on multiple disorders.

Given that transdiagnostic factors appear to account for the majority of the associations between exposures and disorders, disorders and subsequent disorders, and disorders and outcomes, a significant future research question involves determining what, if anything, disorder-specific variance tells us above and beyond transdiagnostic factors.

TOWARD A COMPREHENSIVE TRANSDIAGNOSTIC MODEL

Bifactor models

One recent development has been the application of new transdiagnostic models. Internalizing and externalizing are correlated, suggesting the presence of another factor to account for this association. Bifactor models, positing a general psychopathology factor that saturates all diagnoses (in addition to internalizing and externalizing), are gaining empirical traction (7,8). Bifactor models will be a key future direction for understanding comorbidity at the most general level.

New disorders and factors

Transdiagnostic factor models typically are modeled to characterize comorbidity of common mental disorders. However, such models can also capture other disorders, such as schizophrenia spectrum, eating, and sexual functioning disorders. While some of these less common disorders reflect internalizing and externalizing, others represent additional factors. For instance, schizophrenia and related psychotic disorders reflect a unique thought disorder factor (9), and autism spectrum disorders reflect a unique factor as well (10). Expanding transdiagnostic comorbidity models to include new disorders and new factors is a prime future direction.

Links with personality

Internalizing and externalizing are associated with personality traits, such as negative affect and disinhibition, respectively. In terms of abnormal personality, many categorical personality disorders also can be fit into this model. The recent DSM-5 reconceptualization of personality disorders via an alternative dimensional system (11) provides a fertile new research avenue. Indeed, DSM-IV personality disorders can be understood as manifestations of specific combinations of specific facets of these broader dimensions. These domains' link to mental disorder conceptualized more broadly is also clear: at a higher-order level, these domains converge into internalizing and externalizing (12).

INTERVENTION IMPLICATIONS

Transdiagnostic factor models inform intervention in two major ways. The first is conceptual: they help explain why certain psychopharmacological agents, and particular psychotherapy modalities, are effective for multiple, allegedly distinct conditions. Second, they provide a target of intervention: if treatments can lower transdiagnostic liability levels, they may have general impacts across multiple disorders and thus prove efficient. Indeed, one such transdiagnostic treatment is available for emotional (internalizing) disorders, and this is a key direction for intervention research (13).

TRANSDIAGNOSTIC FACTORS IN THE RDoC ERA

Research funding is increasingly focusing on biological investigation of mental disorder, epitomized by U.S. National

Institute of Mental Health's Research Domain Criteria (RDoC) (14).

Transdiagnostic factors are poised to play a major part in RDoC-oriented investigations of psychopathology. First, these factors represent primarily genetic variance (15), highlighting their potential utility in genetic investigations. Second, these factors are closely associated with neurobiological systems, such as internalizing's association with the emotional circuitry common to emotional disorders (13,16).

As such, transdiagnostic factors appear uniquely suited to bridge psychiatric phenomena and biological substrates of behavior, and they thus appear crucial considerations in the RDoC era as research moves increasingly away from categorical diagnoses derived from patient interviews (5,7).

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An empirically based alternative to DSM-5's disruptive mood dysregulation disorder for ICD-11

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The World Health Organization (WHO)'s priorities for the development of the classification of mental and behavioural disorders in the ICD-11 include increasing its clinical utility in global mental health settings (1) and improving the identification and diagnosis of mental disorders among children and adolescents (2).

An issue that has been hotly debated in the area of childhood psychopathology is the assessment, diagnosis and treatment of children with severe irritability and anger (3,4). Although virtually all children display irritable and angry behaviours at times, some children exhibit them more frequently and more intensely, to the extent that they become an impairing form of emotional dysregulation. Recent findings indicate that these children with chronic and severe irritability/anger have not been adequately identified through existing classification systems, are at an increased risk for particular negative outcomes, and have not received appropriate treatment. To the extent that ICD-11 can help clarify the clinical picture of irritability/anger, children and families will benefit from more accurate diagnoses, more useful prognoses, and more effective interventions.

This paper provides a brief overview of the issue, followed by several possible options and the current proposal for the classification of childhood irritability/anger in ICD-11. This proposal represents a markedly different – but we believe more scientifically justifiable – solution to the problems in this area than that selected for DSM-5 (5).

CLINICAL CONCERNS RELATED TO SEVERE IRRITABILITY/ANGER IN CHILDREN

Concern about misdiagnosis

One of the major reasons why researchers and practitioners have been concerned about the classification of severe irritability/anger in children is that this phenomenon is widely believed to account for significant misdiagnosis of children as having bipolar disorder. This is particularly true in the U.S., where rates of bipolar disorder diagnoses in children increased by as much as 4000% between 1994 and 2003 (6).

The growing incidence of pediatric bipolar disorder appeared to be due to diagnostic errors or changing diagnostic conventions, since risk factors for the disorder had not changed and international data did not show a similar increase (7). The view that mania and hypomania could present as irritability among children appeared to underlie this changing diagnostic pattern (4,7).

Notably, a large majority of the children diagnosed with bipolar disorder based on this interpretation of irritability would have also met the diagnostic requirements for oppositional defiant disorder (ODD) (4). Though generally grouped with conduct disorder and other disorders characterized by disruptive behavior, ODD is a disorder of emotional dysregulation (8), partially defined by affective symptoms of irritability and anger (5,9) and sharing significant comorbidity and continuity with mood and anxiety disorders (10,11).

Thus, increasing rates of bipolar disorder diagnosis in children could reflect: a) diagnostic confusion regarding the presentation of bipolar disorder among children; and b) the presence of more severe symptoms of emotional dysregulation in children more properly considered as having ODD.

Concern about outcomes

Seeking to clarify the relationship between irritability and bipolar disorder, researchers at the U.S. National Institute of Mental Health began investigating "severe mood dysregulation" (SMD), a syndrome characterized by chronic abnormal levels of anger or sadness, hyperarousal evident in insomnia or agitation, and heightened verbal or physical reactivity (12). SMD and severe irritability/anger in childhood were found to predict anxiety and depressive disorders, but not bipolar disorders, in adolescence and adulthood (13-15).

At the same time, researchers have examined the "irritability dimension" of ODD, which typically includes often losing one's temper, being touchy, and being chronically or frequently angry, but not the hyperarousal symptoms of SMD. It has long been established that a significant proportion of children with ODD follow a developmental pathway

leading to more serious antisocial behaviours characteristic of conduct disorder (16). However, children with these irritable/angry symptoms of ODD appear to follow a different course, with outcomes more commonly including later depression and anxiety (17-19), as well as peer victimization (20) and greater treatment resistance and functional impairment following treatment (21).

Overall, severe irritability/anger appears to be a clinically significant feature and predictor of outcomes across development, from early childhood (22,23) through adulthood (15), with similar findings in girls and boys. Further, irritability/anger may have distinct genetic underpinnings from resistant behaviours and conduct problems (24). Clearly, this is an area deserving careful clinical attention.

Concern about selecting appropriate interventions

During the period of increasing diagnostic rates of childhood bipolar disorder in the U.S., there was also an increasing tendency to use medications appropriate for adult bipolar disorder in an attempt to ameliorate high levels of anger and irritability in children (6,7), despite a paucity of clinical trials of these medications with child populations. However, children with severe irritability and anger are unlikely to exhibit manic or hypomanic episodes, either at the time of initial evaluation or in subsequent years (4), so that medications for bipolar disorder are probably not an appropriate treatment for them. On the other hand, there are several empirically based psychosocial interventions and medications that can be effective in treating childhood anger and reactive aggression (16,25). An improved diagnostic classification of childhood irritability/anger should help to facilitate more effective treatment.

How to address these concerns?

The developers of the DSM-5 (5) elected to address these concerns by adding a new diagnosis, disruptive mood dysregulation disorder (DMDD). Grouped among depressive disorders, DMDD is defined primarily by two features, present in multiple settings: a) frequent, severe temper outbursts, and b) persistent irritability evident every day for most of the day.

The addition of this new disorder has been met with several negative reactions among the professional community (e.g., 26). These critics note that DMDD is based on limited research, is not sufficiently distinct from existing disorders (e.g., ODD), and may further contribute to increasing rates of mental disorders diagnoses and medication use among children.

Initially, the ICD-11 Working Group on the Classification of Mental and Behavioural Disorders in Children and Adolescents had recommended the inclusion of a modified version of DMDD (27) in the ICD-11. Reflecting the lack of consensus in the field, this proposal was later rejected by the ICD-11 Working Group on Mood and Anxiety Disorders, and the issue was taken up by an expanded group of experts appointed by the WHO. This article reflects the discussions and recommendations of that task group.

DIAGNOSTIC OPTIONS: A SEPARATE DISORDER OR A SPECIFIER OF AN EXISTING DISORDER

A separate disorder

The rationale for introduction of DMDD in DSM-5 was developed largely out of the research on SMD (4). However, several limitations of this rationale should be noted.

First, SMD research is still early in its development and comes from a small number of research groups, primarily in the U.S.. Additional independent and international research is needed, particularly to support validity of the diagnosis and its utility in a global classification system.

Second, in the process of adapting SMD (the provisional research syndrome) into DMDD (the DSM-5 diagnosis), several significant changes were made, including removing hyperarousal (e.g., insomnia, agitation, distractibility, racing thoughts) from the essential criteria and removing low intelligence (IQ<80) from the exclusionary criteria (5,12). Consequently, the DMDD diagnosis had not been subjected to peer-reviewed research prior to the DSM-5 proposal.

When DMDD was finally examined in field studies (28) and secondary analyses (29-31), evidence arose of limited reliability, a lack of psychiatric consensus, and very high rates of overlap with other disorders. These findings are consistent with concerns raised in the professional community regarding DMDD (26) and suggest that the diagnosis is likely to be problematic in clinical settings.

It is therefore unclear from the existing evidence that a new disorder category should be created. Although the DMDD diagnosis has been presented as a solution to the misdiagnosis and overmedication of children, its inclusion may in fact contribute to diagnostic confusion and create a new target, with a higher base rate, for drug development and trials. The task group appointed by the WHO did not consider that DMDD represents a meaningful response to the concerns described above related to the diagnosis, outcomes, and treatment of youth with severe irritability and anger.

A specifier for ODD

There is an alternative, empirically based solution that considers all of the available research on anger and irritability in children. As summarized above, numerous studies on SMD and ODD dimensions have found that children with severe irritability/anger are at a significant and specific risk for internalizing disorders and other poor psychosocial outcomes

over time. The great majority of these children would *already* meet the diagnostic requirements for ODD and are not likely ever to develop bipolar disorder (4). Moreover, research evaluating different models of ODD dimensions (23,32) provides an empirical basis for how best to define the irritability/anger dimension within an existing diagnostic category.

The task group has recommended that WHO not accept DMDD as a diagnostic category in ICD-11, but rather approach the issue in an alternative, more conservative and more scientifically justifiable way. Specifically, the group has proposed that ICD-11 include a specifier to indicate whether or not the presentation of ODD includes chronic irritability and anger. We believe this option provides the most parsimonious basis for identifying and appropriately treating children with this maladaptive form of emotional dysregulation.

Prior to the approval of the ICD-11 by the World Health Assembly, anticipated in 2017, proposals for ODD and related disorders will be subject to empirical evaluation and scrutiny by the global professional community through several avenues. These include a public review and comment process (see updates at http://apps.who.int/classifications/icd11/browse/l-m/en), and Internet-based and clinic-based field studies conducted through WHO's Global Clinical Practice Network (see http://www.globalclinicalpractice.net to register) and WHO's network of international field study centers.

The WHO will make final decisions about the classification of chronic irritability and anger in children and further refine the diagnostic guidelines for ODD and related disorders on the basis of the evidence generated through these processes.

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Is schizophrenia a spatiotemporal disorder of the brain's resting state?

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Recently, the brain's resting state activity, i.e., the brain's neural activity in the absence of any specific tasks or stimuli (1), has gained prominence in neuroimaging and in psychiatric research. This resting state activity can be spatially characterized by various neural networks showing close functional connectivity. These include the default-mode network (DMN), mostly consisting of cortical midline structures showing strong low frequency fluctuations (2), the sensorimotor network, the salience network, and the control executive network (CEN) (3). These networks are interrelated in continuously changing constellations (4).

The resting state activity can also be characterized by fluctuations in different frequency bands, ranging from infraslow (0.0001-0.1 Hz) over delta (1-4 Hz), theta (5-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz) to gamma (30-180 Hz). These different frequency bands are coupled with each other (5), constituting a complex temporal structure (6). One can therefore characterize the brain's resting state activity as an integrated spatiotemporal structure that must be understood in a physiological and functional sense, rather than an anatomical and structural one (7,8).

There have been numerous investigations of resting state activity and functional connectivity in schizophrenia (e.g., 9,10). Resting state functional connectivity within the cortical midline structures/DMN tends to increase, while functional connectivity of the CEN, including the lateral prefrontal cortex, is rather decreased in schizophrenia (9). This increased functional connectivity in midline regions appears to be compatible with the observation of stronger low frequency fluctuations in schizophrenia, particularly in the anterior midline regions (10).

How are these changes in the resting state's spatial structure related to the symptoms in schizophrenia? Investigations in healthy subjects associated the negative relationship, or anticorrelation, between the DMN and the CEN with the balance between internal (self-related) and external (environment-related) mental contents in awareness (11-13). If the resting state activity and functional connectivity in medial regions/DMN is stronger, the focus will be primarily on internal mental contents that are more related to the own self, the own thoughts, and the body (12). In contrast, stronger resting state activity and functional connectivity in lateral regions/CEN leads to increased external mental contents in awareness (12).

Most importantly, this predominance of external mental contents in awareness takes place at the expense of the internal mental contents, with a reciprocal balance between them: either the load of internal mental contents is high and that of external mental contents is low or, conversely, the latter predominate while the former recede into the background (11,12). Such reciprocal balance between internal and external mental contents is mediated neuronally by the anticorrelation between midline regions/DMN and lateral regions/CEN.

Using the psychedelic drug psilocybin to mimic psychosis in healthy subjects, Carhart-Harris et al (14) observed a decreased anticorrelation between DMN and CEN. This was also reported by other investigations in patients with schizophrenia (15).

The anticorrelation between DMN and CEN makes possible a clear distinction between internal and external mental content by balancing them reciprocally. Decrease in anticorrelation, or its conversion into positive correlation between DMN and CEN, resolves that distinction: external mental contents are now no longer reduced when internal mental contents are strong. This makes possible confusion between internal and external mental contents. For instance, external (or internal) mental contents may interfere with, and penetrate into, the ongoing processing of internal (or external) mental contents. This is typically observed in symptoms such as thought insertion, thought withdrawal and passivity symptoms in schizophrenia. One may want to describe the confusion between internal and external mental contents as "self-environment blurring", which may represent a "basic spatial disturbance" underlying passivity symptoms and ego disorder in schizophrenia.

Confusion between internal and external contents with "self-environment blurring" may also underlie auditory hallucinations. Several studies demonstrated abnormally high resting state activity and functional connectivity in the auditory cortex during auditory hallucinations (16). Why, though, during auditory hallucinations are the voices experienced as external rather than internal? This may be related to the DMN and CEN and their relation with the auditory cortex. More specifically, the DMN seems to be less connected in the resting state to the auditory cortex which, in contrast, is rather strongly connected to CEN (15). Such disengagement of DMN functional connectivity from auditory cortex and the latter's association with CEN may account for the assignment of an external origin to the hallucinated voices rather than relating them back to an internal origin (17). Auditory hallucinations and their localization in the environment – rather than in the own

self – may therefore be yet another instance of internal-external confusion and "self-environment blurring" which, put in cognitive terms, is often referred to as deficit in self-monitoring or self-recognition (18).

In addition to internal-external confusion, temporal features, as investigated in EEG, may play a central role in generating auditory hallucinations. Angelopoulos et al (19) reported an increase in phase synchrony in the alpha band of the auditory cortex before and during the onset of auditory hallucinations. Moreover, increased phase-phase coupling between theta and gamma in fronto-temporal areas and the temporal electrode T7, indicating the auditory cortex, was observed during the experience of auditory hallucinations (20). This suggests that the abnormal coupling of auditory cortical resting state activity to other regions/networks such as CEN may be temporally mediated by abnormally increased phase synchrony.

In conclusion, recent neuroimaging results highlighted the brain's resting state activity and its abnormalities in psychiatric disorders such as schizophrenia. However, the exact meaning of the resting state abnormalities for psychiatric symptoms remains unclear. Based on recent findings, I here suggest directly linking abnormalities of the resting state's spatiotemporal structure to psychopathological symptoms such as ego disturbances and auditory hallucinations in schizophrenia.

Future studies may aim to target and investigate directly the spatiotemporal structure of the various schizophrenic symptoms. This may lead to the development of novel forms of interventions aiming to "normalize" the brain's resting state and the spatiotemporal structure of its neural activity.

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Public mental health: the time is ripe for translation of evidence into practice

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Public mental health deals with mental health promotion, prevention of mental disorders and suicide, reducing mental health inequalities, and governance and organization of mental health service provision. The full impact of mental health is largely unrecognized within the public health sphere, despite the increasing burden of disease attributable to mental and behavioral disorders. Modern public mental health policies aim at improving psychosocial health by addressing determinants of mental health in all public policy areas. Stigmatization of mental disorders is a widespread phenomenon that constitutes a barrier for help-seeking and for the development of health care services, and is thus a core issue in public mental health actions. Lately, there has been heightened interest in the promotion of positive mental health and well-being. Effective programmes have been developed for promoting mental health in everyday settings such as families, schools and workplaces. New evidence indicates that many mental disorders and suicides are preventable by public mental health interventions. Available evidence favours the population approach over high-risk approaches. Public mental health emphasizes the role of primary care in the provision of mental health services to the population. The convincing evidence base for population-based mental health interventions asks for actions for putting evidence into practice.

Key words: Public mental health, mental health, mental health promotion, prevention of mental disorders, mental health services, mental health policy, wellbeing, stigma, human rights

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The field of public mental health approaches mental health issues at the population level. The need for a public health approach to reduce the burden of mental health problems is increasingly accepted, and this paper aims to summarize current thinking and trends in the field.

According to the World Health Organization (WHO), mental health is not just the absence of illness, but is rather conceptualized as a state of wellbeing in which the individual realizes his/her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his/her community (1). Consequently, public mental health is not just about the occurrence and prevention of mental disorders in the population, but also includes the promotion of mental health and wellbeing (2). Public mental health thus encompasses the experience, occurrence, distribution and trajectories of positive mental health and mental health problems and their determinants; mental health promotion and prevention of mental disorders; as well as mental health system policies, governance and organization.

In spite of their impact, mental health issues have been largely neglected in public health agendas. In order to successfully introduce these issues in the political agenda, a new approach was developed, primarily in Europe, in the 1990s. In this approach, neither the high prevalence of mental disorders nor the need for more resources in psychiatry was used as an entry point. Instead, it was highlighted that mental health is an integral component of public health, and that it has a significant impact on individual countries and their human, social and economic capital. The aim was to raise mental health from its professional, organizational and even political isolation within psychiatry to the broader sphere of public health, and to shift the focus from the individual to the population level, so that mental health could be perceived as a matter of interest for everybody (3).

It is now recognized that the foundations of mental health are laid in early life, and even in the prenatal period (4). Poor nutrition, exposure to toxic substances (such as alcohol) during pregnancy, trauma during labour, maternal depression, parental neglect, physical and sexual abuse, and other forms of trauma and lack of stimulation impact a child's cognitive development and socio-emotional wellbeing (5). Later in life, social relationships are critical for promoting wellbeing and buffering against mental ill-health (6,7).

Individual, familial and societal determinants of mental health often lie in non-health policy domains such as social policy, education and urban planning. Consequently, the "Health in All Policies" approach (8) was developed, targeting determinants of mental health across policy areas in the whole population, reaching out to areas other than the health sector, and highlighting the links of mental health to productivity (9). This approach forms the basis of many modern mental health policy documents.

Major individual socio-economic risk factors for mental health problems and suicide are poverty, poor education, unemployment, high debt, social isolation and major life events (10-12). Actions to promote mental health within disadvantaged groups and hence reduce mental health inequalities are important constituents of public mental health actions (13).

MENTAL HEALTH PROMOTION

Mental health promotion aims to improve the mental health of a population by strengthening wellbeing. Researchers and experts in the field tend to agree that the concept of wellbeing comprises two main elements: feeling good (hedonic wellbeing) and functioning well (eudaimonic wellbeing). Happiness and enjoyment are aspects of hedonic wellbeing. Resilience (the capacity to cope with adversity), sense of mastery of one's life, and sense of coherence and optimism are characteristics of eudaimonic wellbeing (14). Standardized measures of wellbeing have been used in population-based surveys (15,16), and there are several countries in Northwestern Europe (e.g., England, Iceland and Scotland) that perform repeated measures of mental wellbeing in the population.

Common principles and recommendations for modern mental health promotion were laid by the Melbourne Charter in 2008 (17). The charter provides a framework which recognizes the influence of social and economic determinants on mental health and mental illness, and identifies the contribution that diverse sectors (including but not exclusive to health) make in influencing the conditions that create or ameliorate positive mental health. The charter stresses that mental health promotion is everybody's concern and responsibility; that mental wellbeing is best achieved in equitable, just and non-violent societies; and that mental health is best promoted through respectful, participatory means where culture and cultural heritage and diversity are acknowledged and valued (17). Effective mental health promotion builds on cross-sectoral collaboration with non-health sectors, including education, housing, employment and industry, transport, arts, sports, urban planning and justice.

An important target for mental health promotion intervention is parenting, including early parent-child interaction and approaches to discipline in child upbringing. Promoting a nurturing early interaction between caregivers and the child increases the resilience of children in the face of adverse life events and promotes life-long mental health and wellbeing. Home visitation programmes that provide counselling, as well as a specific intervention to strengthen parent-child interaction, have been shown to be effective when delivered by trained lay women in developing countries (18), and by trained nurses in developed settings (19). Such programmes have been found to improve maternal sensitivity, to reduce criticism and harsh upbringing and to improve attachment of children. Parenting programmes also prevent mental disorders: e.g., the primarily behavioral Webster-Stratton programme, also known as the Incredible Years Programme, has been successful in reducing the occurrence of conduct disorders (20).

The past two decades have seen a significant growth of research and good practice on mental health promotion in schools (21). Activities operate under a variety of headings, not only "mental health", but also "social and emotional learning", "emotional literacy", "emotional intelligence", "resilience", "life skills" and "character education". Interventions focus on skills and the curriculum, teacher education, peer support or a whole school approach including work on school ethos. Positive impacts include the reduction of depression, aggression, impulsiveness and antisocial behavior, as well as the development of proficiencies that promote mental health such as cooperation, resilience, a sense of optimism, increased problem solving skills, empathy and a positive and realistic self-concept. School programmes have consistently been shown to have positive moderate to strong effects on specific social and emotional skills and competences (22). Small to moderate effects of interventions have been also reported on positive mental, emotional and social health and wellbeing in general (23). Programmes have also shown to help prevent and reduce early sexual experience, alcohol and drug use, violence and bullying in and outside schools, to promote pro-social behavior and, in some cases, to reduce juvenile crime. Furthermore, mental health promotion programmes in schools significantly improve academic performance. Data indicate that successful school programmes include those with sequential and integrated skills curriculum, active forms of learning to promote skills, focus on skill development and explicit learning goals (24).

In the adult population, the workplace is an important setting for mental health promotion. Actions can be implemented at an organizational level or targeted at specific individuals. The former can target managers and include measures to promote awareness of mental health and wellbeing in the workplace and improve their skills in risk-management of stress and poor mental health. This can be achieved by examining job content, working conditions, terms of employment, social relations at work, modifications to the physical working environment, flexible working hours, improved employer-employee communication and opportunities for career progression. Actions targeted at individual workers can include modifying workloads, providing cognitive behavior therapy, time management training, exercise programmes, journaling, biofeedback and goal-setting. The most researched interventions are based on individual skills training implemented by means of cognitive, communication and daily life skills development, relaxation, meditation and mindfulness training, job stress management, and problem solving. Currently, the highest efficacy ratios have been attained in studies aiming to reduce stress and absenteeism levels, while intervention efficacy is reportedly lower regarding job satisfaction improvement and mental health enhancement. Stress reduction (coping improvement) interventions seem to be better known and easier to implement than those aimed at increasing employees' job satisfaction. Structuring employment to create "good work" brings health benefits to the individual, financial benefits to the corporation and both direct and indirect improvements to the fabric of society (25).

For older people, the most promising interventions promoting mental health include meaningful social activities, tailored to the older individual's abilities and preferences. Studies have shown that associations exist between social capital in the ageing population and mental health (26,27). Crucial components of the individual-level social capital concept, such as social support and social network size, are negatively associated with depressive symptoms and depression. Research has highlighted that civic mistrust and lack of reciprocity or social participation (i.e., low individual-level social capital) are associated with depressive symptoms among older adults. Psychosocial interventions aiming to increase the social contacts of older participants tend to improve mental wellbeing and reduce feelings of loneliness. A meta-analysis has shown that social activities among older people significantly improve positive mental health, life satisfaction and quality of life and reduce depressive symptoms when compared to no-intervention (28).

PREVENTION OF MENTAL DISORDERS

Prevention of mental disorders has a long history. The early ideas of the mental hygiene movement, at the beginning of the 20th century, were first translated into experimental activities in primary health care, schools and public health practices. However, the systematic development of science-based prevention programmes and controlled studies to test the effectiveness of preventive interventions in the mental health field did not emerge until around 1980. Since then, the multidisciplinary field of prevention science in mental health has developed at a rapid pace, generating evidence showing that preventive interventions can influence risk and protective factors, and reduce the incidence and prevalence of some mental disorders.

Primary prevention addresses wider determinants across whole populations, and is of special interest to public mental health. Depending on the target group, primary prevention can be universal, selective or indicated. Selective prevention focuses on groups at higher risk of developing a disorder. Indicated prevention targets individuals who are identified as having minimal but detectable signs or symptoms foreshadowing a mental disorder, or biological markers indicating predisposition for mental disorder, but who do not meet all diagnostic criteria for a disorder at that time. An example of highly effective selective prevention is given by interventions to support parenting and children in families with mental disorders. A recent systematic review and meta-analysis indicated that the risk of mental disorders in the offspring can be reduced by 40% by preventive interventions (29).

In public mental health, the main arenas of preventive work are outside the health setting, e.g., in schools and workplaces. Bullying among youth is a significant public health problem; it is prevalent and frequently has a detrimental mental health impact reaching into adult life (30,31). A meta-analysis of strategies to prevent school bullying concluded that whole school approaches, including multiple disciplines and complementary components directed at different levels of school organization, more often reduced victimization and bullying compared to interventions that only included classroom-level curricula or social skills groups (32). Prevention of bullying would improve mental health outcomes for many young people, and advocating effective anti-bullying prevention programmes is an important part of public mental health activities.

Public mental health activities also aim at strengthening communities. Community systems-strengthening interventions focus on developing empowering processes and building a sense of ownership and social responsibility within community members. An example of such an intervention is the Communities That Care (CTC) Programme, which has been implemented successfully in the U.S. and is currently being adopted and replicated in several developed countries. The CTC intervention activates communities to implement community violence and aggression prevention systems (33). Evaluations at various CTC sites have indicated improvements in youth outcomes such as reduction in school problems, weapons charges, burglary, drug offences and assault charges.

There is rich evidence showing that conduct disorders, aggression and violence of young people can be prevented. The most successful preventive interventions focus on improving the social competence and pro-social behavior of children, parents, peers and teachers. Universal interventions which have had a successful impact on conduct problems are all school-based and include classroom behavior management, enhancing child social skills and multimodal strategies involving parents. Moreover, school- or community-based programmes for selected child populations at risk have successfully targeted child social and problem-solving skills and/or parent management skills, resulting in a decrease in negative parent-child interactions and teacher ratings of conduct problems at school (34).

Recent research demonstrates that depressive episodes can be prevented in a cost-effective and even cost-saving way (35). Preventive interventions can reduce the incidence of new episodes of major depressive disorder by about 25%. Adding a stepped-care model to the preventive intervention may reduce the number of new episodes even more (36). Methods with proven effectiveness include educational, psychotherapeutic, pharmacological, lifestyle and nutritional interventions. School-based programmes targeting cognitive, problem-solving and social skills of children and adolescents have achieved a reduction in depressive symptom levels of 50% or more a year after the intervention (37). Also anxiety disorders can successfully be prevented by strengthening emotional resilience, self-confidence and cognitive problem-solving skills in schools (38).

Substance abuse disorders can be prevented by universal policy actions aimed to reduce the availability of alcohol and drugs. Effective regulatory interventions include taxation, restrictions

on availability and total bans on all forms of direct and indirect advertising. When applied to alcohol, education and persuasion strategies usually concern decreased alcohol consumption, the hazards of driving under the influence of alcohol and related topics. Despite their good intentions, public service announcements are considered an ineffective antidote to the high-quality pro-drinking messages that appear much more frequently through paid advertisements in the mass media (39).

Universal and selective interventions are not yet viable strategies in the prevention of psychoses. The indicated prevention approach and early identification and intervention hold some promise to reduce the burden of schizophrenia and other psychoses. Typically, there is delay of 1–2 years between the onset of schizophrenia and initiation of treatment, due to failure in identifying psychosis. A prolonged duration of untreated psychosis has been linked to poorer outcomes. Several population-based indicated preventive programs have been developed to reduce the duration of untreated psychosis. Improving community awareness and increased mental health literacy of the general population reduced the delay into treatment in the Norwegian Treatment and Identification of Psychosis Study (TIPS) and subsequent studies in Australia (40).

PREVENTION OF SUICIDES

Suicides can be prevented by public health actions, and suicide prevention has consistently been shown to be highly cost-effective. Public health approaches to suicide prevention have to integrate societal and cultural viewpoints with medical and psychological ones to develop strategies that will save lives in an effective and measurable way.

Considerable evidence is available for the effectiveness of broadly applied population-level interventions. The restriction of access to common and highly lethal suicide means, such as toxic substances and firearms, has been successful in reducing suicides (41). Restriction of one suicide mean seems not to lead to a switch to another, as suicidal persons tend to have a preference for a specific method (42). Responsible media coverage of suicides, based on media guidelines and monitoring of stigmatizing media reports, have been linked to reduced stigmatization in press and reduction of suicides (43,44).

Community-based multi-level interventions targeting primary care providers, gate keepers, general populations and patients with their relatives have been linked to reductions in suicide (45,46). The evidence for targeted interventions, which address high-risk groups such as people who self-harm, people bereaved by suicide, and people with severe mental illness, is less convincing but promising (47).

Although suicide rates are higher in some risk groups than in the general population, universal approaches hold the potential to prevent a greater number of deaths (48). For example, in times of peace, when most firearm-related deaths are suicides, enforcement of gun-control policies (e.g., purchase restrictions, waiting times for gun purchase, higher age limits, licensing of firearm owners, safe storage precautions) can reduce numbers of firearm suicides (49). Empirical data suggest that firearm regulations, which function to reduce overall gun availability, have a significant deterrent effect on male suicide, while regulations that seek to prohibit high-risk individuals from owning firearms have a lesser effect (50).

MENTAL HEALTH SERVICES

Design, management and evaluation of mental health services and systems are important tasks of public mental health. Today, mental health service provision is in a global transition from hospital-based to community-based systems (51). The change reflects the growing evidence of what constitutes cost-effective care, but also acknowledges the failures regarding social inclusion and human rights of the old institution-based care system (52). Available evidence indicates that community-based and diversified mental health systems, with a wide range of services, are superior to hospital-centred mental health systems, according to a range of outcomes. For instance, community-based, well-developed and multifaceted mental health services have been linked to lower suicide rates than hospital-based traditional services (53). Discharged patients benefit from well-developed community care; community follow-up has been associated with a significant reduction in suicides among recently discharged psychiatric patients (54).

The recent history of mental health services can be seen in terms of three periods: first, the rise of the asylum; second, the decline of the asylum; and third, balancing mental health services (51). In the first era, the medical model prevailed. Later, it has been supplemented by an emphasis on autonomy and human rights of service users. During the last ten years, the recovery approach, stressing the first person view and personal journey of the service user, has greatly contributed to the public mental health view on how a modern mental health care system should be constructed. In a recovery-oriented system of balanced care, the focus is on services that are provided in normal community settings, as close to the population served as possible, and based on individual needs. Development and evaluation of recovery orientation and person-centeredness in mental health care are current challenges in public mental health (55,56).

A core element of modern mental health care is the empowerment of service users and informal carers. Historically, people with mental health problems have lacked a voice. Empowerment translates into being treated with dignity and respect in mental health services and participation of users and carers in decisions. Key issues that users and carers have expressed as important to advocate for are: rights to autonomy and self-determination, to acceptable and accessible services, to user-led evaluation of services; the

right for everyone to be recognized as a person before the law without discrimination, the de-stigmatization of mental disorders, and more inclusive and respectful services with user and carer involvement. Increased use of peer support and "experts by experience" in the provision of mental health services will support empowerment of service users and improve services (57).

A public health policy supporting the integration of health and social services, and the mainstreaming of mental health services into primary care, improves access to care on the whole. Integrating mental health services into general health care is often the most viable way of closing the treatment gap and ensuring that people get the care they need. Primary care responsibility for common mental disorders should be supported by accessible referral systems and specialist supervision (58). Providing even minimal psychotherapy in primary care can prevent full-blown depression (59). Programmes aimed at education of primary care physicians have improved the detection of depression and even led to a decrease in suicides due to depression (60). The use of new media, such as e-mental health and smart phone technologies, and the use of lay health counsellors, may boost dissemination of mental health interventions, especially in low- and middle-income countries.

Public mental health does not only deal with the organization of mental health services; it also strives to comprehensively cover all aspects of service user needs, including supported housing and vocational support. Collated evidence suggests that supported employment schemes, which consist of arranging early placement in normal work with variable support from staff, may offer better outcomes than sheltered or transitional employment approaches. People suffering from mental disorders wishing to work should be offered the option of supported employment as part of their treatment package. Evidence indicates that supported work improves clinical outcomes and fosters social inclusion of people with severe mental disorders (61).

International benchmarking, based on comparable data, is an important moving force for the development of mental health services in countries. Unfortunately, mental health information systems, in most countries, are geared towards hospital data, which are of less interest when developing a community-based mental health service provision system. Many highly relevant aspects of modern service provision, such as patient choice, service user empowerment and respect for human rights, are hardly ever covered by health information systems (62).

FIGHTING STIGMA AND DEFENDING HUMAN RIGHTS

Stigmatization of people with mental disorders is a core concept in understanding the field of public mental health (63). Stigma has an in-depth influence on the status of mental health services, their resource allocation and their attractiveness to the workforce. It represents a barrier to help-seeking behavior among people with mental health problems, and affects provision of services negatively (64).

Stigma and stereotypes form negative public attitudes towards people with mental health problems and psychiatry as a whole (63). Discrimination of people with mental disorders is a common manifestation of stigma. International studies have shown that discrimination of people with mental disorders is consistently common across cultures (65,66). Overall, there is a lack of parity between mental and physical disorders, in that people with mental disorders as well as the services they are provided are less valued.

Consequently, actions against stigma are core activities in public mental health. Unfortunately, not even large-scale and expensive anti-stigma campaigns have shown much promise in achieving changes in public attitudes (67,68). A combination of positive social contact with people with mental disorders, protest against stigmatizing messages and measures, and education seems to be most effective in fighting stigma (69,70). Social contact has shown to be the most promising evidence-based intervention method, including "proxy" contact, for example a narrative through a film (71). Public protests have played a limited role in mental health campaigns compared to other civil rights movements, perhaps due to the very deeply held prejudice within society and the potential for ridicule (72). At best, anti-stigma activities such as providing social contacts are mainstreamed in school curricula and training of professionals.

Mental disorders are inextricably linked to human rights issues. The stigma, discrimination and human rights violations that individuals and families affected by mental disorders suffer are intense and pervasive. The United Nations Convention on the Rights of Persons with Disabilities (73), adopted in 2006, affirms that people with mental health disabilities have the right to full participation and inclusion in society, including the right to live independently, the right to education, and the right to work. The convention, and related pressure from the international community, will increasingly put human and fundamental rights issues at the forefront of new regional and national mental health policies across the globe. In countries with well-developed legislation, there is an increasing movement away from potentially discriminatory separate mental health legislation to fusion laws covering all kinds of impairments and health needs (74).

CONCLUSIONS

Public mental health is coming of age and is increasingly being accepted as an important and integral part of both public health and mental health. However, in many countries there are major shortcomings in training opportunities and research activities. A recent European mapping indicates that public mental health research is concentrated in the most affluent countries, in

spite of major needs in less affluent countries (75).

A recent expert consensus statement on research needs in public mental health (76) stressed that positive mental health and protective factors should be prioritized when planning future research actions and strategies. Furthermore, the need for using interdisciplinary perspectives in order to better understand the complexity of mental health has emerged, as well as the fact that the theory base of public mental health research, including conceptual definitions and frameworks, should be strengthened across all research initiatives in the field.

Many challenges remain in the field of public mental health research, both in the identification of risk, protective and resilience factors for mental health across the lifespan and in the development and implementation of effective and evidence-based public mental health interventions. Taken together, however, the evidence base for public mental health interventions is convincing, and the time is now ripe to move from knowledge to action.

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Addressing social injustice: a key public mental health strategy

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The primary goal of public mental health is to reduce the burden of mental disorders, scaling up an array of evidence-based interventions aimed at the prevention and treatment of these disorders. Given the absence of evidence that the treatment of mental disorders, unlike many other health conditions, can reduce their population burden, one must pin one's hopes on interventions aimed at mental health promotion and the prevention of these conditions.

Much of the discourse in public mental health, and the emphasis of Wahlbeck's paper (1), is to put into practice interventions that meet the widely accepted criteria of "evidence", which, with a few notable exceptions, is defined by efficacy proven through randomized controlled trials or, at the very least, some other controlled evaluation. However, these research designs are unable to evaluate interventions which act at levels higher than individuals or relatively small clusters of individuals (such as schools), and thus it is not surprising that most of the recommended interventions target individuals (e.g., parenting interventions) or small groups of individuals (e.g., life skills training in schools). The few exceptions lie in regulatory interventions at the national level, such as alcohol taxes or restriction of methods for suicide, where time-series analyses can allow causal inferences with some confidence, as there are unlikely to be other confounders in the context of the immediate impacts of these interventions.

It is not surprising, then, that even though "the societal determinants of mental health often lie in non-health policy domains" (1), most actions which are promoted by public mental health practitioners tend to focus on individuals. This commentary urges us to also pay as much attention to actions which need to be taken higher up the causal pathway, targeting the structural (or societal) determinants operating at the national, regional and global levels.

The rich literature from social epidemiology shows us that the most pressing determinants of mental health in all populations are structural: poverty (both absolute and relative), gender inequality, social exclusion and conflict. For obvious reasons, interventions targeting these determinants do not lend themselves easily to experimental evaluation, and when they do (as has become increasingly evident with the application of experimental methods to evaluate poverty alleviation interventions), mental health outcomes are rarely measured (2). However, this does not mean that the strong, cross-national, observational evidence which is available should not be acted upon.

With few exceptions, the vast body of the epidemiological studies consistently demonstrates that mental disorders are commoner in people who are socially disadvantaged, exposed to violence and conflict, or displaced for one reason or another (3). The global economic system has led to a massive increase in global wealth and a remarkable reduction in levels of absolute poverty in most countries. But, at the same time, the rapid growth of the global economy – particularly fierce in the new millennium as several large, previously low-income, countries accelerate their march towards "development" and global financial markets are deregulated – has also led to the worsening in several other determinants: increase in financial instability for countries, sometimes leading to unexpected and dramatic economic collapses; a gathering pace of climate change and environmental degradation fuelling increasing uncertainty in livelihoods; conflicts driven by the need to control fossil fuels and other natural resources; growing insecurity of employment as businesses operate globally, moving to any location where they can minimize the cost of labour; and the massive growth in income inequality in most countries creating deeply divided societies. These changes are not the ingredients for promoting public mental health.

It is arguable whether, in the face of such a large scale onslaught on the basic values which underpin a healthy society, individual interventions to promote mental health can have any meaningful population level impact. It is for this reason that public mental health must champion policy interventions which address structural determinants that operate within and across all countries. We should expect that interventions which successfully address structural determinants such as absolute and relative poverty or gender based violence or conflict prevention will produce downstream beneficial effects on population mental health. And there is an evidence base, derived from country level case studies (since structural determinants are typically addressed at the national level), that such interventions can improve mental health outcomes. The dramatic reduction in suicide rates in China over the past decade has, at least in part, been attributed to improved living conditions in rural areas and greater empowerment of young women (4). The higher rates of self-reported well-being and lower rates of mental disorder and substance use in countries with lower levels of income inequality is another case in point (5). And surely one does not need an experimental study to demonstrate that people who live free of war and hunger enjoy better mental health.

Public mental health is as much about politics and ideology as medicine and science. A world in which

the wealth of a few is privileged over the welfare of the majority and where social justice and equity, both within and between nations, are not considered pre-eminent values to promote healthy populations, is one in which mental health problems will inevitably become more common. Public mental health must not only equip people and communities to better cope with the stressors created by a dysfunctional world, but also target the very drivers of this dysfunction.

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Public mental health: evidence to policy

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Public mental health is difficult to define, because there are contested boundaries and terminology. In producing the Chief Medical Officer's Annual Report 2013 (1), we became increasingly concerned about the lack of consensus over fundamental issues in public mental health in England, including: a) the definition and key components of public mental health; b) the relation of concepts within mental health to one another; c) how mental health variations of importance are measured and experienced; d) the value placed on mental health and its consistency across society; e) our approach to the generation, accumulation and use of evidence in policy.

Public mental health came into focus in England in 2008, when the Government Office for Science published the Foresight Report on the topic of "mental capital" and "wellbeing" (2). That report provided a major impetus for political and policy interest in framing mental health policy in terms of "wellbeing", which continues to gather pace. Foresight suggested that "achieving a small change in the average level of wellbeing across the population would produce a large decrease in the percentage with mental disorder, and also in the percentage who have sub-clinical disorder (those 'languishing')" (2).

With the tempting prospect of a "wellbeing" approach to public mental health potentially promising the primary prevention of mental disorder, the "wellbeing" agenda and a diversity of associated narratives have since been prominently embedded throughout mental health policy in England. A necessary concurrent step in the rapid ascendancy of wellbeing would obviously need to be the production of a robust supporting evidence base, using clear and agreed definitions and metrics. We reviewed the evidence in depth and found it wanting (3).

Concerns have crystallized that wellbeing is difficult to define, difficult to measure and therefore difficult to integrate in any meaningful way into public mental health (4-6). When combined with contested boundaries within mental health and the widespread use by researchers and policy makers of an array of unvalidated proxy wellbeing measures of varying lengths and sophistication, the production of a body of wellbeing related evidence that is scientifically robust enough to support policy making is difficult. In particular, we reject the use of items validated for measurement of disorder – most notably the General Health Questionnaire (GHQ) – as a measure of wellbeing (7-10).

The psychometric relationships between "positive" and "negative" mental health variations of importance in populations are not yet sufficiently understood, but they almost certainly do not exist on a continuum (3). This is a complex field, and those promoting a wellbeing approach to mental health simply must engage with new combinations of items. Furthermore, we cannot say with confidence that wellbeing narratives are safe for low scorers on the widely used wellbeing scale, the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS), in which psychiatric distress in terms of probable GHQ morbidity remains a key unresolved question (3).

A further cause for concern is that an approach to mental wellbeing that incorporates measures of disorder has spawned a policy agenda in which terms describing very different populations are used interchangeably. The result is inconsistent blurring of the boundaries between population approaches to positive mental health and wellbeing promotion, prevention of mental illness, and treatment and rehabilitation, with little or no thought about the interrelated concepts in question. This has resulted in much of the wellbeing evidence review literature, on which public mental health policy in England has been built, inappropriately describing the results of studies in more established disciplines into the prevention and treatment of mental illness as part of a "wellbeing" evidence base to which they cannot scientifically be said to apply. "Proxy" outcomes are

unscientifically rebadged as "wellbeing" outcomes, critically compromising the evidence base upon which policy is built and funding allocated.

The Foresight hypothesis – namely that wellbeing interventions in mental health can be effective in the primary prevention of mental disorder – is unlikely to be true, since wellbeing and mental disorder do not exist on a clear continuum (3). Indeed, since this argument and mathematical model was first articulated in 1996 (11), evidence for wellbeing (or indeed any) interventions in public mental health that "shift the population curve", originally described by G. Rose (12), has simply not been forthcoming. In the absence of any empirical evidence, we reject the appropriateness of continuing to build policy upon this premise at this time.

Much of the commonly cited evidence in policy circles for wellbeing intervention evaluations as related to mental health is located within the grey literature – i.e., papers and reports which have not been subjected to independent peer review and are often published by the organization which carried out the research. Other fields within mental health already self-govern within the space of the accepted hierarchy of evidence. Yet we continue to hear concerning and irresponsible pronouncements that grey literature should be considered as of equal importance in the evidence base for wellbeing, and that the Chief Medical Officer should take a "leap of faith" regarding the case for wellbeing in mental health.

In reviewing the evidence and policy for public mental health, we argue, therefore, that it should no longer be framed in terms of "wellbeing". Instead we call for public mental health in England to follow the model developed by the World Health Organization (WHO) during the last decade, culminating in the WHO Mental Health Action Plan in 2013 (13-15). Drawing upon those reports, we conceptualize public mental health as consisting of "mental health promotion", "mental illness prevention" and "treatment and rehabilitation", terms which enjoy greater consensus about their definition (16) and are not mired in the significant challenges we have identified.

If we take this approach and ignore all studies and reports that do not meet scientific standards, we are left with a field of wellbeing that is much diminished in size and relative importance to the concept of public mental health. Generic statements about "improving wellbeing and mental health" should give way to a far more refined approach: at both a local and national level there are ample opportunities in England for mental health promotion, mental illness prevention and treatment and recovery from common mental disorder that we have the potential – and the evidence base – to address effectively (1).

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Applied public mental health: bridging the gap between evidence and clinical practice

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Wahlbeck (1) describes a public mental health approach at a population level. His proposal is far reaching, including not only the reduction of mental illness or specific psychiatric disorders, but the promotion of mental wellbeing, positive mental health and happiness. The targets vary widely, including parenting, education, housing, employment, justice, etc..

The interventions include relaxation, meditation, mindfulness training, job stress management, cognitive behavioral therapy, biofeedback, exercise, health education, social networking, etc.. The strategies include health promotion, improvement of mental health services, reduction of stigma, fight for human rights, etc.. The author concludes that challenges remain in identifying risk, protective and resilience factors for mental health problems across the lifespan, and developing effective and evidence-based public mental health interventions.

One cannot disagree with the mandate. However, the breadth is overwhelming. Many of the actions described require partnerships well beyond public health, psychiatry or even medicine, and fall in the domain of social policy, government, and the will of the people in a functioning democracy. The actions impinge upon social values and the limits of governmental reach, which vary considerably by culture or country. Consider the public health problems of violence, which are often related to firearms. Prevention may engage issues such as enforcement of gun control legislation, raising minimum age requirements for gun ownership, reforming gun licensing, and imposing restrictions on gun purchases. Identifying the risk factors and health education alone may be insufficient.

Safe food practices, immunization, public health education, and improved sanitation have been successful over the past century in increasing life expectancy and improving quality of life (2). Parallel public health initiatives for mental wellness will require a similar mobilization of government and business efforts based on known risks. Although social change itself may improve mental health, there will need to be a confluence of the common good for this to happen. Even then, there is little guarantee that programs will be effective or resources sufficient to sustain them (3).

Challenges exist on several levels. Governments move slowly, individuals seldom agree on priorities and fiscal considerations, and the public and large corporations resist increased taxation. How do you implement a policy that bridges the gap between public health evidence and clinical practice? Studies of community rates and risks of psychiatric disorders are now available in many parts of the world, and psychiatric epidemiology has been linked to the global study of disability. While the rates of psychiatric disorders vary by country, the risk factors are reasonably consistent across countries and cultures. The phrase "no health without mental health" is not merely a slogan; linkages between mental and physical illness are strong and bidirectional. Therefore, reducing psychiatric disorders and especially intervening early can have widespread beneficial effects.

Defining public mental health is a challenge and one with which the field has struggled. I would begin by focusing on evidence-based interventions applied to early manifestations of psychiatric disorders. Cross-national epidemiologic research documents long delays between psychiatric disorder onset and first treatment contact. The promotion of mental health, wellbeing or positive mental health or happiness does not easily fit in this early detection model (2).

In countries at all levels of economic development, much of the detection of mental illness occurs within primary care. With the Affordable Care Act in the U.S., the role of primary care providers in the detection of mental illness is likely to expand. We need to combine public health models with brief evidence-based psychosocial interventions in clinical practice for patients with early signs of disorder.

Why would one recommend a psychosocial intervention or psychotherapy? The reasons are not obscure. Patients in distress overwhelmingly express a preference for talking to someone or for counseling (4). Controlled clinical trials convincingly demonstrate the efficacy of several brief psychotherapies. These interventions have been defined in manuals and have been adapted to different ages and cultures (5,6).

Let me propose a new profession or a subspeciality of older ones. I call it applied public mental health. Applied public mental health would link training in public health, which is not a clinical profession, with one of the clinical professions. Social work might be a natural partner, but there may be others.

The focus would be on reduction of psychiatric illness and early symptoms rather than mental wellness, although increasing "wellness" might be an important by-product. This new profession would be grounded in an understanding of psychiatric risk factors, skills in several evidence-based psychotherapies, adaptation of treatments to different cultures and contexts, and developing new interventions or amalgamating old ones. Traditional roles providing direct assistance with access to social services and other resources would, of course, be included.

There are urgent calls for this change. An editorial appeared in September 2012 in *Nature* was entitled "Therapy deficit: studies to enhance psychosocial treatments are scandalously undersupported" (7). The World Health Organization is already incorporating brief evidence-based psychotherapies into its portfolio and has issued guidelines for managing care in health settings (8). While psychotherapy is fading from consciousness and practice in some developed countries, it is being enthusiastically embraced in developing countries hurt by HIV, natural disasters, wars, or political strife (9). With this model, a victim of natural disaster may be helped to deal psychologically with loss and grief as well as receive emergency provisions and an application for housing. Persons with serious, recurrent psychiatric disorders would be triaged to psychiatrists and other physicians (10,11).

Brief evidence-based psychotherapies are being applied in many situations all over the world (9). The problem is that training in these treatments is a cottage industry and developed in an *ad hoc* manner for each situation. While the training for these programs can be of very high quality, this approach is inef-

ficient, insufficient, and not sustainable. In the U.S., with the exception of cognitive behavioral therapy in psychiatric residency training programs, courses in evidence-based psychotherapy are now not an accreditation requirement (12). Certification standards are either absent or *ad hoc*. Applied public mental health could be a subspeciality of public health and a clinical profession, for which training in brief evidence-based psychotherapies would be essential.

Rates of psychiatric disorders, particularly depression and anxiety, are high in primary care patients, and among victims of natural disasters, civil wars, violence, sexual abuse, chronic medical illness, the unemployed, new mothers, recently divorced, etc.. These individuals frequently need social, economic and legal services. In order for these services to be effective, however, the distressed individuals also need a therapeutic alliance and someone to talk to and sort out their history, their resources and concerns. I am not advocating long-term psychotherapy except where it is indicated for the small number of people with severe and enduring psychiatric disorders.

In the context of Wahlbeck's comprehensive proposal, a focus on short-term evidence-based psychotherapy implemented with the guidance of public mental health specialists is modest. The broader goals should not be lost, recognizing they require advocacy and the public will. In the meantime, however, small but dedicated efforts to improve the delivery of mental health care that are cost-effective and evidence-based should be sought. The guiding principles should include a focus on early intervention, integration with primary care where possible, a patient centered orientation, and an integration of clinical and public health perspectives. It is more efficient to have psychosocial interventions taught in formal educational programs than in grass roots *ad hoc* training courses.

At present, public health programs identify risks but do not teach clinical applications, while social work and other counseling programs are not grounded in public health, and training in evidence-based psychotherapies is rarely required. These disciplines have much to offer each other in bridging the gap.

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Mental disorder: a public health problem stuck in an individual-level brain disease perspective?

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K. Wahlbeck provides a range of cogent arguments supporting the view that the natural perspective for mental health is in the realm of public health. In reality, however, the perspective of public health is not dominant in academic psychiatry or in the way mental health services are organized. The dominant model in academic psychiatry is embedded in an individual-level perspective of brain disease, although there is considerable debate as to how successful this dominant approach has been (1).

A student wanting to find out about psychiatry may get the impression that two languages are spoken in mental health: a public health one, taking into account the natural perspectives of high prevalence, graded trajectories from health to illness, social determinants, empowerment and self-determination, resilience, positive mental health and prevention; and a biomedical one, focusing on illness and diagnostic labels, brain disease, animal research, genetic liability, biological determinants and pharmacological interventions.

The existence of two languages in mental health research is one of the explanations of the limited crosstalk between areas distributed over the public health and natural sciences, even though

the application of scientific paradigms to mental health research, including those derived from neuroscience, psychiatry, public health, epidemiology, social science, sociology, psychology and philosophy, has expanded exponentially. In other words, research in mental health has expanded exponentially, but in widely different directions, showing signs of increasing fragmentation rather than integration. If natural science and public health are to join forces, this will have to be at the level of research endeavours in which the results are interpreted on the basis of a common language.

There are some pointers as to which elements may be used to construct a common language. First, research in public health highlights powerful effects of the social environment on onset and persistence of syndromes of mental ill-health, the existence of vulnerable and resilient subgroups, and possible cognitive, neural and behavioural mediation of environmental effects. Second, research in psychology and psychiatry indicates that most mental disorders as defined in DSM and ICD represent quantitative deviation from health. Third, research in basic population genetics highlights the importance of (epi)genetic variation in terms of short-term and long-term adaptation to the social environment. Fourth, research in social neuroscience is highlighting the role of the brain in enabling man to navigate the social world and is building models of the way in which our current context – which includes both the social environment and our internal states and traits – impacts on how we attach meaning to social cues. There is increasing interest in the role of culture in these processes, for example how cultural variation may impact on social cognition and the process of empowerment in relation to one's circumstances.

The above four elements indicate that genetic variation and neural processes form the biological roots of human sociality, resulting in the mutual constitution of cultures and selves; they also suggest that health and illness result from complex interactions between the physical, cultural, and social environments. Thus, a common theme emerges linking deviation from mental health, genetic variation and neural function, which can be formulated as dynamic adaptation to the individual-level and wider social environment. Dynamic adaptation to the environment may constitute a point of entry towards a common language in mental health research, linking social and natural sciences.

However, this perspective contrasts with the current practice of research in biological psychiatry, which typically involves comparisons between a group of severely ill patients constrained by DSM or ICD criteria of disorder, and healthy, or "super-healthy", controls on static measures of, for example, allelic frequency or cortical thickness. In other words, the role of genetic and neural variables in dynamic adaptation to the social world, including at the level of intentionality and meaning, is typically not taken into account.

Public health approaches in mental health research can be introduced focusing on genetics, neuroimaging and animal models, using the perspective of dynamic adaptation to the environment. For example, what potentially links the different approaches in mental health research is the level at which social and cultural influences are studied, and how these might interact with each other. Public health research is of particular interest in the area of how the wider social environment may impact on risk for and resilience against mental disorders. Examples of such contextual variables are social cohesion and trust, social capital, social integration, ethnic density, population density, social divide or social inequality. Research has shown that these types of contextual variables are strongly associated with mental outcomes (risk and resilience), and interact with individual-level characteristics (e.g., individual-level ethnic group and ethnic density).

As there is a paucity in cross-discipline approaches, this type of research has yielded little in terms of causality, biological and psychological mediators and moderators, and developmental pathways. It is reasonable to assume that the impact of the wider social environment will be mediated by individual-level cognitive and (cross-species) biological factors and that it will be moderated by the same factors. It is clear that a rich potential exists for collaboration between public health scientists on the one hand, and mental health and neuroscience researchers on the other.

While it may be attractive to align cross-species behavioural research paradigms, resulting in a multilevel perspective on underlying neural mechanisms, there is an additional need to co-align and co-evaluate this work with "mental" paradigms, for example from experimental psychology. A good starting point to bring together research on behavioural, neural and cognitive mechanisms around a single paradigm is to study the impact of a certain environmental exposure (at the level of repeated within-person momentary micro-environment, the individual level, or the contextual level of the wider social environment) on mental, behavioural, neural, cellular and molecular outcomes in a single observational or experimental "social" paradigm, taking into account moderation of environmental influence by genetic factors.

For example, childhood adversity and having a minority position in society are important social risk factors with powerful effects that can be described in terms of developmental mental, molecular, cellular, neural circuit, cognitive and behavioural effects, in association with evidence of moderation by genetic variation. Bringing these together in a single collaborative research effort, linking the different mechanisms, will make it possible to enrich the outcome of individual research efforts synergistically.

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Public mental health: a call to action

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K. Wahlbeck (1) convincingly argues that the prominent role of social factors in wellbeing and mental health is supported by overwhelming evidence. He states that a series of studies have shown how evidence-based programs to prevent mental disorders can be translated into everyday practice. However, he cautions that there is a lack of action in the most affluent countries, while there is an even wider gap between possible ways of intervention and current funding in the less affluent ones. Furthermore, he emphasizes the need for interdisciplinary research to broaden the theory-base of programs aimed at the promotion of public mental health. Let us briefly examine these arguments.

There is indeed an abundance of studies showing an association between poverty and social exclusion on the one hand, and poor mental health on the other (2,3). However, correlation is not causation, and it may be argued that variables not detected in these studies – such as unknown familial influences including environmental and (epi-)genetic factors – may explain the observed correlations. But they either cannot be easily targeted (such as unknown familial factors) or are not even amenable to social interventions (such as genetic factors).

Against such therapeutic nihilism, two arguments can be raised. First, a series of animal experiments and human studies have shown that social stress factors, particularly exclusion, stigmatization and discrimination, directly impact on the neurobiological correlates of mental disorders, impair cognitive capacities and promote aggression, drug intake and negative mood states (4,5). Indeed, even fluid IQ as a measure of complex cognitive capacities has been associated with variation in dopaminergic neurotransmission, which in turn is strongly affected by stress exposure (6-8). Second, most twin research has relied on the (controversial) assumption that gene-gene interactions are only additive and cannot exponentially increase similarity (e.g., when variation in multiple genes increases neurotransmitter synthesis and at the same time decreases both reuptake and metabolism). On the other hand, the "equal environment" assumption on which most twin studies are based does not differentially capture complex genotype-phenotype interactions.

We caution that both supraadditive genetic effects as well as the presence of complex genotype-phenotype interactions could lead to an overestimation of genetic effects, which could in turn override environmental effects in twin study designs that assume only additive interactions (9). Hence, the current absence of evidence for environmental effects in many twin studies is not evidence of absence. Moreover, there is emerging evidence that the effects of genetic variation on behavioral phenotypes are amenable to targeted behavioral interventions, such as cognitive training (10). These considerations call for study designs that look at complex genotype-phenotype interactions and assess not only genetic but also epigenetic effects (11).

With respect to Wahlbeck's argument that insufficient funds are spent on preventive programs in affluent countries and that there is a wide gap between available funds and social needs in the less affluent ones, one can only but agree and call for direct action. Epidemiological studies suggest that mental disorders impose a huge burden on individuals and their families, which is further augmented by social exclusion and stigmatization (12,13). It may be exactly due to this persisting stigma that, in spite of good evidence for the effectiveness of preventive programs, even rich countries do not provide sufficient funds. For those countries that are less affluent, some tough choices have to be made: it may be less helpful to promote hospital care if there is a lack of social consultation, as we experienced in Afghanistan and Mali, while educating social workers, nurses and general practitioners may have to take priority (14,15).

Wahlbeck calls for interdisciplinary research to promote the theory basis of public health. Indeed, we strongly agree and suggest that both quantitative and qualitative research has its place in this respect. While animal experiments, longitudinal studies and epidemiological data can provide a quantitative account of the interaction of social and individual factors contributing to mental health and distress, qualitative studies can generate new lines of research and explore what a given situation really means for patients and their relatives as well as the general population. Indeed, neuroscience has turned social (16) and it is time for epidemiology and social psychiatry to embrace multi-level approaches to mental health and to put viable programs into practice.

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Building behavioral health systems from the ground up

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Wahlbeck's paper (1) provides a succinct and accurate overview of the public health approach to global mental health. Conceptually, public health incorporates not just evidence-based interventions from high-income countries, but also significant emphases on positive behavioral health, prevention, recovery, and social, cultural and environmental factors.

Expanding global mental health to include positive behavioral health – and therefore all people – offers the advantage of attention to developmental needs, resilience, prevention, and recovery (2). The behavioral health field has ignored these issues and the related empirical research findings for too long. Relatedly, shifting from "mental health" to "behavioral health" could underscore the broad focus on healthy behaviors rather than a narrower focus on mental illness. As one ramification, mainstreaming behavioral health to the entire population may reduce stigma for those who experience the most severe disabilities.

The practical implementations of the Movement for Global Mental Health have been criticized extensively (3). Despite its holistic and laudable rhetoric, implementation attempts have largely involved an expansion of Western evidence-based biomedical or psychological interventions delivered via lay health workers and have not been sensitive to cultures and communities. Local communities often object to the imposition of Western models of individual mental illness when the problems are widespread, the culture is not so individualistic, and behaviors are obviously related to war, poverty, gender discrimination, lack of opportunity, and so on. The failure to engage communities and understand cultural values and norms has sometimes worsened rather than relieved widespread community distress (4).

The use of lay health workers helps to expand services and engender trust (5), but these workers typically make diagnoses and dispense medications or psychological therapies following a Western medical model. How could community engagement efforts align more closely with local culture? One basic strategy could be to start with local people on the ground. "Top-down" solutions (i.e., those developed by government experts) that are imposed on communities are often bureaucratic, reductionistic, overly prescriptive, and insensitive to local culture and context. The expensive and inefficient Veterans Administration Healthcare system in the U.S. is often cited as an example of the failure of top-down systems (6).

By contrast, "ground-up" approaches (i.e., those developed by local stakeholders and communities) may better serve the goals of public mental health by valorizing local knowledge, competence, and resources. People on the ground – those experiencing behavioral health problems, their families, and their communities, aligned with local leaders, professionals, healers, and health workers – may in fact be in a better position to recognize local needs and resources, to understand local culture, to select and adapt appropriate evidence-based practices, and to innovate solutions. Local culture, however, may sometimes perpetuate stigma and even violations of human rights – hence the need for collaborations with professionals via mutual learning. Learning communities (multi-disciplinary groups focused on a specific health issue) have successfully combined local stakeholders with outside experts to discuss, select, and evaluate potential solutions (7).

Community engagement could be enhanced on a global basis via several strategies. First, governments should give priority and funding to ground-up approaches. Community engagement in

health care has a long and rich tradition, including principles and strategies for identifying and solving problems (8). Local community activation has in fact often produced positive changes and sometimes led to national and international health reforms: witness the women's health movement in the 1960s and the AIDS movement in the 1990s in the U.S..

Second, the field should recognize that people with behavioral health syndromes generally have goals that differ from those of professionals (9). Rather than more and more medications to reduce symptoms, people generally want support in finding meaningful functional roles. If local people (rather than industry, government, and the medical profession) were to choose services and goals, behavioral health would shift dramatically. For example, women who are oppressed and abused would be likely to emphasize education, advocacy, legal action, employment, and financial independence rather than polypharmacy.

Third, healthcare systems should encourage people to develop natural resources, e.g., clubs, peer-support groups, spirituality, yoga, and other mindfulness-based therapies (10). These interventions, delivered by lay community members, are widely available in culturally specific forms and languages and can enhance prevention, resilience, treatment, and recovery. Government should encourage and strengthen these natural supports in local communities before assuming that more hospitals, professionals, and medications are the answer.

Fourth, lay health care workers should be given the opportunity to collaborate with the people in their communities in selecting the medical and psychosocial interventions that they want and obtaining the training that they need to be effective (11). Likewise, they should be given the choice to veto or adapt interventions that are perceived as harmful or culturally insensitive. Such an approach may require extensive discussions within communities and suspension of Western hegemonic beliefs about the immutability of science-based interventions.

Fifth, behavioral health technologies should be used to enhance all of these efforts in ways that maximize choice and cultural tailoring. A wide variety of web-based and mobile health applications are demonstrating effectiveness for prevention, empowerment, resilience, treatment, and maintenance (12). Low-income and middle-income countries are rapidly developing the connectivity that could facilitate widespread distribution, perhaps through lay health workers. Expanding and using these resources could helpfully overcome what is often perceived as the lack of a professional workforce while simultaneously empowering local communities.

Global attention to positive behavioral health for all people is essential. We would not gainsay efforts to increase access to evidence-based interventions, but current efforts should include a meaningful understanding and respect for local cultures, communities, and resources.

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Mental health services and public mental health: challenges and opportunities

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K. Wahlbeck (1) presents an excellent overview and critical analysis of the current thinking, trends and challenges in public mental health. He also makes a strong case for the need to translate the existing evidence into practice, and for developing research in the key areas of public mental health.

Acknowledging the fact that mental health issues have been largely neglected in public health agendas, Wahlbeck rightly highlights the importance of the new approach consisting in the use of arguments based on the impact of mental health on human, social and economic capital of countries, as an entry point to introduce mental health issues in the political agenda, instead of only using arguments based on the high prevalence of mental disorders.

The results of research on social determinants of mental health and

mental-ill health are now so strong, that it is easy to document the need of integrating mental health in all policies, reaching out to areas other than the health sector (2). We can now contribute to the improvement of mental health using information on social and economic determinants to inform service planning, organize programmes for promotion and prevention, develop advocacy for social change, and influence authorities outside the health sector to take action aimed at the promotion of mental health (3).

Therefore, I agree that the integration of mental health into non-health policies should be actively pursued. In my view, however, other approaches should also be used. Given the high comorbidity between mental disorders and physical illnesses, the integration of mental health into other health policies should also be prioritized. This is particularly true regarding the integration of responses to mental disorders and other chronic diseases. Epidemiological studies have consistently showed the strong links between mental disorders, major non-communicable diseases and several communicable conditions such as HIV/AIDS and tuberculosis. They are chronic, they share common determinants, they have severe consequences in terms of disability, they are highly interdependent, and tend to co-occur (4).

Although further research is needed, particularly in low-income countries, innovative models of integrated care have proved to be effective. In order to effectively respond to the challenges of integrated care, a public health approach is required, including a focus on disease prevention and health promotion, together with the provision of accessible, comprehensive and coordinated services (4).

I also strongly agree that the design and evaluation of mental health services and systems are important elements of public mental health. The growing evidence of the huge burden that mental disorders represent, and the significant treatment gap existing both in developing and developed countries, confirm that the development of new models of mental health services initiated in the 1980s continues to be a major challenge for the improvement of mental health of the populations, and it can only be handled with a public health perspective (5).

As noted by Wahlbeck, there is now a broad consensus on the need to shift from the model of care based on institutions to a system that relies much more on community-based care, and to integrate mental health in the general health system.

According to the World Health Organization's "pyramid of care", formal community-based mental health services, in conjunction with mental health services in general hospitals, are considered to have a central role in the improvement of mental health care for several reasons (6). They contribute to better accessibility. They are associated with continuity of care, greater users' satisfaction, increased adherence to treatment, better protection of human rights and prevention of stigmatization (7). They contribute to the establishment of a structured collaboration with the primary health care services, and facilitate collaborative models of care involving combinations of pharmacological and psychosocial interventions delivered in a stepped care manner, which are effective in the treatment of people with mental and physical comorbidities (8,9). They facilitate the coordination, and in some cases the joint funding and management, of health and social care services, as well as the collaboration of health services with services of the employment sector, that are needed to ensure the psychosocial rehabilitation component of care provided to people with severe mental disorders (10).

As highlighted by Wahlbeck, community-based services also provide better conditions to ensure respect for patients' human rights and recovery oriented care, as well as to empower and encourage such persons to make decisions affecting their lives, which is a core principle of the modern perspective of mental health care.

There is, however, another important advantage of community mental health services that, in my view, should also be stressed: the potential they have to facilitate an effective coordination between care, prevention and promotion. First, because they share with prevention and promotion programmes a public health perspective. Second, because they are often organized according to the catchment area model, thus facilitating the creation of synergies, in a certain geographic area, between people with mental health professional expertise and people from other fields (primary care services, schools, work places, non-governmental organizations, and other key agents in the community).

The implementation of policies and plans aimed at the transition to a model based on community services has proved to be a complex process, which usually faces important barriers (11). The integration of responses to mental disorders and other chronic diseases, as well as the coordination between community care and prevention and promotion programmes, will certainly also have to face significant barriers in their implementation. To overcome these barriers, studies on the effectiveness of prevention and promotion interventions should be extended to low-income countries, where they have been very scarce until now, and much more implementation research on mental health policy and services development should be performed.

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The effectiveness of public mental health policies: stressing the return on investment

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In recent years, public mental health has become an essential part of mental health, as convincingly pointed out in the paper by K. Wahlbeck (1). Public mental health is conceived as a theoretical framework, as an academic field or medical discipline, or as an integral part of health service provision. This conceptual flexibility contributes both to the strengths and to the weaknesses of the public mental health approach.

Although developments have been made in recent years, a feasible definition of "public mental health" and its major aspects such as mental health promotion is still lacking. This might be due to the comparatively short history of the concept, but it seriously limits its strategic power. In part as a consequence of this, evidence for the potential social capital impact of public mental health policies is not strong.

So, despite the progress outlined in Wahlbeck's paper, many countries currently seem much more willing to acknowledge public mental health as a theoretical concept or framework than to apply specific features of it into routine mental health care or other societal sectors. Among others, the social welfare and educational systems, the labor market and administration, and the criminal justice sector may benefit in the long run, if public health mental health policies are seriously and thoroughly implemented.

Enlarging the evidence base about the benefits of public mental health policies meets serious methodological challenges. For solid findings, research activities should assess determinants and effects across sector boundaries. When doing so, many and often widely fragmented services, agencies or institutions have to be included and analyzed simultaneously with similar and standardized methods.

This is a well-known challenge to community mental health care and services research. The fragmentation of psychiatric services and their separation from sectors such as the social welfare or the labor administration afflict many mental health care systems. The cost of under-, double- or over-provision caused by this phenomenon is estimated as high. Many strategies are being developed and efforts are being made to address the negative consequences of fragmentation, such as treatment discontinuation or marginalization and neglect of specific risk groups. These efforts, however, are often themselves costly or have only limited effects.

Public mental health activities might be seen as accelerating or multiplying the efforts against the detrimental effects of service or sector fragmentation. However, this has to be clearly demonstrated. Analyzing effects across societal sectors usually requires complex research designs, time and patience – in other words, a lot of funding for long-term and inter-sector studies. Additionally, such studies must communicate their findings in a language likely to be understood by decision makers. In order to raise awareness and convince politicians or agencies, any beneficial outcome of public mental health policies should be translated into economic terms or expressed in financial values. In principle, adapted economic methods for measuring extra-financial value across societal sectors are available, such as the social return on investment approach (2). However, these methods are not applied broadly enough in public mental health (3).

Innovative steps may help to address this problem. New directions in neurosciences are highlighting the detrimental effects of urbanicity or urban upbringing on neural stress processing (4,5). If confirmed in larger samples, such findings may have far reaching public mental health consequences. If so, it might be rather shortsighted not to model population health effects and economic impacts as a component of studies that are focusing on such as-sociations.

If this becomes an agreed research agenda, public mental health could get access to and participate in the budgets spent for research in neurosciences. Both allies might benefit from the collaboration. Usually it takes decades until neuroscience findings are translated into interventions or policies ready for being marketed or implemented into routine care. This process might be significantly accelerated by the above collaboration, as the development of interventions and policies is public mental health's core business.

Societies all over the world should be receptive to this multifaceted integrative potential of public mental health.

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Public mental health: the need for a broader view of the issues

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K. Wahlbeck's paper (1) provides a good overview of the field of public mental health. Right from the first paragraphs, the paper makes it explicit that public mental health deals with mental health promotion, prevention of mental disorders and of suicide, integrated and comprehensive mental health service, and the fight against stigma and human right abuses. These issues are of importance to every country or community, irrespective of their level of economic or social development. There may of course be a need for contextualizing the specific solutions to the various challenges that the issues pose, but developing those solutions should nevertheless be on the public health agenda of every country, from the low- to the high-income categories.

The relevance of these issues to every country, irrespective of their developmental stage, is an important point to stress. Even though psychiatry constantly grapples with the challenge of finding the most valid ways to categorize and classify mental health problems, any notion that seeks to deny, either explicitly or implicitly, that human beings share some common biological features irrespective of their race is an absurd one. Those features make them vulnerable to develop health, including mental health, problems irrespective of where they live. It is of course also true that those health problems are influenced by where and how they live and may respond differently to various interventions, some of which may also be shaped and informed by where people live. So, while it can be said that "diagnoses" are social constructs, shaped by current understanding and consensus and reflecting the imperfect nature of the process of classifying them (2), the disorders that they seek to characterize are not. Mental disorders have consequences everywhere and, while there can be debates about the labels we ascribe to them, practicing clinicians know that the syndromes they deal with have effects on the lives of those experiencing them.

A review of public mental health is in a sense a review of global mental health, and to deny the importance of one is to deny the relevance of the other. In this regard, and in addition to the points articulated in Wahlbeck's paper, the emphasis must be placed on bridging the gap in treatment for mental disorders.

Global mental health is essentially the mobilization of resources to meet the challenges of population health needs and strive for equity in doing so. Given the large unmet need for mental health service in low- and middle-income countries, it is understandable that global mental health will often be seen as having a major focus on those countries. However, treatment gap for mental disorders exists everywhere across the world (3). Also, the gap is driven by essentially the same issues across the world: inadequate resources, inequity, and lack of parity with physical health. Inequity exists between countries in their ability to provide adequate mental health service for their populations, but it also exists within countries, including high-income countries. Stigma is an overarching issue and often dictates what resources are made available to provide mental health service.

Addressing the challenge posed by poor policy attention to mental health service and the negative attitude to persons with mental disorders by the public requires a good understanding of the principles of public health. Unfortunately, a lack of that understanding by mental health professionals has been a major barrier to developing effective mental health service (4). Responding to the treatment gap for mental disorders is a public health imperative for which public and political support is crucial. Concerted advocacy efforts are required. The skills necessary for mounting such efforts, however, are unfortunately uncommon among mental health professionals.

A broad perspective of public mental health will emphasize what is known about the burden of mental disorders, and the social determinants that underlie the burden, but will also focus on the issues that engender inequity between communities in their access to adequate mental health care, lack of parity between mental and physical conditions, and the overarching barriers that stigma and policy neglect constitute. Efforts at building leadership and advocacy skills

among mental health practitioners and stakeholders and at improving access to care through appropriate capacity building for non-specialists must be of central concern to public mental health (5).

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Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study

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This is a study of the metabolic and distal cardiovascular/cerebrovascular outcomes associated with the use of second-generation antipsychotics (SGAs) compared to antidepressants (ADs) in adults aged 18-65 years, based on data from Thomson Reuters MarketScan® Research Databases 2006-2010, a commercial U.S. claims database. Interventions included clinicians' choice treatment with SGAs (allowing any comedications) versus ADs (not allowing SGAs). The primary outcomes of interest were time to inpatient or outpatient claims for the following diagnoses within one year of SGA or AD discontinuation: hypertension, ischemic and hypertensive heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidemia, and obesity. Secondary outcomes included the same diagnoses at last follow-up time point, i.e., not censoring observations at 365 days after SGA or AD discontinuation. Cox regression models, adjusted for age, gender, diagnosis of schizophrenia and mood disorders, and number of medical comorbidities, were run. Among 284,234 individuals, those within one year of exposure to SGAs versus ADs showed a higher risk of essential hypertension (adjusted hazard ratio, AHR=1.16, 95% CI: 1.12-1.21, p<0.0001), diabetes mellitus (AHR=1.43, CI: 1.33-1.53, p<0.0001), hypertensive heart disease (AHR=1.34, CI: 1.10-1.63, p<0.01), stroke (AHR=1.46, CI: 1.22-1.75, p<0.0001), coronary artery disease (AHR=1.17, CI: 1.05-1.30, p<0.01), and hyperlipidemia (AHR=1.12, CI: 1.07-1.17, p<0.0001). Unrestricted follow-up results were consistent with within one-year post-exposure results. Increased risk for stroke with SGAs has previously only been demonstrated in elderly patients, usually with dementia. This study documents, for the first time, a significantly increased risk for stroke and coronary artery disease in a non-elderly adult sample with SGA use. We also confirm a significant risk for adverse metabolic outcomes. These findings raise concerns about the longer-term safety of SGAs, given their widespread and chronic use.

Key words: Second-generation antipsychotics, essential hypertension, diabetes mellitus, hypertensive heart disease, stroke, coronary heart disease, hyperlipidemia

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Second-generation antipsychotics (SGAs) were introduced approximately 20 years ago as supposedly safer and better-tolerated alternatives to first-generation antipsychotics for the treatment of schizophrenia and related disorders (1-3). They have proven to be effective for schizophrenia (4,5), but their use has extended to major mood disorders (6,7) and a broad range of other psychiatric illness (8,9).

The initial optimism about safety was refuted by the well-documented adverse metabolic effects of these drugs (10-13). U.S. Food and Drug Administration (FDA)'s warnings about severe metabolic side effects were followed by the establishment of guidelines for cardiometabolic monitoring in patients prescribed antipsychotics (14). Clinically relevant, unfavorable cardiometabolic effects, including obesity, diabetes mellitus, hypertension, and abnormal blood lipids, were commonly reported across the lifespan, from children and adolescents to the elderly (10,15-18).

However, despite well-documented proximal cardiometabolic side effects that are established risk factors for future cardiovascular and cerebrovascular events, data on the potential adverse cardiovascular and cerebrovascular consequences of SGA use are scarce and, even for high-metabolic risk agents, contradictory (19). Limited and often inconclusive documentation of such adverse events has largely been confined to studies of the elderly, who are closer to experiencing such events but also have a high medication-independent risk profile for myocardial infarction and stroke (20-38).

As the majority of patients receiving SGAs are younger adults, and even children and adolescents (39), we sought to examine the potential detrimental metabolic, cardiovascular, and cerebrovascular effects in a non-elderly adult population. Given that these adverse consequences are very clinically significant but relatively uncommon and require longer-term follow-up, we studied a large sample using a healthcare claims database.

METHODS

Database

We obtained the study data from the Thomson Reuters MarketScan® Research Databases, a commercial U.S. claims

database, for years 2006-2010. This database contains individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. Data for individual patients are integrated from all providers of care, maintaining all healthcare utilization and cost record connections at the patient level.

Patients were excluded from the database for the following reasons: a) no enrollment in 2006; b) enrolled in a health plan that did not capture medication claims nor mental health and substance abuse claims; c) unavailable person level enrollment data, making it impossible to differentiate patients from other enrollees, as well as identify subjects with no claims data; d) age <18 or >65, as the primary sample of interest was non-elderly adults; e) claims in 2006 for any of the medical diagnoses used as outcomes; f) claims for any of the medical diagnoses used as outcomes prior to first observed SGA exposure or antidepressant (AD) treatment; g) follow-up <6 months in 2007-2010; and h) no exposure to SGA or AD treatment in 2007-2010.

The start date for the study was defined as the first exposure to SGA or AD in 2007-2010. The rationale for choosing a minimum of 6-month follow-up from the start date was to allow sufficient time for an outcome of interest to be observed after starting SGAs or ADs. The study end date was defined as a subject's last known date of enrollment in a health plan that captured drug and mental health claims or 365 days after the last exposure to SGA or AD. Subjects were followed through their study end, which allowed different event types to be observed within a subject.

Subjects not enrolled consecutively in a health plan during a year were assumed to have been enrolled for all months prior to their final month of enrollment. Any month skipped between the first and last month of enrollment was assumed to be either an error or that having an outcome of interest during that month was unlikely. Subjects not enrolled in a drug prescription or mental health/substance abuse claims program for consecutive years had their end date defined to be the last date of enrollment in a health plan that captured both drug claims and mental health/substance abuse claims. These observations were censored because we did not know if any outcomes of interest occurred during these periods. Subjects with this pattern of sporadic enrollment in a health plan that captures drug and mental health or substance abuse claims accounted for <1% of the entire sample.

SGA inception cohort

The SGA inception cohort included subjects aged 18-65 years without SGA use and without medical diagnosis claim of any of the outcomes of interest in 2006, i.e., within 12 months prior to the study period (2007-2010), or any point prior to the start of SGAs, and initiating continuous SGA treatment for at least 4 weeks during 2007-2010.

Continuous use was defined as no more than 1 week without use of an SGA (i.e., not having an SGA prescription refilled when the supply of the previous prescription runs out). This assumption was based on the last prescription fill date and the days' supply, which was used to calculate when a prescription should have been refilled. Medication claims for a SGA supply <1 week or >180 days were excluded, as this was deemed either an inappropriate trial or clinically implausible. The use of other concurrent medications, including ADs, was allowed, but not accounted for in this cohort.

Comparison cohort

The comparison cohort included the remaining subjects aged 18-65 years without SGA use, AD use, or a medical diagnosis claim of any of the outcomes of interest in 2006, i.e., within 12 months prior to the study period (2007-2010), or any point prior to the start of ADs. Additionally, patients initiated continuous AD treatment for at least 4 weeks during the study period. Medication claims for an AD supply <1 week or >180 days were excluded. Unlike the SGA cohort, which may have been exposed to ADs, the AD cohort was not exposed to SGAs during the entire study period. The use of other concurrent medications, excluding SGAs, was allowed, but not accounted for in this cohort.

We chose an AD initiator cohort as the comparison group in order to balance background risk factors present in SGA initiators that are based on mental illness and unhealthy lifestyle behaviors, including smoking, which are related to a higher risk for the studied outcomes, all of which have been associated with depression and even AD treatment too (40-42). Moreover, using defined initiation time point in both cohorts allowed us to control for severity of mental disorder, while having a time point of discontinuation allowed us to use the same rule for right-censoring in both groups in the primary analysis.

Outcomes

Primary outcomes of interest were times to inpatient and outpatient claims for the following diagnoses within one year of treatment discontinuation (ICD-9 codes in parentheses): hypertension (401, 402), ischemic and hypertensive heart disease (410, 413, 414), cerebrovascular disease (434, 435), diabetes mellitus (250), hyperlipidemia (272), and obesity (278). Secondary outcomes included the same diagnoses at last follow-up time point, i.e., not censoring the observations at 365 days after the last exposure to either SGAs or ADs, in order to examine the robustness of our findings and allow for longer-term carry over effects.

Statistical analysis

Cox (proportional hazards) regression analysis, censoring patients without an event of interest at 365 days after

Table 1 Sample characteristics

	Total	SGA exposed cohort	AD exposed cohort	p
N	284,234	31,207	253,027	
Age, years±SD	44.46±10.74	44.91±11.16	44.40±10.69	<0.0001
Males, N (%)	83,606 (29.41)	10,224 (32.76)	73,382 (29.00)	<0.0001
Number of medical disorders at baseline, median (Q1, Q3)	5.00 (2.00, 9.00)	7.00 (3.00, 12.00)	5.00 (2.00, 9.00)	
Patient years of follow-up censoring patients 365 days after treatment discontinuation, median (Q1, Q3)	1.49 (1.00, 2.62)	1.55 (1.00, 2.87)	1.48 (1.00, 2.59)	<0.0001
Patient years of follow-up not censoring patients 365 days after treatment discontinuation, median (Q1, Q3)	2.55 (1.62, 3.36)	2.63 (1.62, 3.55)	2.54 (1.62, 3.34)	0.0001
Patient days of treatment exposure, median (Q1, Q3)	180 (60, 480)	150 (60, 420)	180 (60, 480)	<0.0001
Mood disorders diagnosis, N (%)	60,906 (21.43)	22,681 (72.68)	38,225 (15.11)	<0.0001
Schizophrenia diagnosis, N (%)	2,027 (0.71)	1,842 (5.90)	185 (0.07)	<0.0001
SGAs prescribed during the study, N (%)				
Aripiprazole		7,316 (2.57)		
Asenapine		8 (0.00)		
Clozapine		60 (0.02)		
Olanzapine		2,901 (1.02)		
Quetiapine		12,094 (4.25)		
Risperidone		3,362 (1.18)		
Ziprasidone		1,469 (0.52)		
Mixed SGA group (see text)		3,997 (1.41)		

SGA – second-generation antipsychotic, AD – antidepressant, Q1 – quartile 1, Q3 – quartile 3

last exposure to the studied medication or last date of health plan enrollment, was used to separately model each outcome of interest as a function of exposure group (i.e., SGA versus AD). The proportional hazards assumption was evaluated by plotting the log negative log of the survival function by the log of time.

Adverse outcomes that were significantly associated with SGA exposure in the univariable Cox regression analysis were further explored using multivariable Cox regression analysis. The multivariable models included treatment group, age, gender, diagnosis of schizophrenia, diagnosis of mood disorder, and a medical morbidity count. Schizophrenia and mood disorders were identified by inpatient and outpatient claims. The medical morbidity count was generated by summing the number of unique medical diagnoses recorded for each subject in 2006, which was used as a covariate in order to adjust for potential differences between the SGA and AD groups regarding overall medical morbidity, (related) lifestyle behaviors, and/or medical service utilization that could increase the risk for the studied outcomes. By definition, medical comorbidities excluded those used as outcomes, as patients had to be without these diagnoses in 2006 and prior to starting SGAs or ADs.

The above analyses were repeated without censoring subjects 365 days after their last SGA or AD exposure, respectively. In these analyses, the study end was redefined to be the date the respective outcome of interest occurred or the last date of enrollment in a health plan. Again, subjects were only censored for the specific outcome of interest that occurred, being followed for all other outcomes that had not occurred until last date of enrollment in a health plan.

Since individual SGAs differ regarding their short- and medium-term cardiometabolic adverse effect profile (11,13, 15,17,18), we also performed subgroup analyses to evaluate the intermediate metabolic and distal cardiovascular and cerebrovascular risks of the five most frequently used SGAs, i.e., aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Unfortunately, the clozapine and asenapine groups were too small to perform reliable analyses. Whenever more than one SGA was used, a subject was classified based on the SGA that was received for the majority of the study period (i.e., more than two-thirds of a subject's "exposure" to a specific SGA). If no single SGA was received for >67% of the study period, a subject was classified as belonging to the "mixed SGA" group.

RESULTS

The sample (N=284,234) included 83,606 men and 200,628 women, with a mean age of 44.46±10.74 years. Details of the sample are provided in Table 1.

In univariable Cox regression analyses, SGA exposure was associated with a significantly increased risk for all the outcomes of interest (Table 2). In addition to the well-established proximal metabolic risks of SGAs, such as essential

Table 2 Univariable metabolic and cardiovascular risk associated with SGA exposure at one year

Outcome: claims diagnosis	Hazard ratio (95% CI) for SGA users vs. AD users	Chi square	p
Essential hypertension	1.27 (1.23-1.31)	208.1066	<0.0001
Diabetes mellitus	1.73 (1.63-1.83)	335.1633	<0.0001
Obesity	1.24 (1.18-1.32)	56.1796	<0.0001
Stroke	2.12 (1.83-2.45)	99.5837	<0.0001
Hypertensive heart disease	1.56 (1.33-1.84)	28.9700	<0.0001
Myocardial infarction	1.40 (1.13-1.72)	9.8147	0.0017
Angina	1.32 (1.15-1.51)	15.4601	<0.0001
Coronary artery disease	1.52 (1.39-1.67)	82.8166	<0.0001
Transient ischemic attack	1.70 (1.48-1.95)	57.3919	<0.0001
Hyperlipidemia	1.28 (1.24-1.33)	175.9416	<0.0001

SGA – second-generation antipsychotic, AD – antidepressant

hypertension, diabetes mellitus, obesity, and hyperlipidemia, there was a significantly increased risk for myocardial infarction (hazard ratio, HR=1.40, CI: 1.13-1.72), stroke (HR=2.12, CI: 1.83-2.45), angina (HR=1.32, CI: 1.15-1.51), hypertensive heart disease (HR=1.56, CI: 1.33-1.84), coronary artery disease (HR=1.52, CI: 1.39-1.67), and transient ischemic attack (HR=1.70, CI: 1.48-1.95).

In multivariable Cox regression analyses, adjusting for gender, age, schizophrenia, mood disorders, and medical morbidity count, the risk for stroke, hypertensive heart disease and coronary heart disease remained significantly higher in the SGA exposure group (Table 3).

Table 4 presents univariable and multivariable Cox regression analyses for outcomes of interest when participants were not censored at one year, serving as a sensitivity analysis for our primary analyses of outcomes at one year after SGA or AD discontinuation. The univariable analyses were consistent with the results within one year of discontinuation. The multivariable results for the uncensored data (Table 4) were also consistent with the primary results restricting follow-up to 365 days post exposure (Table 3).

Results from the multivariable analyses comparing AD users with clinicians' choice SGA treatment groups are shown in Table 5. Individual antipsychotic groups differed considerably in size, resulting in differences in power to detect significant differences in outcomes compared to AD users. Even despite this confound, patients exposed to olanzapine, quetiapine and mixed antipsychotic use had a higher number of adverse metabolic and cardiovascular outcomes (i.e., 6, 8 and 7 out of the ten examined outcomes) compared to risperidone, aripiprazole and ziprasidone (i.e., 2, 4 and 5 out of ten examined outcomes) (Table 5).

In addition to the risk data presented, the actual incidence rates per 1000 person-years for the outcomes of interest are presented in Table 6.

DISCUSSION

We used a commercial claims database with broad coverage of health insured non-elderly adults in the U.S. to examine the risks associated with SGA use compared to AD use within one year of exposure and without restriction of follow-up after discontinuation during a 4-year period, 2007-2010. Despite exclusion of the elderly, we observed a statistically and clinically significant increased risk with SGA use vs. AD use for proximal cardiometabolic risk factors and outcomes, such as essential hypertension, dyslipidemia, and diabetes mellitus, confirming prior reports (10-16). However, importantly, we also observed an increased risk for distal and generally difficult-to-study cardiovascular (i.e., coronary artery disease) and cerebrovascular (i.e., stroke) outcomes, both with and without restriction of the follow-up period after

Table 3 Multivariable Cox hazard ratios for significant adverse outcomes of interest at one year

Outcome: claims diagnosis	Hazard ratio (95% CI) for SGA users vs. AD users[a]	Hazard ratio (95% CI) for age (10 year increments)	Hazard ratio (95% CI) for gender (male vs. female)	Hazard ratio (95% CI) for medical morbidity count	Hazard ratio (95% CI) for mood disorder	Hazard ratio (95% CI) for schizophrenia
Essential hypertension	1.16 (1.12-1.21)***	1.60 (1.59-1.62)***	1.35 (1.32-1.39)***	1.01 (1.01-1.01)***	0.98 (0.95-1.01)	1.24 (1.12-1.38)***
Diabetes mellitus	1.43 (1.33-1.53)***	1.53 (1.49-1.56)***	1.20 (1.14-1.26)***	1.00 (1.00–1.01)***	1.12 (1.06-1.19)***	1.74 (1.48-2.04)***
Obesity	0.96 (0.89-1.02)	0.92 (0.91-0.94)***	0.56 (0.52-0.58)***	1.01 (1.00–1.01)***	1.51 (1.44-1.58)***	1.46 (1.24-1.72)***
Stroke	1.46 (1.22-1.75)***	1.71 (1.60-1.82)***	1.21 (1.06-1.39)**	1.04 (1.03-1.05)***	1.25 (1.07-1.45)**	1.43 (0.94-2.18)
Hypertensive heart disease	1.34 (1.10-1.63)**	1.70 (1.60-1.81)***	1.58 (1.39-1.80)***	1.02 (1.01-1.03)***	0.98 (0.84-1.16)	1.37 (0.85-2.20)
Myocardial infarction	1.04 (0.82-1.33)	2.15 (1.98-2.35)***	2.72 (2.33-3.18)***	1.03 (1.02-1.04)***	1.20 (0.99-1.45)	0.81 (0.38-1.75)
Angina	1.03 (0.87-1.21)	1.90 (1.80-2.00)***	1.43 (1.29-1.58)***	1.04 (1.03-1.04)***	1.06 (0.93-1.20)	1.00 (0.63-1.60)
Coronary artery disease	1.17 (1.05-1.30)**	2.24 (2.15-2.32)***	2.24 (2.09-2.40)***	1.03 (1.02-1.03)***	1.06 (0.97-1.16)	1.38 (1.06-1.81)*
Transient ischemic attack	1.17 (0.99-1.38)	1.76 (1.66-1.86)***	1.14 (1.01-1.29)*	1.04 (1.04-1.05)***	1.19 (1.04-1.37)*	1.46 (0.98-2.17)
Hyperlipidemia	1.12 (1.07-1.17)***	1.58 (1.56-1.61)***	1.42 (1.38-1.46)***	1.01 (1.01-1.02)***	1.03 (1.00–1.07)	1.21 (1.08-1.36)**

SGA – second-generation antipsychotic, AD – antidepressant
[a]adjusted for gender, age, psychiatric diagnosis and medical morbidity count, *p<0.05, **p<0.01, ***p<0.0001

Table 4 Univariable and multivariable Cox hazard ratios when participants are not censored one year after last medication exposure

Outcome: claims diagnosis	Univariable hazard ratio (95% CI) for SGA users vs. AD users	Multivariable[a] hazard ratio (95% CI) for SGA users vs. AD users
Essential hypertension	1.29 (1.25-1.33)***	1.18 (1.14-1.22)***
Diabetes mellitus	1.67 (1.59-1.76)***	1.39 (1.30-1.48)***
Obesity	1.25 (1.18-1.31)***	0.94 (0.88-0.99)*
Stroke	2.17 (1.90-2.48)***	1.49 (1.26-1.75)***
Hypertensive heart disease	1.60 (1.38-1.85)***	1.39 (1.17-1.66)**
Myocardial infarction	1.49 (1.19-1.81)**	1.01 (0.79-1.29)
Angina	1.34 (1.19-1.51)***	1.05 (0.91-1.21)
Coronary artery disease	1.54 (1.42-1.67)***	1.18 (1.07-1.31)**
Transient ischemic attack	1.80 (1.59-2.04)***	1.25 (1.08-1.46)**
Hyperlipidemia	1.27 (1.23-1.32)***	1.11 (1.06-1.15)***

SGA – second-generation antipsychotic, AD – antidepressant
[a]adjusted for gender, age, psychiatric diagnosis and medical morbidity count, *p <0.05, **p<0.01, ***p<0.0001

medication discontinuation. Each of these findings was confirmed and consistent even when age, gender, and medical morbidity were taken into account.

The risk for stroke in subjects on SGAs has received substantial attention (22-38). Most, but not all, studies documented an increased risk for stroke in SGA users; however, without exception, these studies included elderly subjects (generally ≥65 years) (22-38), and most focused on patients with dementia (22-38). To the best of our knowledge, the present study is the first documentation of a clinically significant increase in stroke risk, as well as coronary artery disease risk, in a younger population (mean age=44.46 years) receiving SGAs. While increasing age, male gender and medical morbidity also significantly contributed to the risk for stroke and coronary artery disease, these additional risk factors did not detract from the risk increase associated with SGA exposure.

Our examination of long-term adverse outcomes by individual SGA or mixed SGA group has to be considered very preliminary and interpreted with caution. Reasons for this include the vastly different sample sizes of the individual SGA groups, making it more likely to show a significant difference compared to AD users the larger the sample size per subgroup was. In this context, it is notable that olanzapine (N=2,901) and mixed SGAs (N=3,997), which were among the smallest groups, were also among the three treatments with the highest number of adverse metabolic and cardiovascular effects. Conversely, although aripiprazole (N=7,316) was prescribed to the second highest number of patients, it was in the lower risk group, together with risperidone (N=3,362) and ziprasidone (N=1,469), for which power was much lower and may have been insufficient to detect a significant difference compared to AD users. However, the non-random treatment assignment is an even larger confounding factor. Clinician's choice treatment with SGAs is vulnerable to a channeling bias, i.e., the preferential use of lower risk agents in higher risk patients and vice versa. In any case, these data underscore the need to establish which antipsychotics may possess lower short- and, particularly, long-term cardiovascular and cerebrovascular risk. Such studies need to be sufficiently large and avoid or control for channeling bias.

The strength of a healthcare claims database is the ability to study large numbers of subjects who are not restricted to those consenting to participate in research over a relatively long duration of time. This may have allowed for our observation of increased cardiovascular and cerebrovascular risk in this younger population, which may not be evident in smaller clinical samples.

Table 5 Multivariable Cox hazard ratios for significant adverse outcomes of interest by SGA risk group

Outcome: claims diagnosis	Hazard ratio (95% CI) for aripiprazole (N=7,316) vs. ADs	Hazard ratio (95% CI) for olanzapine (N=2,901) vs. ADs	Hazard ratio (95% CI) for quetiapine (N=12,094) vs. ADs	Hazard ratio (95% CI) for risperidone (N=3,362) vs. ADs	Hazard ratio (95% CI) for ziprasidone (N=1,469) vs. ADs	Hazard ratio (95% CI) for mixed SGAs (N=3,997) vs. ADs
Stroke	0.95 (0.65-1.39)	1.60 (1.06-2.41)*	1.60 (1.26-2.01)***	1.71 (1.15-2.54)**	1.05 (0.54-2.05)	1.64 (1.16-2.32)**
Obesity	1.14 (1.01-1.28)*	0.80 (0.66-0.97)*	0.86 (0.78-0.94)**	0.86 (0.71-1.02)	1.08 (0.88-1.34)	1.09 (0.95-1.24)
Diabetes mellitus	1.22 (1.06-1.40)**	1.38 (1.16-1.60)**	1.36 (1.23-1.50)***	1.61 (1.37-1.89)***	1.78 (1.44-2.20)***	1.73 (1.51-1.98)***
Essential hypertension	1.00 (0.93-1.08)	1.17 (1.06-1.28)**	1.24 (1.18-1.31)***	1.05 (0.95-1.15)	1.25 (1.10-1.43)**	1.25 (1.15-1.35)***
Hyperlipidemia	1.09 (1.01-1.19)*	1.20 (1.08-1.33)**	1.08 (1.02-1.15)*	1.01 (0.90-1.13)	1.27 (1.10-1.46)**	1.23 (1.12-1.35)***
Hypertensive heart disease	1.12 (0.76-1.66)	1.18 (0.72-1.93)	1.39 (1.07-1.81)*	0.90 (0.52-1.58)	1.74 (0.97-3.12)	1.92 (1.34-2.75)**
Angina	0.51 (0.34-0.77)**	1.05 (0.70-1.56)	1.24 (1.01-1.53)*	0.61 (0.36-1.02)	2.02 (1.34-3.05)**	1.09 (0.78-1.54)
Myocardial infarction	0.84 (0.51-1.41)	1.67 (1.04-2.68)*	1.15 (0.83-1.59)	0.63 (0.30-1.34)	0.40 (0.10-1.61)	1.03 (0.60-1.76)
Coronary artery disease	0.88 (0.70-1.11)	1.20 (0.94-1.55)	1.27 (1.10-1.46)*	1.03 (0.78-1.35)	1.36 (0.96-1.92)	1.30 (1.04-1.63)*
Transient ischemic attack	0.80 (0.56-1.14)	1.13 (0.75-1.71)	1.21 (0.97-1.51)	1.13 (0.75-1.71)	1.64 (1.02-2.61)*	1.47 (1.07-2.00)**

SGA – second-generation antipsychotic, ADs – antidepressants, *p <0.05, **p<0.01, ***p<0.0001

Table 6 Incidence of events per 1000 person-years

Outcome	SGA users (cases per 1,000 person-years)	AD users (cases per 1,000 person-years)
Essential hypertension	79.2	62.7
Diabetes mellitus	23.4	13.5
Obesity	23.2	18.5
Stroke	3.7	1.8
Hypertensive heart disease	2.9	1.8
Myocardial infarction	1.7	1.2
Angina	4.0	3.0
Coronary artery disease	9.3	6.1
Transient ischemic attack	4.1	2.4
Hyperlipidemia	59.1	46.0

SGA – second-generation antipsychotic, AD – antidepressant

Nevertheless, database studies also have limitations. These include the non-randomized treatment groups, naturalistic treatment setting and lack of information about unhealthy lifestyle behaviors, including smoking. In order to reduce the effect of unhealthy lifestyle behaviors and other background risk factors that we were unable to measure, we used a psychiatric control group in an inception cohort design, choosing AD use as our control. We made this choice because both depression and ADs have been associated with metabolic syndrome and its components as well as with distal adverse cardiovascular and cerebrovascular outcomes (40-42). However, since patients receiving SGAs and ADs may differ in specific risk factors for the outcomes under investigation, we used covariates in the Cox regression analyses to adjust for potentially relevant differences. Covariates included traditional risk factors, such as gender and age. In addition, we adjusted the analyses for a primary diagnosis of schizophrenia or mood disorder as well as for a medical comorbidity count. Notably, while each of these covariates was significantly related to the outcomes of interest, the higher risk in SGA users persisted even when adjusting for these variables.

Another limitation is lacking information about the duration and severity of the current illness episode. However, to mitigate against this problem, we used the inception cohort design focusing on patients with illness severity prompting clinicians to initiate treatment with an SGA or AD. Additionally, while the treatment was clinician and patient driven, the naturalistic database approach ensures greater generalizability of the findings than in controlled trials, that ordinarily also have higher attrition rates.

Further, we did not have body mass index and laboratory data available, so that the diagnoses, particularly of more proximal cardiometabolic risk factors and metabolic outcomes, may be an underestimate. In this context, we cannot fully rule out a surveillance bias in that SGA treated patients may have had more measurements of body weight and laboratory parameters than AD treated patients. However, although monitoring guidelines exist for SGAs (14,43), they are notoriously seldom followed, and several studies failed to observe any change in monitoring after the warning about metabolic effects of SGAs by the FDA and guideline development and promulgation (44). Nevertheless, even if a surveillance bias may have led to a greater detection of cardiovascular risk factors and metabolic outcomes, the cardiovascular and cerebrovascular outcomes are much less dependent on detection bias and diagnoses are not made by laboratory testing, which strengthens our results.

A further limitation is that data were only available from 2006 to 2010, and that 2006 through the first date of SGA or AD exposure was used as a "baseline period". Therefore, we do not have any details of medical history on subjects included in our study prior to 2006. We used an absence of drug claims for SGAs and ADs in 2006 as a proxy for no past SGA and AD use. Although it is possible that our study subjects could have used SGAs prior to 2006, this fact would only bias towards the null hypothesis, as the AD group could have had carry over effects from prior SGA use. Further, although we "only" had a 2-year median follow-up, even this still relatively short observation period was sufficient to demonstrate significant elevations of risk for both proximal and more distal cardiovascular and cerebrovascular risk factors and endpoints, which adds to the concern regarding the widespread use of SGAs, especially for off-label conditions (8,9).

Cigarette smoking is a risk factor for both cardiovascular and cerebrovascular disease. It is also more common in people with a psychiatric diagnosis and who are on psychotropic medicines (45). Moreover, smoking rates are generally reported to be higher in schizophrenia than in subjects with mood disorders (46). Our database did not allow us to obtain smoking information by subject, so that the effect of cigarette smoking as a confounding factor cannot be definitively excluded. However, the fact that the risk for SGAs versus ADs held even when the diagnoses of schizophrenia and mood disorders were entered as covariates into the analyses, strengthens our results as not likely being attributable to a differential frequency of cigarette smoking.

In the U.S., increased use of SGAs over the last 20 years has been clearly documented (8,39). SGAs are effective for psychotic and mood disorders (4-7); however, they are also widely used for numerous off-label conditions (8,9,39), and an ever-increasing number of patients is being prescribed this class of psychotropic agents without appropriate monitoring (44). Our data suggest that the risks associated with SGA use extend beyond the adverse metabolic risks that are well-known (10-18). It is highly likely that the increased risk for major cerebrovascular and cardiovascular events we observed is a downstream consequence of these well-documented metabolic risks (13,15). Greater care should be exercised in monitoring and mitigating the adverse metabolic consequences of SGAs, even in a younger population, and these medications should be used with greater caution, especially in conditions for which a sufficient evidence base for efficacy and safety is missing.

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The first two authors contributed equally to this work.

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Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial

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Major depressive disorder (MDD) is a prevalent and disabling condition, and many patients do not respond to available treatments. Deep transcranial magnetic stimulation (dTMS) is a new technology allowing non-surgical stimulation of relatively deep brain areas. This is the first double-blind randomized controlled multicenter study evaluating the efficacy and safety of dTMS in MDD. We recruited 212 MDD outpatients, aged 22–68 years, who had either failed one to four antidepressant trials or not tolerated at least two antidepressant treatments during the current episode. They were randomly assigned to monotherapy with active or sham dTMS. Twenty sessions of dTMS (18 Hz over the prefrontal cortex) were applied during 4 weeks acutely, and then biweekly for 12 weeks. Primary and secondary efficacy endpoints were the change in the Hamilton Depression Rating Scale (HDRS-21) score and response/remission rates at week 5, respectively. dTMS induced a 6.39 point improvement in HDRS-21 scores, while a 3.28 point improvement was observed in the sham group (p=0.008), resulting in a 0.76 effect size. Response and remission rates were higher in the dTMS than in the sham group (response: 38.4 vs. 21.4%, p=0.013; remission: 32.6 vs. 14.6%, p=0.005). These differences between active and sham treatment were stable during the 12-week maintenance phase. dTMS was associated with few and minor side effects apart from one seizure in a patient where a protocol violation occurred. These results suggest that dTMS constitutes a novel intervention in MDD, which is efficacious and safe in patients not responding to antidepressant medications, and whose effect remains stable over 3 months of maintenance treatment.

Key words: Deep transcranial magnetic stimulation, major depressive disorder, treatment resistance, response, remission, maintenance treatment

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Major depressive disorder (MDD) is a highly prevalent and disabling condition associated with significant morbidity and mortality (1,2). It has been estimated that 20-40% of patients do not benefit adequately from available interventions, including pharmacotherapy and psychotherapy (3). The lack of sufficient treatment response and the enormous impact of the disorder make the development of alternative treatment approaches a priority.

Repetitive transcranial magnetic stimulation (rTMS) has been proposed as one such novel treatment (4-6). TMS involves passing an electrical current through a coil placed against the scalp. The rapidly changing electrical current creates a time-varying magnetic field, which passes unimpeded through the scalp and skull and induces an electrical field in the cortex. This electrical field changes neuronal activity at the site of stimulation and within interconnected neuronal networks. TMS pulses applied in a repetitive train is referred to as rTMS.

The H-coil is a novel rTMS tool, which enables direct stimulation of deeper and larger brain volumes (7-10). This coil is designed to affect extensive neuronal pathways, including deeper cortical regions and fibers targeting subcortical regions, without a significant increase of the electric field induced in superficial cortical layers (7-10). Several open feasibility studies showed a clinically meaningful therapeutic action of H-coil deep TMS (dTMS), which was maintained by continuation of treatment for up to 18 weeks (11-15). These initial studies suggested that a stimulation intensity of 120% of the individual resting motor threshold (but not a more shallow stimulation induced by lower intensities) induces an antidepressant response.

Conventional rTMS procedures have been investigated in several psychiatric disorders, including unipolar depression, schizophrenia and bipolar disorder (16-18). A small number of acute (3-6 week) large scale randomized controlled multicenter trials have examined the antidepressant

properties of conventional rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) (19-21). Two of these studies showed significant antidepressant effects of rTMS, compared to placebo, in medication-free patients who had not responded to previous antidepressant treatment (19,21).

Though antidepressant properties of prefrontal rTMS have been clearly demonstrated in patients who did not respond to one antidepressant medication in the current episode, response and remission rates in these large controlled trials were small to moderate. Therefore, additional multicenter sham-controlled studies are needed to establish the short- and long-term efficacy of rTMS in patients suffering from therapy-resistant MDD (19,22).

In this study, we have addressed two key issues that may be critical for the antidepressant effect of rTMS. First, most clinical rTMS protocols have stimulated the left DLPFC. Recent studies have shown that different DLPFC subregions stimulated by standard protocols vary considerably in terms of their connectivity with medial prefrontal structures such as the subgenual cingulate gyrus (23,24), which appears to be an important region involved in the pathophysiology of MDD (25). Thus, it may be advantageous to stimulate less focally and more deeply to reach connecting fiber tracts. Second, conventional rTMS has been investigated over short acute treatment periods ranging from 3 to 6 weeks. The clinical durability of antidepressant effects over longer periods has not been studied before in randomized controlled trials.

We conducted a double-blind randomized placebo-controlled multicenter trial to investigate the efficacy and safety of H-coil dTMS applied daily as monotherapy in subjects with MDD who had either failed one to four antidepressant trials or not tolerated at least two antidepressant treatments in the current episode. The acute treatment phase of 4 weeks was followed by a maintenance treatment up to 12 weeks.

METHODS

Study overview

The study was conducted at 20 medical centers (13 in the U.S., four in Israel, two in Germany, and one in Canada), with active enrolment extending from October 2009 until January 2012. Institutional review board approval was obtained at all sites. The trial was carried out under an investigational device exemption from the U.S. Food and Drug Administration (FDA). An independent data and safety monitoring board reviewed participant safety and study progress.

The study design included three phases: a wash-out phase (1-2 weeks), during which patients were tapered off all antidepressants, mood stabilizers and antipsychotics; a 4-week acute treatment phase (daily treatment with dTMS or sham TMS), and a 12-week maintenance phase (two treatments per week of dTMS or sham TMS).

Subjects

Patients were recruited via public media advertisements and physician referrals. Site personnel phone-screened potential participants, and those meeting inclusion and exclusion criteria underwent additional on-site screening. All subjects signed an informed consent document before undergoing any study procedures.

Eligible subjects were antidepressant medication-free (following the wash-out period) outpatients, aged 22-68 years, with a DSM-IV diagnosis of MDD, single or recurrent episode. The duration of current episode was at least one month but no more than 7 years. Subjects were required to have a Clinical Global Impression Severity of Illness (CGI-S) score of at least 4 and a total score of at least 20 on the 21-item Hamilton Depression Rating Scale (HDRS-21) at screening visit. Symptom stability was required during the 2-week wash-out period. Instability was defined as a change of $\pm$30% or more from the total HDRS-21 score that was observed at the screening assessment.

Antidepressant treatment resistance during the current episode was assessed using the Antidepressant Treatment History Form (ATHF, 26). Subjects were required to have failed at least one but no more than four adequate antidepressant treatments, or to have had intolerance to at least two antidepressants in the current episode.

Subjects were excluded if they had a lifetime history of psychosis, bipolar disorder, obsessive-compulsive disorder (current or within the past year), post-traumatic stress disorder or eating disorders. Subjects suffering from anxiety or personality disorders were eligible only if this was not their primary diagnosis. Additional exclusion criteria were any significant neurological disorder or insult; increased risk of seizure for any reason or familial or personal history of epilepsy; lifetime lack of response to an adequate trial of electroconvulsive therapy; prior treatment with rTMS, dTMS or a vagus nerve stimulator implant; pregnancy; presence of intracranial implants or any other metal object within or near the head, excluding the mouth, that could not be safely removed; a present risk of suicide or a history of suicide attempt in the last 3 years.

Study design

Patients were randomly assigned to either active dTMS or sham TMS (1:1 ratio) by an interactive web response system based on the random allocation sequence generated by the study statisticians. They were stratified per center by severity of disease as determined by baseline HDRS-21 scores ($<$26 vs. $\geq$26) and ATHF treatment resistance levels (ATHF 1, level 3 and ATHF $\geq$2, level 1–2 vs. ATHF 2–4, level 3).

During the acute treatment phase, TMS sessions were performed daily in a 5-day sequence (5 days per week) for 4 weeks. During the maintenance phase, subjects were treated

twice a week (with at least 48 hours between sessions) for 12 weeks. Subjects were discontinued from the study at any point if they were considered by the investigators to be at an elevated risk for suicide. Subjects were also discontinued if they did not experience a sufficient improvement in depressive symptoms after 5 weeks of treatment in two consecutive assessments. A sufficient improvement was defined as a decrease of at least one point on CGI-S from baseline.

Antidepressants, mood stabilizers and antipsychotics were not permitted during the study. Sedatives/hypnotics which were prescribed prior to commencement of treatment were allowed to be continued during the study as appropriate. Anxiolytics, sedatives and hypnotics were allowed to be prescribed during the study in a pre-defined dosage range.

Device description

The TMS sessions were delivered using a Brainsway dTMS system with the H1-coil investigational device (Brainsway Ltd., Jerusalem, Israel). The H1-coil has been designed to stimulate deep prefrontal cortex areas that include neuronal pathways associated with the brain reward system (8,14). The coil is placed in a helmet to allow effective cooling during stimulation, and the frame of the inner rim of the coil is flexible in order to accommodate the variability in human skull shape. In addition to the active H1-coil, a sham coil was included in the same helmet. The sham coil mimics scalp sensations and acoustic artifact of the real H1-coil, without inducing neuronal activation, as most of the elements of the sham coil are located far above the patient's head and the electric field induced by the sham coil is negligible and insufficient to induce neuronal activation in the patient's brain (27).

The combined coil was connected to a magnetic card reader, which was, in turn, connected to an electrical switch designed to alternate between the sham and active coils. The card reader was designed to read both operator cards and patient cards that encode the patients' treatment group assignments. When the operator card was swiped by the card reader, the system was set to an active stimulation mode in which the system operator determined the subjects' motor threshold. After completion of this stage, the assigned patient card was swiped by the card reader, and the treatment was administered according to the group to which the subject had been randomized. In this manner, all study personnel were blinded to the treatment assignment.

dTMS protocol

Before starting each treatment, subjects were instructed to insert earplugs to lessen any possible adverse effects on hearing. The individual motor threshold at rest was measured at the beginning of each treatment (with the operator card) by delivering single stimulation pulses to the respective "hot spot" of the motor cortex (27). The left DLPFC was chosen as the treatment target site, and was targeted by placing the coil 6 cm anterior to the "hot spot" according to a ruler attached on the subject's cap. During the first three treatments, sites were allowed to titrate stimulation intensity up from 100% to 120% of the individual motor threshold in order to improve subjects' tolerability to the treatment.

The treatment group received dTMS doses of 18 Hz, at stimulator power output of 120% of the measured individual motor threshold. Each dTMS repetition included 2-sec pulse trains separated by 20-sec inter-train intervals. Subjects received 55 trains in each treatment session, for a total of 1980 pulses per session. Each session lasted about 30 min, of which the dTMS delivery lasted 20 min. The control group received sham (inactive) treatment with identical parameters. Subjects were told that face and hand twitching may occur due to either sham or active treatment.

Efficacy and safety assessments

All efficacy outcome measures were performed by a blinded study rater who was not permitted access to the treatment sessions. Raters were required to pass the study rater certification program, which was developed to ensure adequate scoring reliability and rating skills. Patients were instructed not to disclose any details of the treatment session to the study raters during rating sessions. Furthermore, patients were instructed to report all adverse events only to the device operator. Efficacy ratings were administered at baseline and once weekly until the end of the study (week 16).

The primary endpoint was the change in the total score on the HDRS-21 from baseline to week 5. The secondary efficacy endpoints were response and remission rates at week 5. Response was defined as a reduction of at least 50% in the total HDRS-21 score compared to baseline, and remission was defined by a total HDRS-21 score <10.

Safety was assessed at every treatment visit by the operator. Patients were asked to report any adverse events since their previous visit. Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities. Additional safety evaluations included auditory threshold tests performed at baseline, week 6, and at end-of-study visit. Subjects were also evaluated for cognitive changes at baseline, week 5 and at end-of-study visit.

Statistical analysis

We determined that 85 subjects per group (170 in total) would provide 90% power at a significance level of 5% (two-tailed) in detecting a difference of 3.75 points in the mean change from baseline HDRS-21 scores between treatment and sham groups, considering a standard deviation of 7.5 points (data from pilot study), and assuming an effect

size of 0.5. Allowing for a 15% dropout from the study irrespective of study arm and success of treatment, 200 randomized subjects were required. Approximately 20% of the subjects were expected to leave the study between screening and randomization, thus it was necessary to screen approximately 250 subjects in order to arrive at the point of randomization with at least 200 subjects.

The study results were analyzed for two patient populations: the intention-to-treat (ITT) and the per-protocol (PP) analysis set. The ITT set included all subjects who met the study eligibility criteria and received at least one dTMS/sham treatment. Patients who were not administered stimulation at the protocol-specified intensity (i.e., 120% of their individual motor thresholds) were excluded from the PP cohort. The PP population thus included all subjects from the ITT set who received the protocol-specified treatment and completed the 16-week treatment regimen or withdrew before completion per the study protocol. Comparisons of baseline demographic and clinical characteristics and safety assessments were performed on the ITT analysis set. The primary efficacy analysis was performed using the PP analysis set.

Comparisons of baseline demographic and clinical characteristics between the study groups were performed to ensure that the groups were balanced at baseline and that the randomization was successful. For comparison of means (continuous variables), the two-sample t-test or a non-parametric equivalent was used. For comparison of proportions (categorical variables), the chi-square test or Fisher's exact test was used, as appropriate. The change in HDRS-21 total score from baseline to week 5 (primary endpoint) was compared between the treatment groups using a repeated measures analysis (RMA) of covariance (SAS® MIXED procedure). The analysis, which aims to compare the slopes of the changes in HDRS-21 scores between study arms, included the following fixed effects: time from randomization (in weeks), treatment group, time x treatment group interaction, center (site of study), baseline HDRS-21 score, and ATHF category at baseline. Baseline HDRS-21 score was entered as a continuous variable so as to minimize the potential for co-linearity problems.

Individual subjects' intercepts and time effects were also included in the model as random effects (random intercept and slope model). The principal statistical analysis was a comparison between the slopes of the treatment groups, derived from the time x treatment interaction term from the RMA model described above. The adjusted mean slope of change from baseline in HDRS-21 scores at week 5 post-randomization is estimated from the model (least square means, LS-means) for each study group as well as for the difference between the groups' adjusted mean slopes, and these are presented together with 95% confidence intervals.

Secondary outcome measures were the response and remission rates at week 5. Tertiary endpoints were the change from baseline to week 16, as well as response and remission rates at week 16. The change in HDRS-21 total score from baseline to week 16 was compared between the treatment groups using analysis of covariance of the change from baseline to the last observed value (LOV). Baseline HDRS-21 score, ATHF category at baseline, and site were entered as covariates. The LOV is defined as the last available post-baseline visit data up to and including the last treatment visit or termination visit. The adjusted mean change (LS-means) from baseline in HDRS-21 score at week 16 (LOV) is estimated from the model (LS-means) for each study group, as well as the difference between the adjusted means. These are presented together with 95% confidence intervals.

The overall significance level for this study was 0.05 using two-tailed tests, except for treatment x site interaction that was tested at a significance level of 0.01. Nominal p values are presented. Statistical analyses were performed using SAS® V9.3 (SAS Institute, Cary NC, USA). Effect size was the difference between slopes/pooled standard deviation of baseline HDRS-21 score.

RESULTS

Subjects

Following phone screening of over 900 potential participants, of which 428 were invited for additional on-site screening, 233 subjects were enrolled, of which the ITT set included 212 subjects (excluding subjects who did not comply with the inclusion/exclusion criteria or left the study before receiving a single treatment). Thirty-one subjects in the ITT set who did not receive the adequate TMS regimen as specified in the protocol were excluded to form the PP analysis set (N=181). The PP analysis set thus included only subjects who completed the study without any major protocol violations. For this reason, it was considered the most appropriate for the purpose of assessing the efficacy of dTMS.

Eligible and consenting subjects were randomized to either the dTMS group (N=111; ITT=101, PP=89) or the sham control group (N=122; ITT=111, PP=92). The numbers of patients who dropped out of the study later on as well as the reasons for dropouts are presented in the CONSORT diagram (Figure 1). The two study groups were statistically similar at baseline with respect to demographic parameters, clinical characteristics and HDRS-21 mean scores (Table 1).

Efficacy measures

The primary efficacy endpoint was the change in HDRS-21 total score from baseline to end of week 5, i.e. after subjects had completed 4 weeks of acute dTMS treatment and were one week into the maintenance phase.

In the PP analysis set, the estimated slope in the dTMS group was -6.39 compared with -3.28 in the sham group.

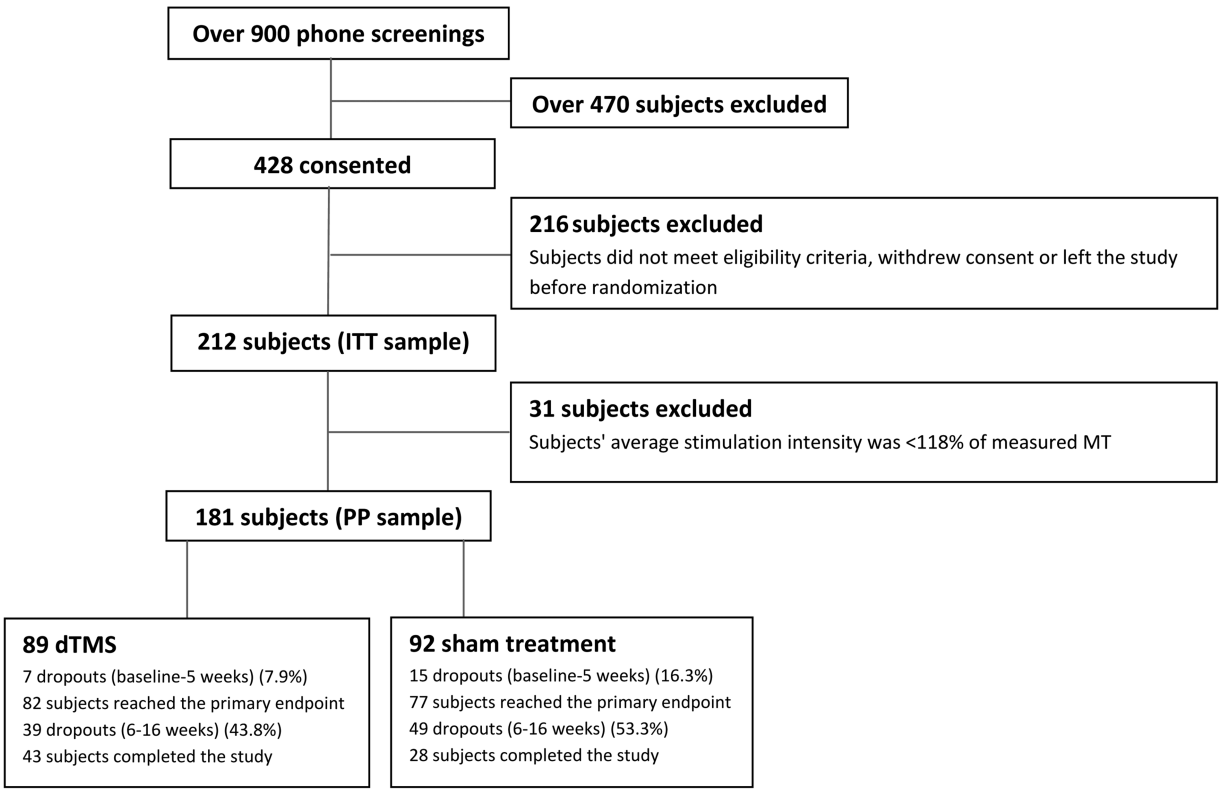

Figure 1 CONSORT diagram. dTMS – deep transcranial magnetic stimulation, ITT – intention-to-treat analysis, PP – per-protocol analysis, MT – motor threshold.

The difference of -3.11 (95% CI: -5.40, -0.83) points between the slopes was statistically significant (p=0.008), with an effect size of 0.76 (Table 2, Figure 2). In the ITT analysis set, the difference of -2.23 points (95% CI: -4.54, 0.07) between the slopes across 5 weeks fell just short of reaching statistical significance (p=0.0578), with a corresponding effect size of 0.58 (Table 2).

The secondary efficacy measures were response and remission rates at week 5. Response rates (PP set) were 38.4% for dTMS versus 21.4% for sham treatment (chi-square test, p=0.0138). Remission rates (PP set) were 32.6% and 14.6% for dTMS and sham TMS, respectively (chi-square test, p=0.0051) (Table 2, Figure 3).

The tertiary efficacy measures were change in HDRS-21 total score from baseline to week 16 and response and remission rates at week 16. The difference of 2.47 points between the LS-means of the active and sham groups at week 16 was statistically significant (p=0.0259). Additionally, the response rates of the PP set at week 16 (LOV) were 44.3% after dTMS versus 25.6% after sham treatment (chi-squared test, p=0.0086). The week 16 remission rates (LOV) were 31.8% and 22.2% in the dTMS and sham groups, respectively (p=0.1492, chi-squared test) (Table 2, Figure 3).

A subset analysis was performed to assess if there was a different response to treatment in subjects who failed one or two medications versus subjects who failed three or more medications in the current episode. The primary and secondary outcome measures were estimated in each subset. The change from baseline over time until the primary endpoint (5 weeks) for the active and sham groups was compared by repeated measures ANOVA models as described for the primary measure above. The difference between the estimated slopes of the dTMS and sham groups was -3.23 points (95% CI: -6.19, -0.27, p=0.0327) in the first stratum (failed one or two medications), and -3.10 (95% CI: -6.76, 0.56, p=0.0958) in the second stratum (failed three or more medications). Remission rates in the first stratum were 36.6% (N=15/41) for the dTMS group and 16.7% (N=8/

Table 1 Demographic data and baseline characteristics of subjects by treatment group (intention-to-treat analysis set)

	dTMS (N=101)	Sham (N=111)	p
Age (years, mean±SD)	45.1±11.7	47.6±11.6	0.1241
Gender (% male)	52.5	52.3	1.000
Ethnicity (% Caucasian)	94.1	87.4	0.6866
Body mass index (mean±SD)	28.1±7.1	27.8±7.0	0.7837
Age at first episode (years, mean±SD)	25.3±11.5	26.9±12.7	0.3357
Duration of current episode (months, mean±SD)	21.7±16.3	19.5±15.2	0.3217
History of suicide attempts (% without any)	88.1	92.8	0.3471
Antidepressants in current episode (%)			
None	-	0.9	0.1880
One	24.8	24.3	
Two	33.7	31.5	
Three	15.8	17.1	
Four	10.9	19.8	
Five or more	14.9	6.3	
Number of failed medications at ATHF level ≥3 (%)			
None	6.9	12.6	0.3838
One or two	71.3	66.7	
Three or more	21.8	20.7	
Baseline HDRS-21 score (mean±SD)	23.5±4.3	23.4±3.7	0.7641
Motor threshold at first treatment (mean ±SD)	59.8±8.3	61.1±8.9	0.2745

dTMS – deep transcranial brain stimulation, ATHF – Antidepressant Treatment History Form, HDRS – Hamilton Depression Rating Scale

48) for the sham group (p=0.032, chi-square test). Remission rates in the second stratum were 28.9% (N=13/45) for dTMS group and 12.2% (N=5/41) for the sham group (p=0.057, chi-square test). So, patients with higher resistance to medications tended to be somewhat less responsive to dTMS, but the effect of treatment was still significant in patients who failed one or two medications and marginally significant relative to the sham group in patients who failed three or more medications (Figure 4).

As an additional measure of clinical efficacy, we calculated the total amount of time (in weeks) during which subjects satisfied HDRS-21 criteria for response and remission. Subjects had to complete a minimum of two weeks of treatment sessions in order to be included in this analysis. The highest obtainable result was 16 (for patients who remitted or responded already in the first week of treatment and remained in remission or response until the end of the study, without leaving the study) and the lowest was 0 (for patients

Table 2 Primary, secondary and tertiary efficacy measures

	ITT			PP		
	dTMS (n=101)	Sham (n=111)	p	dTMS (n=89)	Sham (n=92)	p
Primary efficacy measure						
Slope of change, 5 weeks (95% CI)	−6.17 (−7.78, −4.55)	−3.94 (−5.58, −2.29)	0.0578	−6.39 (−7.97, −4.79)	−3.28 (−4.91, −1.63)	0.0080
Secondary efficacy measures						
Response rate, week 5 (%)	37.0	27.8	0.0310	38.4	21.4	0.0138
Remission rate, week 5 (%)	30.4	15.8	0.0158	32.6	14.6	0.0051
Tertiary efficacy measures						
LS-mean of change, 16 weeks (95% CI)	−8.04 (−9.91, −6.16)	−6.31 (−7.99, −4.62)	0.1040	−8.55 (−10.51, −6.57)	−6.07 (−7.87, −4.27)	0.0259
Response rate, 16 weeks (%)	40.6	26.0	0.0276	44.3	25.6	0.0086
Remission rate, 16 weeks (%)	29.2	22.1	0.2530	31.8	22.2	0.1492

dTMS – deep transcranial brain stimulation, ITT – intention-to-treat analysis, PP – per-protocol analysis, LS – mean-least square mean

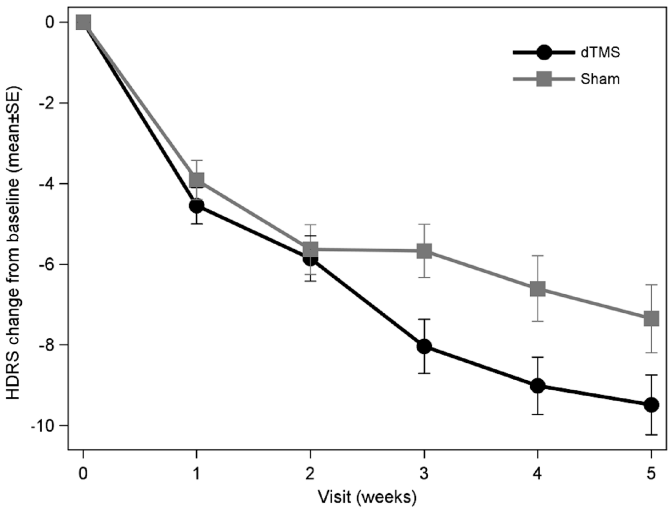

Figure 2 Change in Hamilton Depression Rating Scale (HDRS-21) total score from baseline over time to the primary time point (end of week 5) for deep transcranial magnetic stimulation (dTMS) and sham groups in the per-protocol analysis

who did not achieve remission or response at all). The mean time in response in the dTMS group was 4.9 weeks versus 2.8 weeks in the sham group (p=0.001, Wilcoxon two-sample test). The mean time in remission in the dTMS group was 3.7 weeks versus 2.1 weeks in the sham group (p=0.003, Wilcoxon two-sample test). The distributions of percentage of time in response and in remission out of the total time in the study for the dTMS and sham groups are shown in Figure 5. The mean percentage of time in response in the dTMS group was 36±4% versus 22±3% in the sham group (p=0.002, Wilcoxon two-sample test). The mean percentage of time in remission in the dTMS group was 26±3% versus 16±3% in the sham group (p=0.005, Wilcoxon two-sample test).

Center bias was evaluated by entering the group x site x time interaction into the model for the primary endpoint and assessing statistical significance at the 0.01 level. No statistically significant differences were found in slopes of change from baseline HDRS-21 score between the study groups stratified by center (F=1.10, df=18,151, p=0.36).

Integrity of blinding in patients was assessed using a forced choice questionnaire. Of the 198 subjects who answered the questionnaire (one subject did not respond at all to the forced choice question, one subject discontinued treatment and did not respond, and 12 subjects could not decide what to answer), 138 (69.7%) thought they were receiving the active treatment. Of these, 78 (56.5%) were actually in the dTMS group and 60 (43.5%) in the sham group. This difference was not statistically significant.

Safety measures

Adverse events were defined and reported in the study according to system organ class and preferred term based on the Medical Dictionary for Regulatory Activities classification. Within the dTMS group, three subjects (3.0%) reported application site discomfort, five (5.0%) application site pain, 27 (26.7%) headache, two (2.0%) muscle twitching, two (2.0%) back pain, and two (2.0%) insomnia. Within the sham group, two subjects (1.8%) reported application site discomfort, none application site pain, 21 (18.9%) headache, none muscle twitching, three (2.7%) back pain, two (1.8%) anxiety, and four (3.6%) insomnia. Only one adverse event category showed a significant difference between study groups: application site pain (p=0.02). This effect is commonly reported with TMS treatment.

Eight serious adverse events were reported in seven subjects. Four of them were reported in the sham group (two cases of suicidal ideation, one of nausea and vomiting, and

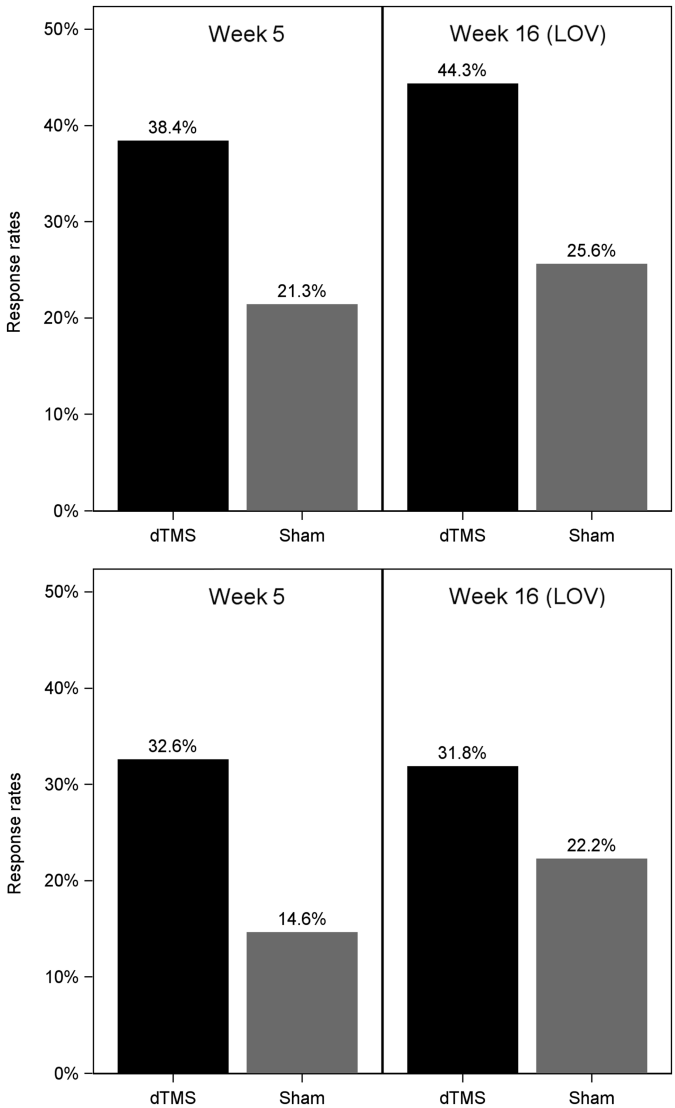

Figure 3 Response and remission rates for deep transcranial magnetic stimulation (dTMS) and sham groups at the end of week 5 and of week 16 (last observed value, LOV) in the per-protocol analysis. Response: p=0.0138 (5 weeks), p=0.0086 (16 weeks). Remission: p=0.0051 (5 weeks), p=0.1492 (16 weeks)

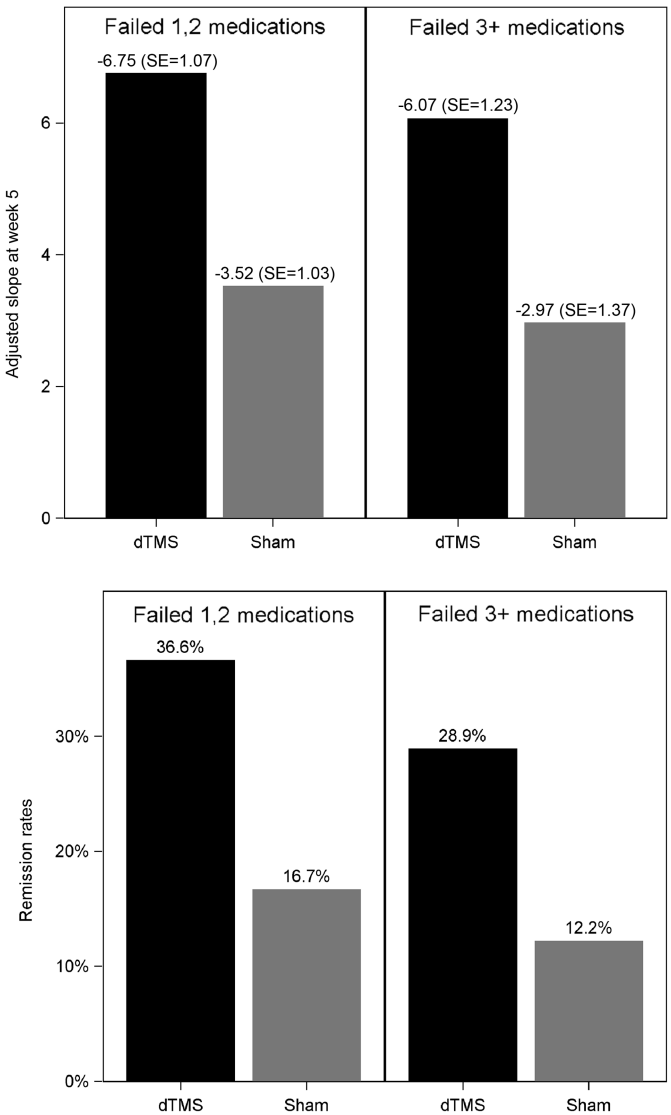

Figure 4 Antidepressant effect of deep transcranial magnetic stimulation (dTMS) in relation to the number of failed pharmacotherapy trials

one of nephrolithiasis); three were reported in two subjects in the dTMS group (one case of elbow fracture, one of cluster headache, and one of seizure); and one was reported in a subject not randomized to the study (a suicide attempt). Only one out of the eight serious adverse events was considered device-related: one subject (female, 26 years old) experienced a generalized seizure which lasted about 2 min. The seizure occurred towards the end of her ninth dTMS treatment session. The patient entered a post-ictal state after the seizure. Following a full neurological examination and several hours of observation in the emergency room, the patient was released with no additional medical intervention. The subject was withdrawn from the study and there were no reported sequelae as a result of the event. The seizure occurred following excessive consumption of alcohol on the night before treatment that was not reported to the treating physician or operator at the time of treatment. The event was reported to the FDA. This serious adverse event was considered device-related, albeit with the caveat that withdrawal from alcohol may have led to a reduction of seizure threshold and consequently to this seizure during dTMS.

DISCUSSION

This double-blind placebo-controlled multicenter study demonstrates the efficacy and safety of dTMS in MDD patients who did not benefit from previous antidepressant treatment. The therapeutic effect was essentially stable during a maintenance phase up to 16 weeks, and a clinically meaningful improvement was seen also in patients who had not responded to three or more previous antidepressant medications.

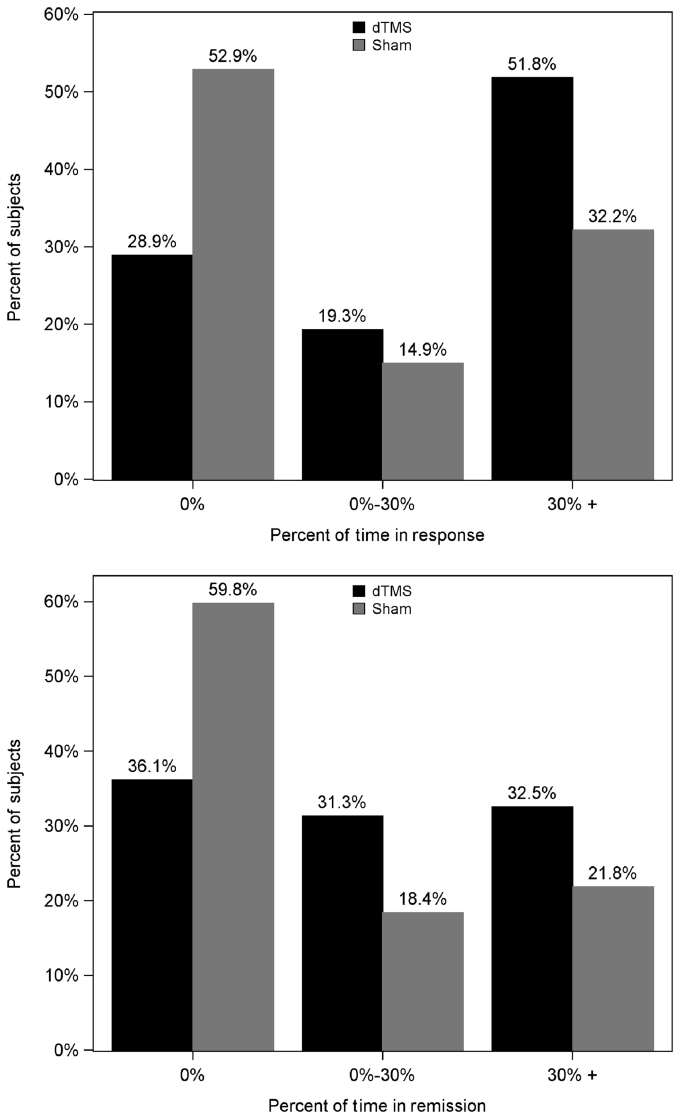

Figure 5 Percentage of patients achieving response or remission for 0%, 0–30% and >30% of the total time in the study in the deep transcranial magnetic stimulation (dTMS) and sham groups

dTMS is a novel type of rTMS which differs from standard rTMS by custom made coils (H-coils) with a greater depth of effective stimulation (7-10). The H1-coil has been specially developed for deeper and non-focal stimulation of dorsolateral and ventrolateral prefrontal areas that also project into other areas of brain reward system. These anatomical targets have been suggested to be particularly relevant for therapeutic effects of non-invasive brain stimulation in MDD (5).

The therapeutic effects of dTMS observed here were clinically relevant and maintained up to week 16. Although this study was not designed to compare the effect of dTMS with that of standard TMS, we hypothesize that the marked antidepressant efficacy of dTMS is related to the novel design of the H-coil, which enables stimulation of deeper prefrontal cortical areas that project into subcortical networks. Recent studies suggest that stimulation of prefrontal cortical regions with extensive connections to the subgenual cingulate gyrus may be crucial for the antidepressant action of standard rTMS (24). Since the exact location of these cortex regions varies greatly between individuals (28), and standard TMS coils exert a more focal and superficial stimulation, optimal stimulation targets may be easily missed with standard coils. Nevertheless, a study directly comparing dTMS and standard TMS is needed to prove the superiority of dTMS. In addition, further studies are needed to clarify which anatomical structures and pathways exactly mediate the therapeutic action of dTMS.

The efficacy of dTMS and standard TMS cannot be compared at the moment because previous studies investigating rTMS not only vary by TMS parameters, but also differ by inclusion criteria, patient characteristics and efficacy criteria. O'Reardon et al (21) reported HDRS-17 response and remission rates of 24.5% and 15.5% in subjects treated with active rTMS for 6 weeks compared to 13.7% and 8.9% in sham-stimulated control subjects. In a duration-adaptive study (3-week acute treatment phase with a 3-week extension for clinical improvers), George et al (19) reported remission rates of 14.1% following active rTMS compared to 5.1% with placebo rTMS. Thus, the results of the current and previous studies not only vary for active treatment groups, but also in relation to the outcome of sham TMS treatment. In the current study, a rather higher response (PP: 21.4%) and remission rate (PP: 14.6%) was observed after sham treatment in comparison to both previous trials (19,21). This could be due to patient selection and to an improved sham condition in which the sham coil was built in the same helmet as the active coil. In this sham condition, most of the elements are located far above the patient's head, generating an electric field that stimulates skin and scalp muscles but is insufficient to produce neuronal activation. Moreover, the operator neither needs to apply electrical stimulation in conjunction with sham TMS, nor to exchange active and sham coils manually as in earlier multicenter studies (19,21).

dTMS was well tolerated by the majority of patients and the main side effect was pain during application, usually not requiring any special care. There was one seizure induced by dTMS in this study, which may have been related to alcohol consumption the night before treatment. To date, out of over 3,500 patients treated with dTMS across studies, there have been five seizures. This risk of seizure with dTMS is quite similar to that of standard TMS and is likely related to the total energy induced by either coil and not the larger distribution and less concentrated electric field induced by the dTMS coil. Notably, the seizure was self-limited and with no persistent medical sequelae.

The present study was the first multicenter TMS study assessing the effects of maintenance therapy. The 12-week period of bi-weekly treatments proved the therapeutic effect of dTMS to be durable long after the acute daily treatment phase, even without concomitant antidepressant medications. Deep TMS at a bi-weekly schedule may be an acceptable alternative to antidepressant therapy for the long term as well.

There are several limitations to this study. First, 14.6% of the ITT analysis set were not treated at the stimulation intensity defined by the protocol and had to be excluded from the PP analysis. This was presumably due to the flexibility of the operator in titrating stimulation intensity from 100% up to 120% of individual motor threshold in order to improve tolerability. Thus, patients were more likely to stay at an intensity below the optimal level compared to trials where rTMS was defined at a fixed intensity after a brief lead-in period (19,21). The importance of adequate intensity (120% of individual motor threshold) should be highly emphasized when training operators to use this system for antidepressant treatment, as lower intensity does not allow stimulation of deep prefrontal cortex areas and is therefore less likely to produce the desired clinical response (14).

Second, patients with psychotic depression were excluded from the study. This decision was based on a previous trial that demonstrated the superiority of electroconvulsive therapy to rTMS in this patient group (29). However, it cannot be ruled out that psychotic patients may benefit from dTMS treatment, particularly if it is administered concomitantly with antipsychotic medication. Third, in the present study patients were withdrawn from antidepressant medications prior to dTMS as required by regulatory authorities. However, in a real-life clinical setting, antidepressant medication that leads to a partial response might be augmented with dTMS treatment. The safety and efficacy of such a strategy was demonstrated in a previous study (13).

In conclusion, the present randomized and placebo-controlled trial demonstrates that dTMS is an effective and tolerable treatment for patients with MDD who have not successfully responded to treatment with antidepressant medications in the current episode. The effects appear durable, with maintenance of efficacy up to 16 weeks. A clinically significant improvement was seen in even the higher treatment-resistant patients.

Acknowledgement

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Prevalence of psychiatric disorders in U.S. older adults: findings from a nationally representative survey

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Data on the prevalence of psychiatric disorders in late life are lacking. The present study addresses this gap in the literature by examining the prevalence of the broadest range of psychiatric disorders in late life to date; comparing prevalences across older adult age groups using the largest sample of adults aged 85+; and exploring gender differences in the prevalence of psychiatric disorders in late life. Using data from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions, we examined the prevalence of past-year mood, anxiety, and substance use disorders, and lifetime personality disorders in a nationally representative sample of 12,312 U.S. older adults. We stratified our analyses by gender and by older age groups: young-old (ages 55-64), middle-old (ages 65-74), old-old (ages 75-84), and oldest-old (ages 85+). The proportion of older adults who experienced any past-year anxiety disorder was 11.4%, while the prevalence of any past-year mood disorder was 6.8%. A total of 3.8% of older adults met criteria for any past-year substance use disorder, and 14.5% of older adults had one or more personality disorder. We observed a general pattern of decreasing rates of psychiatric disorders with increasing age. Women experienced higher rates of mood and anxiety disorders, while men had higher rates of substance use disorders and any personality disorder. Gender differences in rates of most psychiatric disorders decreased with increasing age. These data indicate that psychiatric disorders are prevalent among U.S. older adults, and support the importance of prevention, diagnosis, and treatment of psychiatric disorders in this population.

Key words: Psychiatric disorders, anxiety disorders, mood disorders, substance use disorders, personality disorders, older adults, oldest-old

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We are in the midst of a global demographic shift in population aging, a trend that is the first of its kind in the evolution of the human species (1). In the U.S., the proportion of adults aged 65 years and older is projected to increase from 13% of the population in 2010 to 16% by 2020. Furthermore, the gender gap in life expectancy, with women living longer than men, is narrowing over time (1).

There is current debate in the literature regarding whether prevalence rates of psychiatric disorders increase or decrease in later life. Extant epidemiologic research has primarily focused on trends of psychiatric disorders across the entire adult lifespan, and results have been mixed with respect to the effect of age on the prevalence of disorders.

Research studies using primarily smaller, community-based samples have found that rates of mood disorders increase across the adult lifespan (2-4), while other studies have observed a U-shaped relationship, with the highest prevalence of these disorders among younger and older adults, compared to middle-aged adults (5-7).

In contrast, other studies have shown a reversed U-shaped relationship between age and well-being across the adult lifespan, with increased well-being in young and older adults and decreased well-being in middle-aged adults (8,9). In line with this finding, the literature provides the strongest support for decreased prevalence of mood, anxiety, and substance use disorders in late life (10). This trend of decreased prevalence of psychiatric disorders is corroborated by data from the U.S. Epidemiologic Catchment Area Survey, which indicated a linear decrease in DSM-III psychiatric disorders (excluding dementia) across the adult lifespan (11). Further, data from the National Comorbidity Survey – Replication (NCS-R) revealed that the prevalence of past-year and lifetime DSM-IV mood, anxiety, and substance use disorders were lower for older adults (65+) compared to younger age groups (ages 18-64) (12).

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) demonstrated similar trends when comparing the prevalence of personality disorders among older and younger adults (13). Data from a Canadian population-based sample further supports a pattern of decreased rates of major depression, bipolar disorder, social phobia, agoraphobia, and panic disorder in late life (14).

Research focused on examining trends of psychiatric disorders among older age groups is limited. Specifically, there is a significant dearth of epidemiological research that examines demographic trends of psychiatric disorders across late-life age groups, as several extant data sets do not have adequate sample sizes, particularly of the oldest-old segment of the population (aged 85+).

In a recent study exploring the prevalence of a broad range of psychiatric disorders across older adult age groups, Byers et al (15) found a general decline in the prevalence of DSM-IV past-year mood and anxiety disorders among individuals aged 55+ who participated in the NCS-R. While informative in characterizing the prevalence of mood and anxiety disorders in older adults, the prevalence of past-year substance use disorders and lifetime personality disorders,

and gender-stratified analyses were not reported in this study. Furthermore, the sample size of older adults in the oldest-old age group (85+) was small (N=122).

A small body of research has examined gender differences across late-life psychiatric disorders. Existing data is limited to depression, with the majority of studies indicating that gender differences in the prevalence of this disorder (i.e., higher rates in women) decrease with increasing age (16-20).

To address these gaps in the literature, we analyzed data from a large, nationally representative study of the U.S. adult population. Our aims were: a) to examine the prevalence of the broadest range of psychiatric disorders in the literature to date, including mood, anxiety, substance use, and personality disorders, as well as mental health-related quality of life among adults aged 55+; b) to compare the prevalence of psychiatric disorders across older adult age groups, including the largest extant sample of community-based older adults aged 85+; and c) to examine the relationship between gender and prevalence of late-life psychiatric disorders.

METHODS

Sample and procedure

We analyzed data from Wave 2 of the NESARC, conducted by the National Institute on Alcohol Abuse and Alcoholism between 2004 and 2005. Wave 2 was a follow-up survey to Wave 1, which was conducted between 2001 and 2002. We chose to analyze data from Wave 2 because the first wave did not assess post-traumatic stress disorder (PTSD) or borderline, schizotypal, and narcissistic personality disorders.

Wave 2 of the NESARC surveyed a nationally representative sample of community-dwelling American adults aged 20 years and older residing in the U.S., including the District of Columbia, Alaska, and Hawaii. The sample excluded adults who were deceased, deported, institutionalized, or on active military duty. The response rate was 86.7%, which was the proportion of Wave 1 participants who responded in Wave 2, resulting in a total sample size of 34,653. Consistent with prior geropsychiatry research (21-23), we restricted our analyses to older adults aged 55+, which resulted in a subsample of 12,312 respondents. We compared young-old (55-64; N=5,135), middle-old (65-74; N=3,634), old-old (75-84; N=2,673), and oldest-old (85+; N=870) age groups.

Trained lay interviewers from the U.S. Census Bureau with at least five years of experience conducted face-to-face lay interviews, and all participants provided written informed consent. The U.S. Census Bureau and the U.S. Office of Management and Budget reviewed the research protocol and provided full ethical approval. A more detailed description of methodology and sampling procedures of the NESARC can be found elsewhere (24-26).

Assessments

Psychiatric disorders

The NESARC used the Alcohol Use Disorders and Associated Disabilities Interview Schedule IV (AUDADIS-IV), a reliable and valid instrument designed for lay interviewers to assess DSM-IV psychiatric disorders. The reliability for the AUDADIS-IV ranges from good to excellent across all assessed psychiatric disorders, as detailed elsewhere (26,27).

We examined past-year diagnoses of mood (i.e., major depression, dysthymia, and mania or hypomania), anxiety (i.e., panic disorder with and without agoraphobia, social phobia, specific phobia, generalized anxiety disorder, and PTSD), and substance use (i.e., alcohol abuse and dependence, drug abuse and dependence, and nicotine dependence) disorders. In addition to examining these psychiatric disorders individually, we also generated any mood, anxiety, and substance use categories to assess the prevalence of being diagnosed with at least one psychiatric disorder within each category. We analyzed nicotine dependence individually and did not include it in the any substance use disorder category.

Wave 2 of the NESARC included all ten DSM-IV personality disorders: borderline, antisocial, avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, schizotypal, and narcissistic. In light of empirical support for the classification of personality disorders into clusters A, B, and C using the AUDADIS-IV (28), we further categorized personality disorders into DSM-IV cluster A – odd or eccentric disorders (i.e., paranoid, schizoid, and schizotypal), cluster B – dramatic, emotional, or erratic disorders (i.e., antisocial, borderline, histrionic, and narcissistic), and cluster C – anxious or fearful disorders (i.e., avoidant, dependent, and obsessive-compulsive). We also included an any personality disorder category.

Finally, we created a continuous number of psychiatric disorders variable based on number of diagnosed mood, anxiety, substance use, and personality disorders.

Socio-demographic variables

We included the following socio-demographic variables: age, gender, ethnicity, education, household income, and marital status. We categorized age into four groups (young-old, middle-old, old-old, and oldest-old), as indicated above. We further categorized ethnicity (White, Black, American Indian/Alaska Native, Asian/Native Hawaiian/Other Pacific Islander, and Hispanic), education (less than high school, high school, some college or higher), household income ($0-$19,999, $20,000-$34,999, $35,000-$59,999, and $60,000+), and marital status (married or living with someone as if married, widowed/separated/divorced, never married).

Table 1 Socio-demographic variables in 12,312 adults aged 55 years and older by DSM-IV psychiatric disorders

	N (weighted %)	Any past-year mood disorder N (weighted %)	Any past-year anxiety disorder N (weighted %)	Any past-year substance use disorder N (weighted %)	Any lifetime personality disorder N (weighted %)
Gender					
Male	4938 (45.01)	248 (4.49)	417 (7.90)	345 (6.62)	868 (16.79)
Female	7374 (54.99)	666 (8.64)	1092 (14.24)	105 (1.40)	1045 (12.68)
χ^2 (df)		58.59 (1)***	64.49 (1)***	92.43 (1)***	29.23 (1)***
Ethnicity					
White (non-Hispanic)	8117 (79.25)	567 (6.53)	950 (11.10)	321 (3.91)	1154 (13.67)
Black (non-Hispanic)	2268 (8.90)	158 (6.56)	295 (12.59)	70 (3.59)	441 (19.36)
American Indian/Alaska Native (non-Hispanic)	207 (2.26)	24 (9.75)	36 (15.86)	8 (2.95)	54 (23.99)
Asian/Native Hawaiian/Other Pacific Islander (non-Hispanic)	232 (3.24)	16 (5.83)	17 (7.74)	3 (1.74)	23 (9.45)
Hispanic	1488 (6.34)	149 (9.48)	211 (13.59)	48 (3.25)	241 (17.67)
χ^2 (df)		2.47 (4)	3.37 (4)*	0.87 (4)	5.89 (4)***
Education					
Less than high school	2867 (19.69)	261 (7.97)	370 (12.79)	82 (2.91)	431 (14.75)
High school	3780 (31.83)	256 (6.35)	475 (11.45)	117 (3.07)	524 (13.12)
Some college or more	5665 (48.48)	397 (6.56)	664 (10.78)	251 (4.53)	958 (15.37)
χ^2 (df)		2.67 (2)	2.38 (2)	8.83 (2)***	3.49 (2)*
Household income					
$0-$19,999	4197 (26.36)	407 (9.63)	585 (13.51)	99 (2.36)	705 (16.61)
$20,000-$34,999	2786 (22.48)	194 (6.61)	335 (11.51)	71 (2.35)	411 (13.34)
$35,000-$59,999	2642 (24.09)	180 (6.49)	301 (10.87)	133 (5.00)	405 (14.52)
$60,000+	2687 (27.06)	133 (4.38)	288 (9.69)	147 (5.15)	392 (13.50)
χ^2 (df)		11.16 (3)***	4.33 (3)**	11.72 (3)***	3.81 (3)*
Marital status					
Married/cohabiting	6180 (64.22)	358 (5.39)	611 (10.09)	233 (3.90)	886 (13.66)
Widowed/separated/divorced	5347 (31.44)	489 (9.46)	763 (14.15)	183 (3.23)	886 (15.93)
Never married	785 (4.35)	67 (7.76)	85 (10.57)	34 (5.19)	141 (17.22)
χ^2 (df)		20.19 (2)***	14.09 (2)***	2.14 (2)	4.62 (2)*

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

Mental health-related quality of life

We derived a mental health component score (MCS-12) from the Short-Form Health Survey (SF-12, 29) as a measure of mental health-related quality of life, with higher scores indicating better mental health-related quality of life. Prior research indicates that the MCS-12 has good reliability and validity. Specifically, scores on the MCS-12 correlate strongly with scores on the MCS-36 and have high test-retest reliability (r=0.76) (29).

Statistical analysis

We conducted cross-tabulations to compare the weighted prevalence of socio-demographic variables across the any disorder categories (i.e., any mood, anxiety, substance use, and personality disorders). We then conducted chi-square analyses to evaluate whether socio-demographic characteristics differed among disorder categories. We also conducted cross-tabulations and chi-square analyses to establish the prevalence of all psychiatric disorders across the older adult age groups (i.e., young-old, middle-old, old-old, and oldest-old), and the presence of significant differences among these groups. We further stratified these prevalence estimates by gender.

We conducted bivariate and multivariate logistic regressions to examine the relationship between each older adult age group and the any psychiatric disorder categories, with older adults aged 85+ serving as the reference group. We report unadjusted logistic regression models, as well as models adjusted for socio-demographics.

Table 2 Prevalence of DSM-IV psychiatric disorders and mental health-related quality of life among adults aged 55 years and older

	Total N (weighted %)	Age 55–64 N (weighted %)	Age 65–74 N (weighted %)	Age 75–84 N (weighted %)	Age 85+ N (weighted %)	χ^2 (df)
Mood disorders						
Major depression	751 (5.63)	420 (7.41)	184 (4.58)	107 (3.87)	40 (4.23)	13.06 (3)***
Dysthymia	138 (0.94)	87 (1.34)	27 (0.67)	17 (0.54)	7 (0.77)	4.80 (3)**
Mania or hypomania	207 (1.49)	131 (2.27)	49 (1.26)	23 (0.53)	4 (0.50)	10.24 (3)***
Any mood disorder	914 (6.77)	518 (9.02)	228 (5.68)	128 (4.48)	40 (4.23)	17.28 (3)***
Anxiety disorders						
Panic disorder	185 (1.35)	120 (2.02)	34 (0.91)	23 (0.77)	8 (0.74)	6.10 (3)**
Social phobia	205 (1.45)	129 (2.14)	42 (1.08)	28 (0.83)	6 (0.49)	11.14 (3)***
Specific phobia	766 (5.79)	432 (7.74)	200 (4.91)	106 (3.84)	28 (3.12)	12.84 (3)***
Generalized anxiety disorder	353 (2.80)	206 (3.73)	84 (2.28)	45 (1.78)	18 (2.20)	5.11 (3)**
Post-traumatic stress disorder	484 (3.48)	281 (4.67)	109 (2.75)	80 (2.59)	14 (1.76)	10.31 (3)***
Any anxiety disorder	1509 (11.39)	831 (14.81)	379 (9.45)	239 (8.40)	60 (7.15)	18.76 (3)***
Substance use disorders						
Alcohol abuse/dependence	418 (3.48)	283 (5.58)	93 (2.39)	40 (1.73)	2 (0.06)	34.06 (3)***
Any drug abuse/dependence	50 (0.42)	42 (0.84)	7 (0.19)	0 (0.00)	1 (0.10)	7.93 (3)***
Any substance use disorder	450 (3.75)	308 (6.07)	99 (2.57)	40 (1.73)	3 (0.15)	39.24 (3)***
Nicotine dependence	1123 (9.29)	710 (14.02)	310 (8.49)	90 (3.15)	13 (1.36)	43.47 (3)***
Personality disorders						
Borderline	449 (3.16)	278 (4.66)	106 (2.54)	53 (1.58)	12 (1.19)	13.82 (3)***
Antisocial	176 (1.64)	119 (2.59)	43 (1.34)	12 (0.59)	2 (0.13)	19.96 (3)***
Avoidant	172 (1.30)	111 (1.95)	38 (0.94)	15 (0.58)	8 (0.87)	6.67 (3)***
Dependent	37 (0.26)	22 (0.36)	8 (0.14)	6 (0.24)	1 (0.19)	1.55 (3)
Obsessive-compulsive	779 (6.53)	401 (7.64)	219 (6.33)	118 (4.90)	41 (5.39)	5.53 (3)**
Paranoid	339 (2.30)	197 (3.17)	90 (2.02)	39 (1.24)	13 (1.34)	7.84 (3)***
Schizoid	286 (2.20)	157 (2.83)	73 (1.80)	49 (1.77)	7 (1.13)	4.60 (3)**
Histrionic	105 (0.70)	59 (0.89)	29 (0.67)	11 (0.39)	6 (0.58)	3.13 (3)*
Schizotypal	364 (2.40)	222 (3.53)	74 (1.53)	53 (1.69)	15 (1.05)	11.97 (3)***
Narcissistic	566 (3.91)	303 (4.90)	148 (3.43)	88 (2.95)	27 (2.61)	5.95 (3)**
Any cluster A	809 (5.56)	458 (7.52)	200 (4.40)	121 (4.03)	30 (2.75)	15.10 (3)***
Any cluster B	1013 (7.51)	579 (10.17)	265 (6.57)	137 (4.75)	39 (3.93)	20.42 (3)***
Any cluster C	890 (7.36)	471 (8.87)	242 (6.89)	131 (5.34)	46 (5.97)	7.97 (3)***
Any personality disorder	1913 (14.53)	1018 (18.14)	519 (13.24)	294 (10.36)	88 (10.67)	20.49 (3)***
Number of mental disorders (mean, SE)		0.84 (0.02)	0.50 (0.02)	0.36 (0.02)	0.30 (0.03)	Wald F=108.32***
Mental health-related quality of life (mean, SE)		52.12 (0.18)	52.99 (0.20)	51.93 (0.24)	50.89 (0.52)	Wald F=7.09***

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

We analyzed data using SUDAAN 10.0.1 (30), which employs the Taylor Series Linearization method (31) for variance estimation to account for the complex sampling design of the NESARC. We applied appropriate weighting and stratification variables to these data to ensure generalizability to the U.S. adult population. The statistical weights adjusted the data for socio-demographic variables, response/non-response, and oversampling of Blacks and Hispanics based on the 2000 Census.

RESULTS

Table 1 presents cross-tabulations and results of chi-square analyses of socio-demographic characteristics and weighted DSM-IV prevalence of any past-year mood, anxiety, and substance use disorder, and any lifetime personality disorder. The prevalence of disorders differed significantly by gender, ethnicity, education, household income, and marital status. Specifically, women had significantly higher rates of

Table 3 Odds ratios of having a diagnosis of any DSM-IV past-year mood, anxiety, and substance use disorder and any lifetime personality disorder among young-old, middle-old, and old-old adults compared to the oldest-old (85+) reference group

	Unadjusted odds ratios (95% CI)			Adjusted odds ratios (95% CI)		
	Young-old (55-64) adults	Middle-old (65-74) adults	Old-old (75-84) adults	Young-old (55-64) adults	Middle-old (65-74) adults	Old-old (75-84) adults
Any mood disorder	2.25 (1.54-3.28)***	1.36 (0.92-2.02)	1.06 (0.68-1.67)	4.11 (2.77-6.10)***	2.01 (1.35-2.99)***	1.30 (0.82-2.05)
Any anxiety disorder	2.26 (1.65-3.09)***	1.36 (0.98-1.87)	1.19 (0.84-1.68)	3.38 (2.43-4.70)***	1.77 (1.26-2.47)**	1.38 (0.97-1.97)
Any substance use disorder	41.96 (10.42-168.96)***	17.14 (4.05-72.60)***	11.47 (2.73-48.15)**	38.09 (9.62-150.85)***	16.49 (3.95-68.88)***	11.23 (2.71-46.62)**
Any personality disorder	1.85 (1.36-2.52)***	1.27 (0.92-1.74)	0.96 (0.69-1.36)	2.25 (1.63-3.09)***	1.44 (1.04-1.99)*	1.03 (0.73-1.45)

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

any past-year mood and anxiety disorder, whereas men had significantly higher rates of any past-year substance use disorder and any lifetime personality disorder.

Table 2 shows weighted prevalences of DSM-IV psychiatric disorders among subgroups of older adults aged 55+. The prevalence of any past-year mood disorder was 6.8%, the most prevalent of which was major depression (5.6%). A higher proportion of older adults reported any past-year anxiety disorder (11.4%), the most prevalent of which was specific phobia (5.8%). The prevalence of any past-year substance use disorder among older adults was 3.8%. A total of 14.5% of older adults met criteria for at least one personality disorder, the most prevalent of which was obsessive-compulsive personality disorder (6.5%).

Chi-square analyses indicated that, with the exception of dependent personality disorder, all past-year and lifetime psychiatric disorders differed significantly across late-life age groups. We observed an overall pattern of decreasing rates of mood, anxiety, substance use, and personality disorders with increasing age. We noted slight, non-significant upturns in prevalence rates of past-year major depression, dysthymia, generalized anxiety disorder, and any drug abuse/dependence as well as several lifetime personality disorders from ages 75-84 to ages 85+. The mean number of psychiatric disorders decreased significantly throughout the older adult lifespan, with adults aged 55-64 having the highest number of comorbid disorders. There was a significant difference in mental health-related quality of life across late-life age groups, with a pattern of higher quality of life among adults aged 55-74, and lower quality of life among adults aged 75-85+.

Table 3 presents unadjusted and adjusted logistic regression models examining odds ratios of any DSM-IV past-year mood, anxiety, and substance use disorder and any lifetime personality disorder. Results of these analyses revealed that, as age increased, the odds of mood, anxiety, substance use, and personality disorders decreased. This relationship was especially pronounced for young-old (55-64) and middle-old adults (65-74), who, in adjusted models, had significantly greater odds of having any past-year mood disorder, anxiety disorder, and substance use disorder, and any lifetime personality disorder compared to the oldest-old adult age group (85+).

Table 4 displays weighted prevalence estimates of DSM-IV past-year psychiatric disorders by gender and late-life age group. Across the older adult lifespan, from the ages of 55 to 84, women had higher prevalence rates of past-year mood and anxiety disorders. Men had higher rates of all past-year substance use disorders across this age range in addition to any personality disorder. We observed an overall pattern of narrowing gender differences in the prevalence of psychiatric disorders with increasing age. Figure 1 illustrates this pattern for any past-year mood and anxiety disorders. When examining the oldest-old (85+) age group, the previously observed gender differences in prevalence estimates among adults ages 55-84 dissipated, and in some cases, reversed. Specifically, for adults 85 years and older, men had higher prevalence rates of all past-year mood disorders, as well as past-year PTSD and any anxiety disorder.

DISCUSSION

To the best of our knowledge, this is the largest and most comprehensive study of the prevalence of psychiatric disorders in U.S. older adults to date. The large sample size allowed us to examine, for the first time, gender differences in the prevalence of psychiatric disorders across older adult age groups. The primary contribution of this paper is that it supports the view that disorders become less prevalent across age among older adults, with a leveling off among the oldest age group and a narrowing of gender differences with increasing age.

Our findings regarding the prevalence of psychiatric disorders among older adults are consistent with previous research (15,32). Our pattern of results demonstrating a decrease in the prevalence of psychiatric disorders across the older adult lifespan is supported by previous epidemiological research showing a decrease in psychiatric disorders across both the adult lifespan and specifically among late-life age groups (11-15). However, to the best of our knowledge, the current study is the first to identify a leveling off in

Table 4 Prevalence of DSM-IV psychiatric disorders by gender among adults aged 55 years and older

	Total N (weighted %)		55–64 N (weighted %)		65–74 N (weighted %)		75–84 N (weighted %)		85+ N (weighted %)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Mood disorders										
Major depression	197 (3.62)	554 (7.27)	110 (4.59)	310 (10.05)	44 (2.36)	140 (6.38)	31 (2.93)	76 (4.55)	12 (4.70)	28 (3.98)
Dysthymia	40 (0.61)	98 (1.20)	22 (0.82)	65 (1.83)	6 (0.31)	21 (0.97)	8 (0.41)	9 (0.64)	4 (1.37)	3 (0.45)
Mania or hypomania	69 (1.42)	138 (1.56)	45 (2.09)	86 (2.44)	15 (1.00)	34 (1.47)	7 (0.47)	16 (0.57)	2 (1.27)	2 (0.09)
Any mood disorder	248 (4.49)	666 (8.64)	142 (5.84)	376 (12.00)	58 (3.16)	170 (7.72)	36 (3.24)	92 (5.37)	12 (4.70)	28 (3.98)
Anxiety disorders										
Panic disorder	47 (1.01)	138 (1.62)	33 (1.60)	87 (2.41)	8 (0.49)	26 (1.25)	4 (0.49)	19 (0.97)	2 (0.63)	6 (0.80)
Social phobia	66 (1.23)	139 (1.62)	40 (1.80)	89 (2.45)	14 (0.80)	28 (1.31)	11 (0.81)	17 (0.85)	1 (0.09)	5 (0.70)
Specific phobia	185 (3.75)	581 (7.46)	113 (5.34)	319 (9.99)	43 (2.47)	157 (6.88)	22 (2.04)	84 (5.12)	7 (3.12)	21 (3.12)
Generalized anxiety disorder	88 (1.51)	265 (3.85)	54 (2.10)	152 (5.26)	20 (1.01)	64 (3.32)	10 (0.82)	35 (2.47)	4 (1.64)	14 (2.49)
Post-traumatic stress disorder	140 (2.38)	344 (4.38)	82 (3.12)	199 (6.12)	30 (1.47)	79 (3.79)	21 (1.74)	59 (3.20)	7 (3.39)	7 (0.92)
Any anxiety disorder	417 (7.90)	1092 (14.24)	243 (10.76)	588 (18.60)	100 (5.56)	279 (12.61)	56 (4.73)	183 (11.01)	18 (7.51)	42 (6.96)
Substance use disorders										
Alcohol abuse/dependence	326 (6.23)	92 (1.22)	211 (8.96)	72 (2.42)	81 (4.80)	12 (0.43)	32 (3.42)	8 (0.53)	2 (0.16)	0 (0.00)
Any drug abuse/dependence	33 (0.65)	17 (0.24)	29 (1.24)	13 (0.46)	3 (0.22)	4 (0.17)	0 (0.00)	0 (0.00)	1 (0.29)	0 (0.00)
Any substance use disorder	345 (6.62)	105 (1.40)	227 (9.64)	81 (2.72)	83 (5.00)	16 (0.60)	32 (3.42)	8 (0.53)	3 (0.45)	0 (0.00)
Nicotine dependence	534 (11.09)	589 (7.82)	349 (16.39)	361 (11.80)	146 (9.46)	164 (7.70)	34 (3.20)	56 (3.12)	5 (2.11)	8 (0.96)
Personality disorders										
Borderline	195 (3.33)	254 (3.03)	116 (4.71)	162 (4.62)	49 (2.51)	57 (2.56)	25 (1.70)	28 (1.49)	5 (1.66)	7 (0.95)
Antisocial	142 (3.16)	34 (0.40)	91 (4.52)	28 (0.78)	38 (2.80)	5 (0.15)	11 (1.14)	1 (0.20)	2 (0.37)	0 (0.00)
Avoidant	47 (0.93)	125 (1.60)	30 (1.28)	81 (2.59)	13 (0.91)	25 (0.96)	2 (0.20)	13 (0.86)	2 (0.60)	6 (1.01)
Dependent	8 (0.11)	29 (0.38)	6 (0.16)	16 (0.55)	1 (0.03)	7 (0.23)	1 (0.13)	5 (0.31)	0 (0.00)	1 (0.29)
Obsessive-compulsive	335 (7.06)	444 (6.10)	173 (7.78)	228 (7.50)	89 (6.51)	130 (6.19)	58 (6.43)	60 (3.80)	15 (5.94)	26 (5.11)
Paranoid	116 (2.11)	223 (2.46)	73 (2.96)	124 (3.36)	27 (1.52)	63 (2.42)	13 (0.93)	26 (1.46)	3 (2.28)	10 (0.86)
Schizoid	127 (2.60)	159 (1.87)	66 (2.96)	91 (2.71)	34 (2.18)	39 (1.49)	24 (2.44)	25 (1.29)	3 (2.20)	4 (0.58)
Histrionic	47 (0.73)	58 (0.67)	30 (0.96)	29 (0.82)	9 (0.46)	20 (0.84)	5 (0.51)	6 (0.30)	3 (1.04)	3 (0.34)
Schizotypal	158 (2.49)	206 (2.32)	102 (3.81)	120 (3.27)	40 (1.89)	34 (1.25)	14 (0.84)	39 (2.30)	2 (0.18)	13 (1.50)
Narcissistic	299 (5.49)	267 (2.61)	162 (6.85)	141 (3.07)	80 (4.87)	68 (2.26)	43 (3.36)	45 (2.66)	14 (4.94)	13 (1.41)
Any cluster A	338 (5.95)	471 (5.24)	198 (7.92)	260 (7.14)	88 (4.69)	112 (4.16)	45 (3.94)	76 (4.09)	7 (2.88)	23 (2.68)
Any cluster B	525 (9.99)	488 (5.47)	291 (12.85)	285 (7.53)	145 (8.78)	117 (4.59)	68 (5.72)	68 (4.01)	21 (7.17)	18 (2.25)
Any cluster C	361 (7.58)	529 (7.17)	190 (8.54)	281 (9.18)	98 (7.09)	144 (6.72)	58 (6.43)	73 (4.56)	15 (5.94)	31 (5.98)
Any personality disorder	868 (16.79)	1045 (12.68)	466 (20.26)	550 (16.09)	240 (15.05)	276 (11.58)	126 (11.71)	167 (9.35)	36 (14.53)	52 (8.66)
Number of mental disorders (mean, SE)			0.84 (0.04)	0.85 (0.03)	0.48 (0.03)	0.52 (0.03)	0.34 (0.03)	0.37 (0.03)	0.38 (0.07)	0.26 (0.03)

the prevalence of specific psychiatric disorders among the oldest-old age group.

The overall pattern of decreased rates of psychiatric disorders with increased age can be explained by the socioemotional selectivity theory (SST) (33), and the leveling off in prevalence rates among adults aged 85 and older can be explained by the strength and vulnerability integration theory (SAVI) (34). SST posits that older adults adopt a limited perception of time and a present-focused state of awareness, seek the fulfillment of emotionally meaningful goals, and select the company of familiar social partners, which decreases the likelihood that stressful social situations will occur, and increases the likelihood of experiencing positive emotions (33). Building on the components of SST, SAVI suggests a pattern of increased positivity and well-being until approximately the late 60s and a slight decrease thereafter (34). The slight decrease in well-being may be attributable to older adults' decreased physiological tolerance to

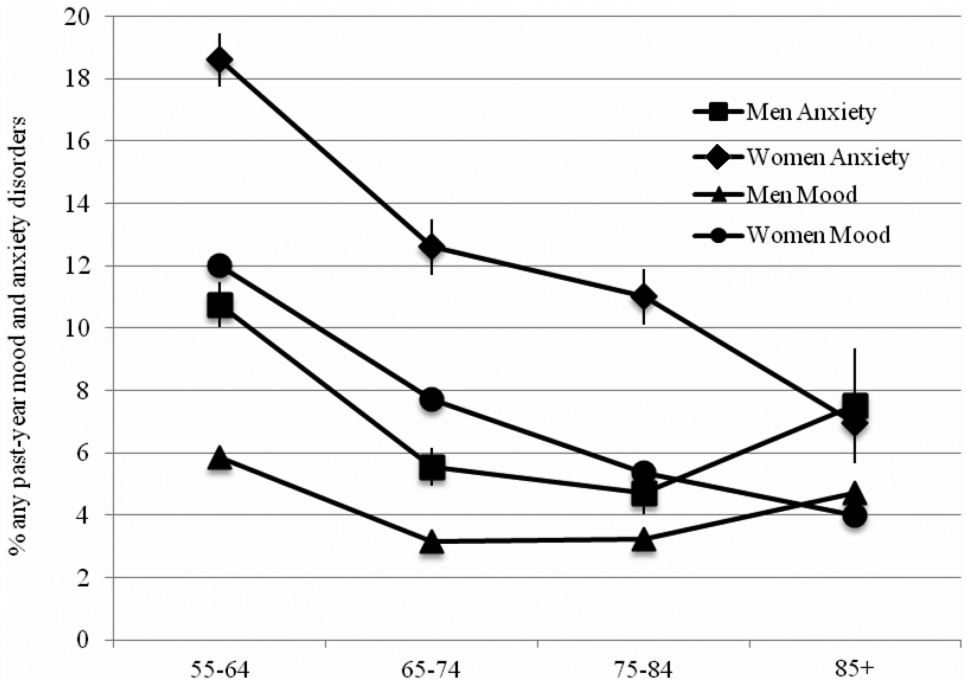

Figure 1 Percentage of respondents with any past-year mood disorder and any past-year anxiety disorder by age group and gender. Error bars represent 95% confidence intervals

stress, which can result in compromised immune functioning when strategies associated with the aforementioned strengths are not applied successfully (34). These theories support the pattern of results observed in this study whereby prevalence rates of psychiatric disorders decline throughout the late-life span, until approximately the age of 85+, where a slight, albeit non-significant increase in prevalence of several psychiatric disorders was observed. Given medical advances and increases in life expectancy rates, it is possible that the vulnerabilities described in SAVI are occurring at a later age for older adults. It could also be the case that older adults who are experiencing more of the vulnerabilities of old age do not participate in survey research such as the NESARC due to illness and institutionalization.

SST and SAVI support the current study's finding of decreased mental health-related quality of life among older adults aged 75-85+. The pattern of narrowing gender differences in the prevalence of psychiatric disorders with increasing age can also be explained by SAVI, with both genders experiencing similar vulnerabilities with increasing age. Furthermore, the decreased gender gap in life expectancy suggests that more men are now living into older age, increasing the likelihood that they will experience the vulnerabilities of old age.

Results of this study must be viewed in light of several limitations. First, the NESARC is a survey of community-dwelling individuals and our findings do not generalize to institutionalized older adults. Second, as is typically the case in epidemiologic surveys, psychiatric disorders were not diagnosed using hierarchical rules. As a result, it is possible that prevalence rates were inflated based on DSM-IV criteria. Third, given the recently published DSM-5, the diagnostic criteria for several of the DSM-IV psychiatric disorders examined in the current study have been modified to various extents. The most prominent change that may affect current findings is the removal of PTSD from the anxiety disorders category and its inclusion in the revised trauma and stress-related disorders category, which would affect our prevalence estimate for any anxiety disorder.

Notwithstanding these limitations, findings of this study make a unique contribution to the literature by highlighting the prevalence of mood, anxiety, substance use, and personality disorders in addition to mental health-related quality of life across the older adult lifespan, and by examining differences in prevalence of these disorders by late-life age groups and gender. Given the relatively high rates of psychiatric disorders among older adults and the leveling off in prevalence rates in older adults ages 85+, these results underscore the importance of prevention, diagnosis, and treatment of psychiatric disorders in this population.

Future research is needed to further examine the reasons why the prevalence of psychiatric disorders decreases across late-life age groups. Moreover, additional research is needed to examine gender-specific psychiatric comorbidity profiles, as well as to develop and evaluate personalized treatments for the oldest-old age group of adults (85+).

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The development of the ICD-11 Clinical Descriptions and Diagnostic Guidelines for Mental and Behavioural Disorders

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The World Health Organization is in the process of preparing the eleventh revision of the International Classification of Diseases (ICD-11), scheduled for presentation to the World Health Assembly for approval in 2017. The International Advisory Group for the Revision of the ICD-10 Mental and Behavioural Disorders made improvement in clinical utility an organizing priority for the revision. The uneven nature of the diagnostic information included in the ICD-10 Clinical Descriptions and Diagnostic Guidelines (CDDG), especially with respect to differential diagnosis, is a major shortcoming in terms of its usefulness to clinicians. Consequently, ICD-11 Working Groups were asked to collate diagnostic information about the disorders under their purview using a standardized template (referred to as a "Content Form"). Using the information provided in the Content Forms as source material, the ICD-11 CDDG are being developed with a uniform structure. The effectiveness of this format in producing more consistent clinical judgments in ICD-11 as compared to ICD-10 is currently being tested in a series of Internet-based field studies using standardized case material, and will also be tested in clinical settings.

Key words: ICD-11, Clinical and Diagnostic Guidelines, clinical utility, Internet-based field studies

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The International Classification of Diseases and Related Health Problems (ICD), which is the international standard for health reporting and health information, is currently in its tenth revision (ICD-10). The World Health Organization (WHO) is in the process of preparing the eleventh revision (ICD-11), scheduled for presentation to the World Health Assembly for approval in 2017. By international treaty, WHO is assigned the responsibility "to establish and revise as necessary international nomenclatures of diseases, of causes of death and of public health practices" and "to standardize diagnostic procedures as necessary" (1). Within the context of WHO policies and procedures for the overall ICD revision, the WHO Department of Mental Health and Substance Abuse has technical responsibility for coordinating the development of the Chapter on Mental and Behavioural Disorders in ICD-11.

The purpose of this paper is to describe the guidance that the Department of Mental Health and Substance Abuse has provided to Working Groups engaged in the ICD-11 revision process, the priorities lying behind that guidance, the procedures implemented by the Department to help the revision process achieve its goals, and the nature of the diagnostic guidance that will be provided to health care professionals as a part of the Clinical Descriptions and Diagnostic Guidelines (CDDG) for ICD-11 Mental and Behavioural Disorders.

Disease classifications have been applied to a large and growing number of purposes, which can be grouped roughly into three major clusters: a) clinical uses; b) public health uses, including provision of a basis for health statistics and a shared language for health policy; and c) disease-related research. Addressing the central clinical purposes of a disease classification, and building on earlier work (2), the WHO has offered the following working definition of clinical utility: "the clinical utility of a classification construct or category for mental and behavioural disorders depends on: a) its value in communicating (e.g., among practitioners, patients, families, administrators); b) its implementation characteristics in clinical practice, including its goodness of fit (i.e., accuracy of description), its ease of use, and the time required to use it (i.e., feasibility); and c) its usefulness in selecting interventions and in making clinical management decisions" (3, p. 461).

On the basis of comments received, structured surveys of practitioners, and input from diverse professional organizations whose members treat individuals with mental and behavioural disorders, the International Advisory Group for the Revision of the ICD-10 Mental and Behavioural Disorders concluded that there was room for significant improvements in clinical utility and that these deserved to be a major guiding principle for the revision process (3,4). Moreover, in light of the rapidly changing state of scientific approaches to mental and behavioural disorders (5-7), the Advisory Group concluded that the revision must take into account well-validated and well-replicated results where they existed, but that it was premature to make still embryonic scientific understandings the major drivers of specific disease definitions. In short, clinical utility deserved to be an organizing priority for the revision so long as it did not sacrifice validity as established by the best available science.

To put the revision process in context, we begin this essay with a brief overview of ICD-10 Chapter on Mental and Behavioural Disorders, approved by the World Health Assembly in 1992. Notably, the time interval between the

ICD-10 and ICD-11 revisions will have been the longest between ICD revisions since the process first began in the late 19th century. Unlike the other chapters in the ICD classification, which confined their content exclusively to the names of disorders plus inclusion and exclusion terms, a glossary of terms was developed in 1974 (8) to accompany the eighth revision of the ICD (ICD-8) (9), approved in 1966. As the introduction to the glossary states, "guidance to the... [mental disorders chapter] of ICD-8 has been added in the form of a glossary because it has become increasingly obvious that many key psychiatric terms are acquiring different meanings in different countries [and] unless some attempt is made to encourage uniformity of usage of descriptive and diagnostic terms, very little meaning can be attributed to the diagnostic side of statistics of mental illness based on the ICD and in many other ways communication between psychiatrists will become increasingly difficult" (8, p. 12).

The version of the ICD-10 that WHO member countries agree to use as the basis for reporting of health statistics is called the International Statistical Classification of Diseases and Related Health Problems (10) and is split into three volumes. Volume 1, known as the "tabular list", contains a listing of all of the medical conditions included in ICD-10 in alphanumerical order, ranging from A00 to Z99. In this statistical version of the ICD-10, none of the diagnostic codes go beyond the fourth character (e.g., F31.0), with each character corresponding to a hierarchical level of the classification. For example, in the code F31.0, the "F" corresponds to Mental and Behavioural Disorders, "F3" corresponds to Mood (Affective) Disorders, the "F31" to Bipolar Affective Disorder, and "F31.0" to Bipolar Affective Disorder, Current Episode Hypomanic.

From the perspective of the WHO Department of Mental Health and Substance Abuse, different versions of the ICD-10 Classification of Mental and Behavioural Disorders were necessary to meet the needs of its various users. The ICD-10 statistical version of the classification contains short glossary-like definitions for each mental and behavioural disorder category, but "is not recommended for use by mental health professionals" and instead is intended for use by "coders or clerical workers and also serves as a reference point for compatibility with other classifications" (11, p. 1). For mental health professionals, the Department developed the CDDG for ICD-10 Mental and Behavioural Disorders (11), often referred to as the "blue book" because of its blue cover, which is "intended for general clinical, educational, and service use" (11, p. 1). For each disorder, a description of the main clinical and associated features is provided, followed by more operationalized diagnostic guidelines that are designed to assist mental health clinicians in making a confident diagnosis.

In addition, the CDDG add greater diagnostic specificity through more detailed categories not included in the statistical version of the classification, represented by 5th character codes. For example, 5th character codes are used to describe complications of acute substance intoxication (e.g., with trauma or other bodily injury, with delirium) and the course of schizophrenia (e.g., episodic with progressive deficit, incomplete remission). National modifications of the ICD-10 intended for use in clinical systems (e.g., the ICD-10-GM, the German Modification, or the ICD-10-CM, Clinical Modification for the United States) often also include these same 5th character codes, and in some cases assign alternative or additional 5th and even 6th character codes to provide additional specificity for local clinical use.

The WHO Department of Mental Health and Substance Abuse also developed Diagnostic Criteria for Research (DCR) (12) (the "green book"), with specified, operationalized diagnostic criteria for each ICD-10 category that were "deliberately restrictive" to allow for the "selection of groups of individuals whose symptoms and other characteristics resemble each other in clearly stated ways" (12, p. 1). Consequently, in contrast to the CDDG, which are designed to allow for cultural variability and clinical judgment, the DCR imposed fixed symptom thresholds (e.g., "at least four of the following") and frequency/duration requirements (e.g., "at least twice a week for 3 months").

The differences between the CDDG and the DCR reflect the different purposes of these two versions of the classification. In clinical settings, the function of the classification is to help the clinician to find the category that is most likely to provide relevant information for treatment and management. Arbitrary or non-consequential exclusion criteria are problematic because they increase false negatives, leaving the clinician with little guidance; as a result their use is minimized in the CDDG. The DCR, on the other hand, had the goal of identifying research populations that were more homogeneous in terms of underlying pathophysiology or treatment response (e.g., for clinical trials). Unfortunately, given limitations in the state of knowledge, such as the lack of biomarkers, narrow disorder definitions based on operationalized criteria (e.g., requirements for a specific frequency or duration of symptoms) have not, to date, improved homogeneity in these ways (13).

The third version of the ICD-10 Classification of Mental and Behavioural Disorders, intended for use in primary care (14), contains only 26 disorders, achieved in part by excluding rarely diagnosed disorders and in part by lumping disorders that are narrowly drawn in the other versions of the classification and that have similar management needs. It includes for each disorder presenting complaints, diagnostic features, differential diagnoses, and management guidelines.

DIAGNOSTIC GUIDELINES IN ICD-10

Each of the broad disorder groupings, or blocks, within the ICD-10 CDDG begins with an introductory section explaining the scope of what is contained within the block and general principles that apply to all of the disorders within it.

The diagnostic information included for each disorder is generally divided into three sections. The first section

contains a description of the main clinical features as well as "any important but less specific associated features". The second section consists of "Diagnostic Guidelines", which are provided to "indicate the number and balance of symptoms usually required before a confident diagnosis can be made". Although statements about the duration of symptoms are often included (e.g., the diagnostic guidelines for schizophrenia state that "symptoms. . . should have been clearly present for most of the time during a period of 1 month or more") (11, p. 88), the introduction to the CDDG notes that such statements are "intended as general guidelines rather than strict requirements; clinicians should use their own judgment about the appropriateness of choosing diagnoses when the duration of particular symptoms is slightly longer or shorter than that specified" (11, p. 2). The third section, "Differential Diagnosis", indicates other ICD-10 disorders that need to be distinguished from the disorder being described.

One factor potentially compromising the clinical utility of the ICD-10 CDDG is the variability of information in terms of both form and content across the various groupings and disorders. The Clinical Descriptions vary widely in length and in the scope of information included. Some focus almost entirely on the presenting features, whereas others contain extensive information about course, gender ratio, associated features and comorbidity. Moreover, the absence of headings makes it difficult for the clinician to locate information of particular interest. The Diagnostic Guidelines also vary greatly in terms of their format across the various sections. In some cases, the guidelines closely resemble diagnostic criteria sets, with lists of lettered items provided. Sometimes a minimum number of items is specified for a "definitive" diagnosis (e.g., at least two for Organic Personality Disorder). In many other cases, however, the diagnostic guidelines are presented as a paragraph of text (e.g., for Post-Traumatic Stress Disorder, PTSD), and sometimes are missing altogether (e.g., for Trance and Possession Disorders).

The greatest degree of variability is in the Differential Diagnosis sections. For a small minority of blocks (e.g., F40-F48 Neurotic, Stress-Related, and Somatoform Disorders), there are sections on differential diagnosis for a majority of the disorders. In most other blocks, however, Differential Diagnosis sections have been included for only a small minority of disorders, often on an apparently idiosyncratic basis. For example, the only disorder in F20-F29 (Schizophrenia, Schizotypal, and Delusional Disorders) with a differential diagnosis section is F20.0 Paranoid Schizophrenia, and the only disorder in F30-F39 (Mood Disorders) with a differential diagnosis section is F34.0 Cyclothymia. Moreover, for those disorders that have a Differential Diagnosis section, there is considerable variability in terms of format and content. For many disorders, the section simply includes a list of disorders preceded by the word "Consider" (e.g., all of the disorders in F00-F09 Organic Mental Disorders), whereas for others there are paragraph-long discussions (e.g., the differential diagnosis for Specific Phobias).

DEVELOPMENT OF THE ICD-11 DIAGNOSTIC GUIDELINES

The uneven nature of the diagnostic information included in the ICD-10 CDDG, especially with regard to the clinically important task of determining a differential diagnosis, has been identified as a major shortcoming in terms of its usefulness to clinicians. This variability in terms of format and content likely reflects the lack of standardized guidance for the preparation of the various sections, each of which was developed by different sets of experts.

Consequently, an initial goal of the ICD-11 CDDG development process was to create a mechanism to ensure consistent and relatively uniform provision of diagnostic information across the various categories. To facilitate this, ICD-11 Working Groups were asked to collate diagnostic information about the disorders under their purview using a standardized template (referred to as a "Content Form") that contained prescribed sections (see Table 1). Because the WHO has final editorial responsibility for the ICD-11 material, the Department of Mental Health and Substance Abuse wanted to ensure that Working Groups understood that they were developing source material that would be used as a basis for the development of the CDDG as well as other versions of the ICD-11. The Content Form was thus framed in light of these objectives, and was designed to provide a combination of technical, administrative, and clinical information.

Specifically, a number of sections of the Content Form were included in order to meet certain requirements of the overall ICD-11 classification model (i.e., relationship to ICD-10, primary parent category, secondary parent category, "children" or constituent categories, synonyms, functional properties, temporal qualifiers, and severity qualifiers). The sections "primary and secondary parent category" and "children or constituent categories" indicate the position of the category in the ICD-11 hierarchy. For example, the parent category for the diagnostic grouping Body Focused Repetitive Behaviour Disorders is Obsessive-Compulsive and Related Disorders, and its "children" and constituent categories include Excoriation Disorder, Trichotillomania, and Other Body-Focused Repetitive Behaviour Disorder.

The sections "functional properties", "temporal qualifiers" and "severity qualifiers" were also included for technical reasons. Ideally, mental disorders should be defined in terms of symptoms and not include activity limitations or participation restrictions, which should be classified using WHO's International Classification of Functioning, Disability and Health (15). However, given that for mental disorders it is sometimes necessary to use functional status to set the threshold with normality (e.g., the diagnostic threshold for phobias depends on the extent to which they impact the patient's functioning) (4), the "functional properties" section is used to indicate the rationale for using functional limitations in the diagnostic definition. The sections for temporal and severity qualifiers are used only in situations where a temporal term (e.g., "chronic") or a severity term

Table 1 Content Form used by ICD-11 Working Groups

I. Category Name
II. Relationship to ICD-10
A. Equivalent ICD-10 Alphanumeric Code and Category Name
B. Relationship of Proposed Category to ICD-10 (select one by circling number)
1. Same category name as ICD-10; no or minor changes in concept
2. Same category name as ICD-10; substantive changes in concept
3. New category name; no or minor changes in concept
4. New category name; substantive changes in concept
5. New category (does not exist in ICD-10)
III. Primary "Parent" Category
IV. Secondary "Parent" Categories
V. "Children" or Constituent Categories
VI. Synonyms
VII. Definition
VIII. Diagnostic Guidelines
IX. Functional Properties (if applicable)
X. Temporal Qualifiers (if applicable)
XI. Severity Qualifiers (if applicable)
XII. Differential Diagnosis
XIII. Differentiation from Normality
XIV. Developmental Presentations
XV. Course Features
XVI. Associated Features and Comorbidities (as known and relevant)
A. Associated symptoms and psychiatric disorders
B. Associated physical symptoms and medical conditions
C. Associated laboratory findings
D. Associated functional limitations and restrictions
XVII. Culture-Related Features
XVIII. Gender-Related Features
XIX. Assessment Issues
Additional References (not already included in above sections)

(e.g., "severe") is used as part of the disorder name. In such situations, these sections serve to provide a definition for the term. The remaining sections of the Content Form contain diagnostic information that is used as the basis for the ICD-11 CDDG for the disorder, with relevant references.

ELEMENTS OF THE ICD-11 CLINICAL DESCRIPTIONS AND DIAGNOSTIC GUIDELINES

Using the information provided in the Content Form as source material, ICD-11 CDDG are being developed by the WHO in consultation with the Working Groups according to a uniform structure. The structure is intended to enhance the clinical utility of ICD-11 CDDG by making it easier for users to locate information of interest and by ensuring that the amount and type of information provided for each disorder would be consistent across the manual. A summary of the categories of information to be provided for each category in the CDDG appears in Table 2. Each of these sections is discussed in detail below, accompanied by the corresponding section from the proposed ICD-11 CDDG for PTSD (16) as an illustrative example.

Definition

The definition of the disorder serves as a summary statement of the common essential features and is roughly 100 to 125 words in length. It will appear in the statistical versions of ICD-11. For example, the definition proposed for PTSD (Table 3, upper portion) is a summarized version of the PTSD essential features (Table 3, lower portion).

Essential (required) features

This section serves to provide relatively explicit guidance regarding the essential features needed to confidently make the diagnosis. The essential features represent those symptoms or characteristics that a clinician could reasonably expect to find in all cases of the disorder. While these lists of essential features superficially resemble diagnostic criteria in their overall format, for the most part they lack the specific and arbitrary duration thresholds and "pick lists" of items that characterize the diagnostic criteria sets in DSM-5 and the ICD-10 DCR. Instead, these diagnostic guidelines are intended to conform to the way clinicians actually make psychiatric diagnosis, i.e., with the flexible exercise of clinical judgment.

Table 2 Standard format for ICD-11 Clinical Descriptions and Diagnostic Guidelines

Category Name
Brief Definition (100 - 125 words)
Inclusion Terms
Exclusion Terms
Essential (Required) Features
Boundary with Normality (Threshold)
Boundary with Other Disorders (Differential Diagnosis)
Coded Qualifiers/Subtypes
Course Features
Associated Clinical Presentations
Culture-Related Features
Developmental Presentations
Gender-Related Features

Table 3 Proposed ICD-11 Clinical Descriptions and Diagnostic Guidelines for Post-Traumatic Stress Disorder (PTSD): definition and essential features

Definition

Post-Traumatic Stress Disorder (PTSD) is a disorder that develops following exposure to an extremely threatening or horrific event or series of events characterized by: 1) re-experiencing the traumatic event(s) in the present in the form of vivid intrusive memories, flashbacks, or nightmares, typically accompanied by strong and overwhelming emotions such as fear or horror, and strong physical sensations; 2) avoidance of thoughts and memories of the event(s), or avoidance of activities or situations reminiscent of the event(s); and 3) persistent perceptions of heightened current threat, for example as indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises. The symptoms must last for at least several weeks and cause significant impairment in personal, family, social, educational, occupational or other important areas of functioning.

Essential features

- Exposure to an event or situation (either short- or long-lasting) of an extremely threatening or horrific nature. Such events include, but are not limited to, natural or human-made disasters; combat; serious accidents; torture; sexual violence; terrorism; assault; acute life-threatening illness (such as a heart attack); witnessing the threatened or actual injury or death of others in a sudden, unexpected, or violent manner; and experiencing the sudden, unexpected or violent death of a loved one.
- Following the traumatic event or situation, the development of a characteristic syndrome lasting for at least several weeks, consisting of three core elements:
  1. Re-experiencing the traumatic event in the present, in which the event(s) is not just remembered but is experienced as occurring again in the here and now. This typically occurs in the form of vivid intrusive images or memories; flashbacks, which can vary from mild (there is a transient sense of the event occurring again in the present) to severe (there is a complete loss of awareness of present surroundings); or repetitive dreams or nightmares that are thematically related to the traumatic event(s). Re-experiencing is typically accompanied by strong or overwhelming emotions, such as fear or horror, and strong physical sensations. Re-experiencing in the present can also involve feelings of being overwhelmed or immersed in the same intense emotions that were experienced during the traumatic event, and may occur in response to reminders of the event. Reflecting on or ruminating about the event(s) and remembering the feelings that one experienced at that time do not constitute re-experiencing.
  2. Deliberate avoidance of reminders likely to produce re-experiencing of the traumatic event(s). This may take the form either of active internal avoidance of relevant thoughts and memories, or external avoidance of people, conversations, activities, or situations reminiscent of the event(s). In extreme cases the person may change his or her environment (e.g., move to a different city or change jobs) to avoid reminders.
  3. Persistent perceptions of heightened current threat, for example as indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises. Hypervigilant persons constantly guard themselves against danger and feel themselves or others close to them to be under immediate threat either in specific situations or more generally. They may adopt new behaviours designed to ensure safety (e.g., only sit in certain places on trains, repeatedly check in vehicles' rear-view mirror).
- The disturbance causes significant impairment in personal, family, social, educational, occupational or other important areas of functioning. If functioning is maintained only through significant additional effort, or is significantly impaired in comparison with the individual's prior functioning or what would be expected, then he or she would be considered impaired due to the disturbance.

Artificially precise language has generally been avoided through the use of phrases such as "including", "characterized by", or "usually", to indicate that some number of symptoms from the list should be present but that the precise number is best left to the clinician's judgment. Such flexibility in language allows the clinician to differentially weigh those symptoms that are particularly severe and impairing, which is generally not possible in operationalized criteria sets because of the complexity this would require. Moreover, an effort has been made to order the essential features according to their importance to the diagnosis.

Although for most disorders setting requirements for a minimum number of symptoms is generally avoided, in some cases symptom thresholds are provided if they have been empirically established or there is another compelling reason for such a threshold. For example, the diagnosis of schizophrenia as proposed for ICD-11 requires the presence of at least two of seven symptoms for a period of at least one month. In contrast, the proposed essential features section for PTSD (Table 3, lower portion) does not include a specific duration requirement, nor does it include complex lists of symptoms with precise cut-offs.

Boundary with normality

This section provides the clinician with diagnostic guidance regarding the differentiation of normal variation in characteristics that may underlie or be similar to the disorder and conditions that are considered to be psychopathological (see Table 4, upper portion).

Strategies for setting this threshold include specifying those aspects of the disorder that are indicative of its pathological nature and indicating typical false positives (i.e., clinical presentations that would be considered non-pathological). For many disorders (e.g., Generalized Anxiety Disorder), the presence of functional impairment or distress is required to make this distinction. In these cases, the rationale for this has been explicitly provided in the "functional properties" section of the Content Form, as described above (see Table 1).

Boundary with other conditions (differential diagnosis)

This section indicates those disorders that should be considered in the differential diagnosis, particularly other dis-

Table 4 Proposed ICD-11 Clinical Descriptions and Diagnostic Guidelines for Post-Traumatic Stress Disorder (PTSD): boundaries with normality and other conditions

Boundary with normality

- A history of exposure to an event or situation of an extremely threatening or horrific nature does not in itself indicate the presence of PTSD. Many people experience such stressors without developing a disorder. Rather, the presentation must meet the above diagnostic requirements of the disorder.
- Normal acute reactions to traumatic events can show all the symptoms of PTSD including re-experiencing, but these begin to subside fairly quickly (e.g., within one week) after the event terminates or removal from the threatening situation. If clinical intervention is warranted in these situations, assignment of the category Acute Stress Reaction from the chapter on Factors Influencing Health Status and Encounters with Health Services (i.e., a non-disorder category) is generally most appropriate.
- PTSD symptoms may also be observed in situations where the stress is continuing and removal is not possible (e.g., war). Under these conditions, PTSD can be differentiated from normal chronic stress reactions by slow, limited, or lack of adaptation to the stressful situation and the presence of a substantially greater degree of continuing distress and interference with functioning.

Boundary with other conditions

- In **Complex PTSD**, people have symptoms that meet the definitional requirements of PTSD plus the added elements of sustained and pervasive difficulties in emotion regulation, negative beliefs about self, and interpersonal functioning.
- Unlike **Adjustment Disorder**, which can persist for up to six months after stressors of any severity, PTSD can only be diagnosed if the individual has been exposed to a severe, usually life-threatening, stressor and presents with the three core PTSD symptoms.
- In some cases, situational or conditioned **specific phobias** can arise after being exposed to a traumatic event but PTSD and phobias can be differentiated particularly by the absence of re-experiencing. Although in phobic responses there may be powerful memories of the event in response to which the individual experiences anxiety, the memories are experienced as belonging to the past.
- In PTSD, **panic attacks** can be triggered by reminders of the traumatic event(s) or in the context of re-experiencing. The presence of panic attacks that occur entirely in the context of event reminders or re-experiencing does not warrant an additional, separate diagnosis.
- In a **Depressive Episode**, intrusive memories are not experienced as occurring again in the present, but as belonging to the past, and they are often accompanied by rumination. However, Depressive Episodes commonly co-occur with PTSD; if the definitional requirements are met for both, both conditions should be diagnosed.
- In PTSD, as opposed to **Schizophrenia Spectrum and Other Primary Psychotic Disorders**, the hallucinatory experiences and delusional beliefs are limited to flashbacks or episodes of re-experiencing related to an identifiable traumatic event.

orders that share presenting symptoms or features. For each of these disorders, the features that serve to differentiate it from the index disorder are described. That is, this section is not simply a list of disorders that should be distinguished from the disorder being described, but rather provides guidance to the clinician about how to make this differentiation. Moreover, as illustrated in the PTSD example in the lower portion of Table 4, if a disorder can be diagnosed concurrently, the circumstances in which this is permitted are elucidated.

Course features

This section of the guidelines provides clinically relevant information regarding the typical course of the disorder, which is defined broadly to include information about age of onset, whether the disorder is persistent or episodic, duration, its likely progression (or remission) over time, and its temporal relationship to life stressors and other disorders (see Table 5, upper portion).

Associated features

Associated features are not part of the essential characteristics of the disorder, because they are not diagnostically determinative, but are so frequently associated with the disorder that they help the clinician recognize the variations in its presentation (see Table 5, lower portion). This section is also used for alerting the clinician to the likelihood that certain clinically important associated symptoms and/or disorders may be present which may require their own assessment and treatment.

Culture-related features

This section provides brief information regarding cultural considerations in making the diagnosis (see Table 6, upper portion). Despite the international nature of the ICD, there was relatively little information about culture-related features in the ICD-10 CDDG.

Developmental presentations

This section describes how symptom presentations may differ according to the developmental stage of the individual, including childhood, adolescence, and older adulthood (see Table 6, lower portion). Many disorders traditionally thought of as "adult disorders" (e.g., depression) can present during childhood. In such instances, the symptom descriptions may be developmentally inappropriate (e.g., children

Table 5 Proposed ICD-11 Clinical Descriptions and Diagnostic Guidelines for Post-Traumatic Stress Disorder (PTSD): course and associated features

Course features

- Onset of PTSD may be gradual or acute. Typically, onset arises soon after the traumatic event (generally within one month to 6 months). However, onset may occur after immediate threats to survival and other life stressors have subsided. In a small number of cases, the diagnostic threshold may not be met for many years after the traumatic event, with clinically significant PTSD symptoms emerging following other life stressors not necessarily associated with the original traumatic event(s).
- The course is often fluctuating and recovery is more common than not. Epidemiological studies suggest that in one third or more of untreated cases, PTSD persists for years, although a briefer pattern may be found where PTSD has arisen in the context of war or large-scale traumatic events.
- Individuals with long-lasting PTSD symptoms may eventually develop Complex PTSD.
- Predisposing factors, including personality traits (e.g., negative affectivity), exposure to previous trauma, or previous history of psychiatric illness, may lower the threshold for the development of PTSD after exposure to a traumatic stressor or aggravate its course.

Associated features

- Common symptom presentations of PTSD may also include general dysphoria, dissociative symptoms, somatic complaints, suicidal ideation and behaviour, social withdrawal, excessive alcohol or drug use to avoid re-experiencing or to manage emotional reactions, and anxiety symptoms (including panic and obsessions/compulsions) in response to trauma memories or reminders of the trauma.
- The emotional experience of people with PTSD commonly includes anger, shame, sadness, humiliation, or guilt, including survivor guilt.
- Common co-occurring conditions include anxiety disorders, depressive disorders, and Substance Dependence or Harmful Use of Substances. The latter may reflect attempts to avoid reminders of the traumatic event(s). Further, prevalence rates of PTSD have been found to be high in individuals diagnosed with Schizophrenia and Bipolar Disorder.
- Somatic complaints such as headache, breathing difficulties and altered somatic perceptions, are common as an aspect of PTSD. PTSD is also associated with increased risk of numerous medical conditions including, but not limited to, circulatory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological disorders, as well as with increased mortality.

with PTSD may repetitively re-enact the trauma in play rather than report "flashbacks") or the disorder may manifest in different ways (e.g., children with depression may present with irritable mood, rather than depressed mood).

Similarly, many if not most disorders that are traditionally thought of as "childhood disorders" can persist into adulthood, with concomitant alterations in their presentation (e.g., Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder). Moreover, the developmental differences across the various stages of childhood (e.g., toddlerhood vs. primary school age vs. adolescence) may also result in varying presentations across the lifespan. Also included in this section are developmental variations that might occur in geriatric patients, among whom mental disorders, especially mood disorders (17), are more likely to be under-diagnosed.

Gender-related features

This section covers gender-related diagnostic issues. These range from gender-linked differences in symptom presentation to gender ratios in terms of prevalence both in the community and in clinical settings.

Table 6 Proposed ICD-11 Clinical Descriptions and Diagnostic Guidelines for Post-Traumatic Stress Disorder (PTSD): culture-related features and developmental presentations

Culture-related features

Culturally sanctioned and recognized expressions or idioms of distress, explanatory beliefs, and cultural syndromes may be a prominent part of the trauma response. They may influence PTSD symptomatology and comorbidity particularly through somatization as well as other emotional, cognitive and behavioural expressions of distress. For example, cultural idioms of distress following exposure to trauma may manifest through somatic symptoms, like ohkumlang (tiredness) and bodily pain among tortured Bhutanese refugees; symptoms like possession states in Guinea Bissau, Mozambique, Uganda, and Bhutanese refugees; susto (fright) among Latino populations; kit chraen (thinking too much) and sramay (flashbacks of past traumas in the form of dreams and imagery that spill over into waking life) in Cambodia. These cultural idioms are not equivalent to PTSD, but influence its presentation and interpretation.

Developmental presentations

PTSD can occur at all ages, but the response can differ depending on the age and developmental stage of the individual. In younger children, responses may include disorganization, agitation, temper tantrums, clinging, excessive crying, social withdrawal, separation anxiety, distrust; trauma-specific reenactments, such as in repetitive play or drawings; night terrors or frightening dreams without clear content; sense of foreshortened future; and impulsivity. Self-injurious or risky behaviours are more frequent in adolescence. Prevalence estimates of PTSD are relatively low in older persons, and low compared to other anxiety disorders in older populations. In general there is a decline in PTSD symptom severity over the life course, although findings on the overall course of PTSD across the lifespan remain inconclusive.

FIELD STUDIES OF PROPOSED ICD-11 DIAGNOSTIC GUIDELINES

The ICD-11 CDDG were developed with the goal of improving clinical utility while maintaining diagnostic reliability. However, whether this is in fact the case remains an empirical question. The WHO is conducting both Internet-based and clinic-based field trials for the mental disorders section of ICD-11, which are designed to investigate both the clinical utility and the diagnostic reliability of the proposed CDDG.

The Internet-based field studies are designed to assess the utility of proposed changes in the diagnostic system, using standardized case material within an experimental design to test whether the ICD-11 CDDG produce more consistent diagnostic behaviour than do the ICD-10 CDDG among a global, multilingual, and multidisciplinary sample of approximately 12,000 mental health professionals from more than 130 countries (see www.globalclinicalpractice.net to register in any of nine languages). Generally, this involves having participants apply either the ICD-10 or ICD-11 CDDG (based on random assignment) to case scenarios validated by multiple experts, so that the participant's adherence to the expert diagnosis can be assessed.

A total of approximately 12 major Internet-based field studies are being conducted in different diagnostic areas. Results available to date indicate superior adherence to ICD-11 CDDG as compared to ICD-10 CDDG, with more consistent diagnostic conclusions across clinicians, countries, and languages, suggesting that the ICD-11 versions are easier to apply and produce more accurate results.

While the Internet-based field studies represent the best and most efficient method for testing the proposed CDDG using a large sample of clinicians from around the world, it is also important for the guidelines to be tested in real clinical settings. Clinic-based field studies of the clinical utility and reliability of proposed CDDG will also be conducted via the WHO's network of International Field Study Centres. Clinic-based field studies will involve pairs of clinicians applying the ICD-11 CDDG to real patients, and will provide substantive data regarding inter-rater reliability and clinicians' assessment of the usefulness of the guidelines. Clinic-based field studies will also provide an opportunity to test other questions that can only be investigated in patient care settings (e.g., whether the ICD-11 guidelines lead to a reduction in the proportion of cases that result in "unspecified" diagnoses).

CONCLUSIONS

The structure presented above for each category in the ICD-11 CDDG is expected to enhance the clinical utility of the manual by providing clearly organized, consistent information across disorders that is flexible enough to allow for cultural variation and the exercise of clinical judgment. The utility and effectiveness of this format in producing more consistent clinical judgments in ICD-11 as compared to ICD-10 is currently being tested in a series of Internet-based field studies using standardized case material, and will also be tested in clinical settings.

Although previous versions of the ICD, as well as the DSM, have typically emphasized clinical utility as their highest priority, this area has in fact received almost no systematic attention (2,18,19). Based on its mission as a global public health agency, the WHO is particularly interested in the clinical utility of the classification because it is critical to the interface between clinical practice and health information. A mental disorders classification that is difficult and cumbersome to implement and does not provide information of value to the clinician has no hope of being implemented accurately at the encounter level in real-world health care settings (3,20,21). As a result, important opportunities to improve clinical practice will be lost. Moreover, a diagnostic system characterized by poor clinical utility cannot be an effective tool for generating data based on those encounters that provide a valid basis for health programs and policies, or for global health statistics.

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Advancing paternal age and psychiatric disorders

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Age of first and subsequent parenthood has been increasing all over the world. From a public health perspective, it is becoming apparent that this shift might have negative consequences. When considering the potential negative effects of late parenthood, focus has traditionally been on older maternal age, which has been associated with multiple adverse outcomes in the offspring (1). More recently, however, the offspring of older fathers have been shown to have increased risk for a wide range of adverse health conditions, including psychiatric disorders.

These findings received considerable attention because they challenge traditional views on male fertility and reproduction. However, research findings on the links between advancing paternal age and psychiatric disorders have not always been replicable, and the mechanism or mechanisms behind the paternal age effect remain unclear, adding to the controversies around the findings.

In this paper we provide an updated overview of the research on the association between advancing paternal age and psychiatric disorders in the offspring and discuss potential biological and social mechanisms.

SCHIZOPHRENIA

Studies dating back to as early as 1958 have shown associations between advanced paternal age and schizophrenia (2). The first modern era study was published in 2001 and reported that, compared with offspring of fathers younger than 25 years, the relative risk (RR) of schizophrenia in offspring of men aged 45 to 49 and 50 years or more was 2.02 (95% CI: 1.17-3.51) and 2.96 (95% CI: 1.60-5.47), respectively (3).

Since then, several studies have replicated these findings, yet negative results have also been reported. Potential confounding factors such as maternal age, parity of the mother, socioeconomic status, birth order, family history of psychiatric disorders, and urbanicity have been examined. A meta-analysis published in 2011, including 6 cohort studies and 6 case-control studies, found that the RR for schizophrenia in offspring of fathers aged $\geq$50 years was 1.66 (4).

AUTISM

In 1970, it was first suggested that there is a link between older paternal age and autism (5). Since then, numerous studies have found associations between autism spectrum disorders and/or infantile autism/autistic disorder and advancing paternal age. The results have been replicated in independent samples all over the world. The association between autism risk and paternal age is therefore robust, although the magnitude of this association has varied greatly.

A meta-analysis on paternal age and autism risk showed that offspring of men aged 50 years or older were 2.2 times more likely to have autism than offspring of men younger than 30 years, after controlling for maternal age and other documented risk factors for autism (6).

OTHER PSYCHIATRIC DISORDERS

Frans et al (7) reported a link between paternal age >55 and bipolar disorder (OR=1.37, 95% CI: 1.02-1.84). The association was strongest for individuals with an early onset of the disorder (<20 years) (OR=2.63). There have also been reports of an association between advancing paternal age and eating disorders (8), attention-deficit/hyperactivity disorder (9) and substance use problems (9).

In addition to psychiatric disorders, advancing paternal age has also been linked to impairments in the general cognitive ability (10), educational outcomes (9) and violent offending (11).

GRANDPATERNAL AGE

Interestingly, two recent studies using the Swedish multigenerational register showed an effect of advancing grandpaternal age on risk for schizophrenia (12) and autism (13), suggesting that age-associated effects may be transmitted across generations.

HOW OLD IS OLD?

There is no universally accepted definition of advanced paternal age but, within genetic counseling for congenital disorders, advanced paternal age is often defined as 40 years and older (14). However, there is no consistent evidence for a dramatic increase in risk for these disorders in offspring of fathers over 40. Instead, the risk increases linearly with paternal age. Therefore, at present, a cut-off at 40 years has no known underlying biological foundation.

Similarly, studies on schizophrenia and autism show no evidence of a threshold effect. Although the risk increase is

not necessarily linear, studies on the relation between paternal age and psychiatric disorders show no consistent evidence for a threshold age where the risk increases dramatically.

PROPOSED MECHANISMS UNDERLYING THE PATERNAL AGE EFFECT

The mechanisms underlying the association between paternal age and psychiatric disorder remain unclear. There are, however, several hypothesized mechanisms. Some hypotheses suggest that there is a causal link, while others argue that the associations can be explained by unmeasured confounding.

De novo mutations

It has been most frequently suggested that the association between advancing paternal age and psychiatric disorders is due to an increased burden of *de novo* mutations in germ cells of older men.

Women are born with their full supply of oocytes, and their meiosis is halted at metaphase II until fertilization. In contrast, male germ cells are produced continuously through reproductive life. More specifically, spermatogonial cells replicate every 16th day, resulting in approximately 200 divisions by the age of 20 years and 660 divisions by the age of 40 years (15). Each time the cell divides, the replication of the genome introduces the possibility of copy-error mutations. As a result of the large number of cell divisions during spermatogenesis, the mutation rate for base substitutions is much higher in men than in women, and increases with paternal age (16). These mutations may be inherited to the offspring and potentially have negative effects on their health.

Although it remains unclear whether new mutations are causing the relation between advancing paternal age and psychiatric disorders or other complex traits, it is possible that mutations are of great etiological importance for mental health. Brain function depends on the functionality of a very high number of genes and non-coding regulatory regions, and therefore the mutational target size is large.

Recent studies using exome sequencing methods confirmed that *de novo* point mutations have a role in the etiology of schizophrenia and autism (17-22). Moreover, Kong et al (18) found that fathers, on average, pass on to their offspring 25 new point mutations at age 20, increasing to 65 mutations at age 40. The study concluded that the mean number of *de novo* mutations in human spermatozoa increases by around 2 per year.

Epigenetic alterations

Modifications in gene expression that are not caused by changes to DNA sequence are referred to as epigenetic alterations. They are mediated principally through changes in DNA methylation and chromatin structure. Although epigenetic features are reversible, it has been suggested that they can by structural inheritance be transmitted to offspring.

Perrin et al (23) and Sipos et al (24) have suggested that epigenetic alterations that occur as paternal age advances may be causally related to the susceptibility to schizophrenia in offspring. Animal models have documented DNA methylation changes associated with paternal age (25). Interestingly, paternal exposure to toxins and nutritional state, as well as age, have been found to influence the development in offspring and sometimes even development of grand-offspring (26).

Characteristics of older fathers

It is also possible that some of the environmental characteristics associated with older fatherhood increase the risk of psychiatric disorder. Some features of men who became first-time fathers at an older age were recently described in a Norwegian population-based study. The study showed that both higher and lower socioeconomic status groups were overrepresented among older fathers compared to younger fathers. OIder fathers were also more likely to engage in negative health behavior and have poorer health (27). However, Ek et al (28) found no association between risk of psychoses and advancing adoptive paternal age, thus not supporting a role of psychosocial environmental factors in explaining the paternal age effect.

Selection into late fatherhood

It has also been suggested that the association between paternal age at birth and psychiatric disorder in offspring is confounded by psychiatric disorders or a genetic liability for psychiatric disorders in the father (29,30). Individuals with genes predisposing for psychiatric illness are more likely to have children with similar disorders. If a genetic liability for psychiatric disorders is also associated with a selection into late fatherhood, this would result in a non-causal association between paternal age and psychiatric disorders in the child. Similarly, if women with a genetic liability for psychiatric disorders tend more to have children with older men, this mating pattern could result in an association between late fatherhood and disorders in the children.

A study from Finland showed that advancing paternal age was associated with schizophrenia in the mother, but not in the father (31). However, other studies do not support this notion. Sibling-comparison studies offer rigorous control for familial confounding factors, including familial liability of psychiatric disorders. While multiple studies support a paternal age effect in autism (6,9,32), results of sibling analyses for schizophrenia have been inconclusive (6,30).

CONCLUSIONS

Advancing paternal age has been associated with a range of psychiatric disorders, with the strongest evidence in autism and schizophrenia. It has also been associated with other adverse neuropsychiatric outcomes. However, the mechanisms behind these associations remain unclear.

Multiple epidemiological study designs and molecular genetic studies, potentially combined with animal studies, could provide the necessary knowledge about the mechanisms that mediate the paternal age effect. The exploration of epigenetic mechanisms and how risk can be transmitted across generations is critical for understanding the etiology behind the paternal age effect. This knowledge might have important implications for clinicians, researchers, those affected by the disorders, and the general public.

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Recovery, not progressive deterioration, should be the expectation in schizophrenia

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Since the time of Kraepelin, schizophrenia has been considered to be a progressive deteriorating illness (1). This perspective has been bolstered by a generation of studies demonstrating deficits in brain volumes on magnetic resonance imaging (MRI) scans and in performance on a broad range of cognitive tasks in individuals with schizophrenia (2).

Despite the introduction of effective pharmacological treatments and evidence-based psychosocial interventions, fewer than one in seven people affected are considered to meet criteria for recovery (3). The possibility that the pathophysiology of schizophrenia involves mechanisms that progress over the longitudinal course of the illness is often assumed to explain the poor outcomes observed (2). Advocates for early intervention have embraced this paradigm as it implies that early treatment has the potential to arrest a disease process that would otherwise continue on an unrelenting march to severe mental deterioration.

While progression of an active disease process would provide a compelling explanation for the poor outcomes so commonly observed, it is not consistent with what we have learned from modern studies of the longitudinal course of structural brain abnormalities, cognitive deficits and clinical outcomes associated with schizophrenia (4). Rather, schizophrenia appears to be associated with stability of these measures over the longer term. It is time to consider the possibility that clinical stability and recovery rather than progressive deterioration should be the expected outcomes from schizophrenia.

STRUCTURAL BRAIN FINDINGS IN SCHIZOPHRENIA

Modern *in vivo* brain imaging technology has provided opportunities to study differences in brain structure in people with schizophrenia and to assess changes in these measures over time. Increases in cerebrospinal fluid (CSF) volumes, together with deficits in both gray matter and white matter volumes, have been reported in patients with chronic schizophrenia and are present to a lesser degree in individuals studied at the time of their first episode of psychosis (5).

The relatively greater differences in brain tissue and CSF volumes in more chronically ill patients could be the result of progression of these differences over the course of the illness. Alternatively, it could be the case that those individuals with more striking differences at the time of the first episode are more likely to have a poor outcome and, as a consequence, are over-represented in more chronically ill samples.

This issue appeared to be resolved when a number of large longitudinal MRI studies reported progressive reductions in brain tissue volumes in patients following a first episode of psychosis compared to healthy controls (6,7). However, subsequent studies in patients (8) and in animals (9,10) have demonstrated that antipsychotic medications can lead to these imaging findings, which may also be reversible to some degree (11,12). The increases observed in the magnitude of structural brain findings over the course of schizophrenia may be better explained by medication effects, together with differences in exposure to alcohol, drugs of abuse, smoking and levels of activity (4).

COGNITIVE DEFICITS IN SCHIZOPHRENIA

The magnitude of cognitive deficits observed in people with schizophrenia has been observed to be associated with measures of community functioning (13) and with the extent of the structural brain differences (14).

Cognitive deficits, like the structural brain differences, are clearly evident at the time of the first episode of psychosis. These deficits are observed to improve to a significant degree in the first year of treatment (15) and have been found to remain stable or improve rather than decline over the longer term (16).

When the cognitive deficits associated with schizophrenia initially develop remains unclear. Some of the deficits are likely apparent early in childhood, while others may reflect a subsequent lag in developmental processes that results in the finding of even greater deficits relative to healthy controls by the time individuals present with a first episode of psychosis (17).

There does not appear to be any period in the developmental trajectory of individuals with schizophrenia during which absolute measures of cognitive performance are actually declining.

CLINICAL OUTCOMES FROM SCHIZOPHRENIA

If both structural brain measures and cognitive functioning are likely to remain stable following the onset of schizophrenia, then why should ongoing deterioration in functioning

occur? It is well established that 70-80% of individuals with a first episode of schizophrenia will experience a remission of psychotic symptoms within the first year of treatment (18). This percentage seems to remain stable when individuals are provided with ongoing comprehensive treatment (19). Relapse of psychotic symptoms following a remission from a first episode of schizophrenia is also observed to occur in over 80% of individuals when studied naturalistically (20). This is largely attributable to discontinuation of antipsychotic medication rather than to the effects of an unrelenting disease process. The risk of symptom recurrence in remitted first episode patients receiving maintenance antipsychotic treatment is estimated to be in the range 0-5% in the first year of follow-up, compared to 78% in the first year off medication and close to 100% after three years off medication (21).

While we may be inclined to try to eventually discontinue antipsychotic medication for those patients who have the best response and remission, this may be misguided. It should not be surprising that those patients who respond most robustly to dopamine D2 antagonists may also be most likely to become ill when those same medications are discontinued. With antipsychotic medication, the large majority of individuals with a first episode of schizophrenia are able to achieve and sustain symptomatic remission. Without medication, few if any patients with a diagnosis of schizophrenia are likely to remain in remission. The total number of patients who are able to achieve remission would be expected to be even higher with early use of clozapine for those patients who fail to remit with first-line antipsychotics (22).

If schizophrenia were by nature a progressive deteriorating illness, then the percentage of patients who achieve remission and recovery should decline with increasing duration of illness, and the percentage with poor outcomes should increase. This does not appear to be the case: the percentage of patients who meet criteria for poor outcome, remission, functional recovery, and recovery does not vary with the duration of follow-up (3,23).

If the majority of patients remit and have the potential to remain in remission, then why have outcomes remained poor for so many? There are many reasons to consider. Many people with schizophrenia are not in treatment, either because services are not available to them or they have chosen not to be involved. Of those who are treated, 20-30% are poor responders to antipsychotic medications. Others have repeated challenges with treatment non-adherence, with consequent relapses and re-hospitalizations. For many, the course of illness is distorted by concurrent problems with substance abuse, intellectual disability, depression and other mental illnesses, in addition to the challenges posed by stigma, poverty and diminished opportunities (24).

WHAT IS "RECOVERY"?

Despite enormous optimism about the potential for comprehensive early intervention programs to improve real world outcomes, it does appear that recovery from schizophrenia is far less common than remission. Relapses and hospitalizations may be largely preventable, but the level of functioning that clinically stable individuals are likely to attain is less clear.

The percentage that will achieve competitive employment would be expected to vary depending on the criteria used (e.g., full-time versus part-time, duration of employment, level of income). When "recovery" is defined as a persistence of symptom remission together with social and vocational improvement, fewer than 15% of individuals with schizophrenia meet this definition (3). The possibility that many remitted patients have goals that differ from those embodied in current definitions of "recovery" may in part explain this finding.

Individuals who have experienced a remission from a first episode of schizophrenia report levels of happiness, satisfaction, success, and positive daily affect that are comparable to age-matched controls, as well as less negative affect throughout their day, despite functioning at much lower levels (25). Data collected as part of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in the U.S. found that, on average, patients reported their level of satisfaction with life/happiness as mixed (i.e. neither satisfied nor dissatisfied with life in general) (26). That self-reported levels of happiness and life satisfaction are not lower may reflect a process of personal adaptation to having a potentially chronic and disabling illness. Preserved levels of happiness and satisfaction in the face of low levels of functioning may also reflect cognitive, socioeconomic and cultural differences.

How recovery from schizophrenia is envisioned is likely to vary greatly between individuals. Psychiatrists have typically embraced a "medical" model of recovery that emphasizes the elimination of symptoms and a return to normal levels of functioning; patients-consumers may find a "rehabilitation model of recovery" more compelling, with its emphasis on creating a meaningful and satisfying life in one's community (27). Identifying those personal goals that are of most importance to each individual patient is critical, as outcomes that are not a personal priority are unlikely to be realized.

While there is room for debate about how recovery should be defined, it should be clear that most individuals with schizophrenia have the potential to achieve a stable remission of symptoms and substantial levels of satisfaction and happiness. Future outcome studies will need to incorporate outcomes that reflect the patient experience. Societal resources will also need to be allocated to support the realization of a broader patient-centered conception of recovery.

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Cyberchondria, cyberbullying, cybersuicide, cybersex: "new" psychopathologies for the 21st century?

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The Internet and related technologies permeate our everyday functioning to the extent that it has become difficult to imagine life without them. As their penetrance increases, so does discussion of, and research into, new problematic behaviours and psychopathologies, especially "Internet addiction" and "online gaming addiction".

However, cybertechnology is also reshaping "established" psychiatric disorders and phenomena, leading to symptoms and manifestations that are both familiar and novel, old and new. Of those, this paper will focus on health-related anxiety, bullying or stalking, suicide, and compulsive sexual behaviour. While far from unique, they illustrate the range of psychological functions that have been reconfigured by the digital revolution – and how simplistic a "big umbrella" approach that reduces the discussion to "technology addiction" is.

CYBERCHONDRIA

Cyberchondria has been defined as an excessive or repeated online searching for health-related information, which is driven by a need to alleviate distress or anxiety surrounding health, but results, instead, in their worsening (1). It is a form of reassurance-seeking behaviour. Rather than obtaining support via online interactions with similarly worried individuals, those with cyberchondria find their anxiety amplified, often because of new pathologies that they discover online and that trigger new worries.

Compared with interpersonal reassurance seeking, performing online health searches can be less predictable, as the Internet is not designed to always provide relevant, accurate, non-conflicting and reassuring information (1). Therefore, information obtained online can increase uncertainty about health, perhaps ultimately leading to cyberchondria in individuals who have greater difficulty tolerating uncertainty (2). Moreover, cyberchondria may be related to a difficulty in distinguishing between credible and non-credible sources of online information. This, in turn, may relate to the individual's level of education, information-processing abilities and technological savviness.

Cyberchondria has been considered a distinct mental disorder and a multidimensional concept with mistrust of medical professionals as one of its key features (3). But the term has also been used to merely denote seeking health-related information online. The prevailing view is that cyberchondria is part of hypochondriasis/health anxiety (1), but conceptual consensus is still lacking. One reason is the uncertainty about the direction of causality: do high levels of health anxiety lead to excessive online health searches (the more plausible possibility and the one that is closer to hypochondriasis/health anxiety) or does "compulsive" seeking of health information online result in heightened health anxiety? Further research is expected to shed more light on this issue.

CYBERBULLYING AND CYBERSTALKING

Cyberbullying has been defined as repeated hostile or aggressive behaviour against others, performed by an individual or a group using electronic or digital media and aiming to inflict harm or discomfort (4). This activity can take many different forms, including email, blogs, chat rooms, and text messaging. The various other terms proposed for this behaviour (e.g., "cyber harassment", "cyber victimization" and "electronic aggression") attest to its frequency. Cyberstalking, a related phenomenon, involves the repeated use of the Internet, email or other electronic communication medium to stalk another person (5), and it may be accompanied by physical stalking.

Cyberbullying diverges in important ways from "traditional" bullying (6). For example, cyberbullying is not based on physical strength, but on technological proficiency or skill, which creates a new dynamic between perpetrator and victim. Also, protection against cyberbullying can be more difficult, because the perpetrator is very often anonymous. Further, the victim is no longer only reachable in the schoolyard or on the school bus, as perpetrators can now strike anywhere and anytime due to the ubiquitous nature of the Internet. Yet another difference is that the harm inflicted and the consequences such as humiliation may be known to a lot more people, because of the ease with which embarrassing information, pictures or other content can be disseminated online.

Cyberbullying and cyberstalking may be a manifestation of conduct disorder, antisocial personality disorder, or various other forms of psychopathology. In addition, cyberbullying victims, perpetrators and "bully-victims" (those who

"switch" from being a victim to acting as a bully) are all more prone to developing a range of psychiatric disorders and behavioural disturbances, including depression, suicidal thinking and suicide attempts (7-9).

CYBERSUICIDE

"Cybersuicide" has been used to describe a range of different behaviours and phenomena. A common aspect appears to be online searching for information on suicide methods. Such searches often begin by typing "best suicide methods" or "how to kill yourself" into online search engines (10). This can lead desperate individuals to pro-suicide websites, forums or bulletin boards that promote suicide as a personal choice. There, they can communicate with like-minded individuals about suicide-related issues. Such interactions may "resolve" the ambivalence inherent to suicidal thinking and persuade some that suicide is the "right" option.

One potential, and particularly tragic, outcome is a "suicide pact": an Internet-arranged agreement between two or more persons to commit suicide together at a certain place and time (11). It may be related to a power differential between its participants or to the romanticising of suicide, akin to a pact between lovers who "have" to escape an intolerable reality and an unaccepting society (12). Online suicide pacts are thought to involve socially isolated individuals with strong ambivalence about life (13). While they do not appear to be common, their prevalence seems higher in Japan (12).

Another novel manifestation of the age-old suicide problem uses the Internet's video-streaming abilities to deliver "webcam suicides", or the live broadcasting of one's death using an online video service. In some instances, this involves low-lethality self-harm behaviours which may represent cries for help (12). Perhaps unsurprisingly, webcam suicides have been associated with pro-suicide online platforms but also with cyberbullying (14).

CYBERSEX

Cybersex is a loose term that encompasses a variety of Internet-mediated sexual activities, some of which have been regarded as pathological. Numerous definitions of cybersex have been proposed, including a suggestion that it is a variant of "Internet addiction" (15). Although the purpose of cybersex activities is to experience sexual pleasure, such activities can have an aggressive or illegal component (e.g., when children are involved). Accordingly, cybersex behaviours range from solitary acts to consensual interactions and coercive contacts (16). They can be limited to excessive viewing of pornographic material, typically accompanied by masturbation, or they can involve compulsive cruising of specialized online bulletins with the purpose of arranging offline sexual encounters.

"Compulsive cybersex" or "cybersex addiction" has been described as repeated failure to control an urge to engage in sexual activities via the Internet and related technologies. This difficulty is presumed to exist because of an irresistible appeal of short-term sexual pleasure, despite the long-term negative consequences. The latter include relationship breakdown, financial problems if sex workers are involved or costly content is viewed, sexually transmitted diseases, and legal problems due to sexual harassment or sexual exploitation of minors. Whether mediated by cybertechnology or not, "hypersexuality" is a controversial entity that was not included even among the conditions for further study in the DSM-5; in contrast, the architects of the ICD-11 have already announced that there is sufficient evidence to introduce "compulsive sexual behaviour disorder" as a new diagnosis (17).

OTHER CYBER-PSYCHOPATHOLOGIES?

The aberrant behaviours and psychopathologies discussed above are not the only ones being reshaped online – they have only received the most attention in the literature. For example, pro-eating disorders websites ("pro-ana" and "pro-mia" sites promoting anorexia nervosa and bulimia nervosa, respectively) have well-documented negative effects on individuals with eating disorders (18), and there is even a case report of a Twitter-induced psychotic episode (19). The Internet has also been seen to encourage the emergence or magnification of certain personality traits, including narcissism, regression and impulsivity (20). Indeed, the range of psychological trouble that can result from, or be exacerbated by, our interaction with digital technology appears as vast as the Internet itself. Further research is clearly needed to better delineate those undesirable effects and to identify individuals who may be particularly vulnerable.

DISCUSSION

It is well known that psychopathology is influenced by social and cultural factors. Therefore, it is not surprising that modern technology, which has radically transformed the sociocultural landscape, has influenced various forms of psychopathology and related behaviours. Several unique features of this influence deserve highlighting.

First, the mass media have played an immense role in bringing attention to aberrant cyber-behaviours and cyber-psychopathologies. This is understandable, given their insatiable appetite for everything that is novel and makes for a "good story". That is especially true if the outcome is dramatic or tragic. Yet, despite the heavy dose of sensationalism that frequently accompanies these stories, there is no evidence of "evil" media intent, and instead of bemoaning the negative coverage, we would do better to enlist media's support. For example, acquainting media outlets with research

advances can better explain how modern technology and mental health interact and can lead to advocacy by media and audiences alike for funds to support further studies. Also, an evidence-based stance and the usage of correct terminology by clinicians and researchers in media interviews can limit the confusing multitude of terms, definitions and meanings, thereby promoting conceptual rigor in the field.

Second, there have been attempts to regard some aberrant cyber-behaviours, such as cyberchondria and compulsive cybersex, as distinct disorders. Several tendencies contribute to that: blaming the Internet and related technologies for the woes of modern life; psychiatry's proneness towards diagnostic splitting and the consequent creation of "new" diagnoses; attraction to what is "trendy" (which often becomes someone's "pet project"); and societal pressure to conceptualize these behaviours and phenomena as illnesses so that something can be done about them. It is crucial not to join the chorus and not to quickly suggest that the Internet is the cause of "modern" psychiatric disorders. Indeed, research has yet to prove, for example, that "cyberchondriacs" and cybersex "addicts" did not already manifest excessive health anxiety or problematic sexual behaviours before they gained unfettered access to relevant websites via speedy Internet connections. The Internet and related technologies might have facilitated the expression of psychopathology in vulnerable individuals, and it would be premature to attribute causality. Instead of succumbing to simplistic notions of "new" disorders, then, we should communicate that aberrant behaviours and psychopathological phenomena do not have to be conceptualized as disorders in order for them to be addressed optimally (e.g., through prevention or minimization of their negative consequences).

The Internet has changed contemporary society primarily because it has facilitated communication and allowed quick access to information, at little or no cost. These same characteristics have played a role in the emergence of some aberrant cyber-behaviours and cyber-psychopathologies discussed in this paper. In addition, the fact that the Internet can be used anonymously to satisfy strong, but strongly frowned upon if not outright illegal, sexual or aggressive urges has been instrumental in the development of other behaviours and phenomena. This underscores that the Internet and related technologies are not inherently "good" or "bad", but that they are rather like a tool that can be used for a variety of purposes, with a variety of consequences.

There is no doubt that the Internet and related technologies are posing new challenges to mental health. These include managing an abundance of accessible information ("information overload") and the accompanying uncertainty; curbing the urge to engage in risky behaviours, including sexual and parasuicidal or suicidal acts, which are made to look "easy" or even "attractive" online; and resisting the temptation to hide behind the anonymity mask to launch opportunistic attacks on others. Large differences seem to exist between individuals in terms of their vulnerability to these challenges and both the specific challenges and vulnerabilities need to be understood better.

Mental health professionals have several tasks here. The first entails what may be called "Internet use education". This would enable Internet users, especially those who may be more psychologically vulnerable, to be aware of the risks and potential harm, and learn how to circumvent the dangers and seek help. Another task is collaboration with experts from other disciplines, such as information technology specialists, to help make the online experience safer (e.g., via blocking "high-risk" websites that may have caused harm in the past). Further, any primary psychopathology that is present (e.g., a "parent condition" such as hypochondriasis in the case of cyberchondria) needs to be targeted using established treatment guidelines. Some modifications of the treatment approaches taking into account the specific aspects and impacts of cybertechnology might need to be made.

All along, the triggers and consequences of the detrimental cyber-behaviours and cyber-psychopathologies need to be addressed directly. Exactly how this is to be accomplished deserves our research efforts and a commitment to explore the whole range of potential negative psychological consequences of the digital revolution – well beyond "Internet addiction" and "online gaming addiction".

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Psychotic symptoms predict health outcomes even after adjusting for substance use, smoking and co-occurring psychiatric disorders: findings from the NCS-R and NLAAS

Psychotic disorders are associated with medical pathologies, and a recent study has shown that these associations extend into the sub-threshold regions of psychosis. Moreno et al (1) found that psychotic symptoms conferred risk for several lifetime physical health problems, including angina pectoris/cardiovascular problems, asthma/pulmonary problems, arthritis, tuberculosis, vision/hearing problems, and mouth/teeth problems. Also, psychotic symptoms were related to risky lifestyle behaviors, such as alcohol consumption and smoking, although these outcomes may have actually functioned as potential mediators. Further, psychotic symptoms are often accompanied by other psychiatric disorders (e.g., 2), which may likewise mediate relationships with medical conditions. Building on the work of Moreno et al, we used data from the U.S. to test whether substance use, smoking and co-occurring psychiatric disorders mediated the relationship between psychotic symptoms and physical health problems.

We analyzed two surveys conducted in the U.S.: the National Comorbidity Survey – Replication (NCS-R), using a nationally representative sample; and the National Latino and Asian American Study (NLAAS), using a national area probability sample with supplements for adults of Latino and Asian national origin. Both surveys adopted multistage clustered sampling designs. Details on the sampling strategy and interview procedures have been provided elsewhere (3). Respondents were included if they were assessed by the non-affective psychosis screen of the Composite International Diagnostic Interview (CIDI), which was administered to a random sub-sample of the respondents of the NCS-R (n=2322), and all respondents of the NLAAS (n=4644). Participants were excluded if they were missing data for any of the variables of interest. The final sample for this study consisted of 6,917 respondents.

Respondents were asked to report the lifetime presence of six specific psychotic experiences, which included two types of hallucinatory experiences (visual and auditory) and four types of delusion-like experiences (thought insertion, thought control, telepathy, and feelings of persecution). Responses were excluded if the experience took place in the context of falling asleep, dreaming or substance use. Respondents were asked (yes/no) if they had ever had the following five conditions in their lifetimes: arthritis/rheumatism, chronic back/neck problems, other chronic pain, stroke, and heart disease.

Demographic covariates included age, sex, ethnicity, income-to-poverty ratio, education, insurance coverage, and region of the country. Substance use included diagnoses of alcohol abuse and dependence, as well as drug abuse and dependence, ascertained through the CIDI. Co-occurring psychiatric disorders included CIDI diagnoses of anxiety disorders (agoraphobia with and without panic disorder, generalized anxiety disorder, panic attacks, panic disorder, post-traumatic stress disorder, and social phobia) and mood disorders (major depressive episode, major depressive disorder, and dysthymia). Smoking was measured by an item that prompted respondents to identify with four mutually exclusive categories: “current smoker”, “ex-smoker”, “only a few times”, or “never”. “Current smoker” and “ex-smoker” were combined, as well as “only a few times” and “never”, to form a dichotomous variable.

All analyses were conducted using the complex sample features of STATA SE 13. Analyses were two-tailed, alpha=0.05. Design-based analyses were used to estimate standard errors that accounted for the complex multistage clustered design of the NCS-R and NLAAS samples. All statistical estimates were weighted to account for individual-level sampling factors, including non-response and unequal probabilities of selection. Odds ratios were calculated using blocked hierarchical logistic regression. First, bivariate logistic regression analyses were used to determine the impact of psychotic experiences on health outcomes. In the second block, the logistic regression analyses were repeated with adjustments for potential demographic confounders. In the third block, analyses were repeated with adjustments for demographic confounders and substance use. In the fourth block, clinical variables were added to the demographic variables to determine whether the effects of psychotic experiences were independent of other mental health conditions. In the fifth block, smoking was added to demographic variables. The final block consisted of demographic variables and all potential mediators. Analyses were repeated with the exclusion of individuals who self-reported a history of a schizophrenia diagnosis, and results did not vary significantly.

After adjusting for demographics, psychotic experiences were associated with the increased likelihood of reporting arthritis/rheumatism (OR: 1.80, p=0.000), back/neck problems (OR: 1.98, p=0.000), headache (OR: 2.08, p=0.000), heart disease (OR: 2.36, p=0.024), other chronic pain (OR: 1.94, p=0.001), and stroke (OR: 1.72, p=0.143). Based on separate models adjusted for individual confounds – co-occurring psychiatric disorders (affective and anxiety),

smoking, and substance use – we found that each of the confounds partially mediated the associations between psychotic experiences and physical health problems, especially co-occurring depressive and anxiety factors (data available upon request). The full model (adjusted for demographic variables and all potential mediators) showed that psychotic experiences still predicted some health outcomes: arthritis/rheumatism (OR: 1.50, p=0.001), back/neck problems (OR: 1.56, p=0.006), headache (OR: 1.64, p=0.000), and heart disease (OR: 2.14, p=0.023). The effect was no longer statistically significant in the full model for other chronic pain (OR: 1.44, p=0.060) and stroke (OR: 1.40, p=0.395).

In conclusion, psychotic experiences were associated with negative health outcomes independent of a psychotic disorder diagnosis, and the effect persisted for arthritis/rheumatism, back/neck problems, headache, and most strongly for heart disease, even with the inclusion of other mediating variables, among which co-occurring psychiatric disorders proved to be the strongest. These findings support screening for health conditions (particularly heart disease) among individuals with psychotic symptoms, regardless of psychiatric diagnosis.

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Anxiety does not predict mortality. A population-based study

Anxiety has been associated with excess mortality in the past decade, but results are inconsistent (1-6). One important concern, which precludes the generalizability of findings from these studies, is the inconsistency in methods. Some studies have used questionnaires assessing symptoms of anxiety, while others have used semi-structured or structured interviews to diagnose DSM anxiety disorders. Moreover, the significant overlap between the symptoms of anxiety and depression makes it imperative to examine confounding or effect-modification by depression, but most existing studies did not address this problem. Finally, the short follow-up of many studies bears the chance of reverse causality, and the follow-up in the literature has rarely exceeded 10 years.

In the population-based Rotterdam Study (7), we identified two sub-cohorts: one, consisting of 2,977 participants (1993-1995), in which there was an assessment of anxiety symptoms, and the other, consisting of 3,079 participants (2002-2004), in which there was an assessment of anxiety disorders. These sub-cohorts were followed for all-cause mortality till 2013. Anxiety symptoms were evaluated by the Hospital Anxiety and Depression Scale – Anxiety (HADS-A), whereas anxiety disorders (generalized anxiety disorder, panic disorder, agoraphobia, social phobia, and specific phobia) were assessed by the Composite International Diagnostic Interview, and diagnosed according to DSM-IV-TR criteria.

We excluded participants with dementia at baseline. We considered depression as a fundamental covariate and adjusted for depressive symptoms (assessed by HADS – Depression) in the analyses of anxiety symptoms, and for DSM depressive disorders (assessed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview) in the analyses of anxiety disorders. We used anxiety and depressive symptoms continuously in analyses, and also dichotomized them using the accepted cutoffs to define clinically relevant symptoms, and to assess the overlap between clinically relevant symptoms of anxiety and depression.

The cohort with anxiety symptoms assessment, whose mean age was 68.7±8.5 years and which included 55% females, had 1,451 deaths during 19.3 years (13.2±5.5 years). The cohort with anxiety disorders assessment, whose mean age was 75.5±6.2 years and which included 59% females, had 1,138 deaths during 11.3 years (7.4±2.5 years). Anxiety symptoms but not disorders were associated with an increased risk of mortality: hazard ratio (HR) per standard deviation (SD)=1.10 (95% CI: 1.02-1.14). This attenuated after adjusting for cardiovascular confounders: HR per SD= 1.04 (95% CI: 1.00-1.10). Neither anxiety symptoms (HR per SD=0.99; 95% CI: 0.92-1.07) nor anxiety disorders (HR per SD=0.99; 95% CI: 0.77-1.29) were associated with an increased risk of mortality after additionally adjusting for depression. There was no evidence of effect modification by gender.

Interestingly, we found an association between anxiety symptoms and excess mortality during a short follow-up of 3 years in men (HR per SD 1.77; 95% CI: 1.28-2.44). This short-term association which disappears with a longer follow-up points to reverse causality (anxiety was possibly secondary to existing morbidities which caused mortality in a short follow-up).

The marginally increased risk of mortality observed with anxiety symptoms was largely explained by the presence of comorbid depressive symptoms. The correlation between symptoms of anxiety and depression was 0.66. Of the 362 (13.3%) participants who had clinically relevant anxiety symptoms, and the 238 (8.8%) who had clinically relevant depressive symptoms, 151 (5.6%) had comorbid depression and anxiety. In contrast, the overlap was much less marked for the disorders: of the 252 (8.2%) participants with anxiety disorders and 81 (2.6%) with depressive disorders, only 36 (1.2%) overlapped. Symptoms of anxiety and depression assessed by items in a self-administered questionnaire such as the HADS-A, e.g., "worrying thoughts go through my mind", may be less specific than those covered in a clinical interview.

In conclusion, anxiety symptoms and anxiety disorders were not associated with excess mortality in our population-based study. The previously observed associations between anxiety symptoms and increased mortality may be largely explained by the presence of comorbid depression, or due to a short follow-up.

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Effects of improved hospital architecture on coercive measures

Coercive measures, such as seclusion and physical or mechanical restraint – with or without medication – are widely used as a last resort in psychiatric practice to prevent serious harm to self or others. However, the effectiveness of these measures is empirically questionable (1). Further, patients perceive them as traumatic and they potentially exacerbate mental illness (2-4). Thus, extensive efforts have been made to reduce their application (5), for example by training staff in social problem solving (6), by placing patients with some specific diagnoses in specialized acute wards (7), or by organizing psychiatric emergency response teams (8). Besides interventions focusing on organizational procedures and personnel, we observed that substantial structural improvements of psychiatric facilities may help to prevent coercive measures.

In early 2011, a large German university psychiatric clinic was moved into a new building with substantially increased ward space (from about 200 sqm for 16-18 patients to 400 sqm for 17 patients), changed room settings (from mainly 2-4 bed rooms to only 2- and 1-bed rooms), improved sanitary arrangement (from 2 toilets/showers per ward to one for each room), more natural lighting (from small windows to almost picture windows), modern home electronics and large balconies.

Additional factors which may influence the application of coercive measures (8,9), such as the staff-to-patients ratio, guidelines for coercive measures, and the distribution of psychiatric diagnoses in the clinic, remained relatively constant. However, staff was slightly reduced after the move and a de-escalation training for the staff had been implemented since 2008.

We compared coercive measures from January 2005 to December 2010 (before relocation) with measures from April 2011 to June 2014 (after relocation) applying two-sample t-tests. A few outlying data points were omitted from the analysis using the 1.5 interquartile range which, however, only marginally affected the results. Data points were averaged per quarter (three months) and represented coercive measures per average occupied beds (varying between 97 and 175). The quarter in which the relocation took place was not considered.

The number and duration of mechanical restraints as well as coercive medication significantly dropped by 50-85% in the three and a half years following the relocation: the mean number of restrained patients per bed decreased from 0.069 to 0.035 ($t(35) = 5.534$; $p<0.001$; 50%), the mean number of days with restraints from 0.227 to 0.083 ($t(35) = 5.153$; $p<0.001$; 63%), the mean duration of restraints (in hours) from 2.156 to 1.039 ($t(35) = 2.973$; $p=0.005$; 52%), and the mean number of coercive medications from 0.043 to 0.006 ($t(35)=6.073$; $p<0.001$; 85%). Thus, the decreased use of mechanical restraints was not compensated by an increased use of coercive medication.

These data suggest that improvements in the structural environment potentially reduce coercive interventions. As the relocation in our observation represents a natural experiment, it certainly lacks the control of potentially confounding factors. However, we speculate that the architectural changes may influence coercive measures via mediators such as increased patients' wellbeing, improved staff-patient relationship, and more opportunities for patients to withdraw from stressful situations.

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Five reasons for teaching psychopathology

The rediscovery of psychopathology is among the top priorities for psychiatric training and practice (1). Early career psychiatrists are not satisfied with the training they receive in psychopathology. They solicit an improvement of their educational opportunities in this field, asking to couple theoretical knowledge with practical clinical skills (2).

For the past generations of residents in psychiatry, as M. Maj reminds us (3), Jaspers' *General Psychopathology* was a prescribed reading. The familiarity with that and other classics of psychopathology helped them to see the DSMs as synopses of available knowledge and diagnostic algorithms to be used for clinical purposes (4). This may not be the case for current residents, which involves a high risk of misunderstanding and oversimplification.

In a survey we carried out among the representatives of national associations of European early career psychiatrists (2), it emerged that trainees, perhaps more than academicians, seem to be well aware of that risk, as they complain about the quality and the quantity of training they receive in psychopathology, and ask for more hours in clinical practice under the supervision of an expert in psychopathology. National and international bodies that are responsible for education in psychiatry should seriously re-consider the importance of psychopathology in training curricula, given its role in psychiatric diagnoses, its importance in understanding and explaining mental disorders, and its capacity to re-humanize psychiatric practice.

There are no common guidelines on training in psychopathology worldwide. There is not even an agreement about the meaning and the purposes of the discipline called "psychopathology" (5). The main misunderstanding is, perhaps, that psychopathology is the name of an old-fashioned religious sect celebrating the dogma that psychiatry should be part of the medical humanities rather than a biomedical science. Actually, psychopathology is a discourse (*logos*) about the sufferings (*pathos*) that affect the human mind (*psyche*). It brings into focus the primary – although not unique – "object" of psychiatry: the *psyche*, that is, patient's abnormal experiences lived in the first-person perspective, embedded in anomalous forms of existence and structured according to unusual meaning patterns.

There are at least five reasons for psychopathology to re-become a fundamental column of psychiatric training. The first reason is the need to provide psychiatrists with a method enabling them to capture the subtle nuances of the patients' experience that constitute the essentials of the "psychiatric object" (6). The precise characterization of these nuances is, at present, the only secure basis for diagnosis and treatment, since experiential symptoms are by far more specific diagnostic indexes than any other kind of symptoms, including behavioural ones (7).

The second reason is the need to acknowledge that what patients manifest is not a series of mutually independent, isolated symptoms, but rather a certain structure of interwoven experiences, beliefs, and actions, all permeated by biographical details (8). What stands in front of the clinician is not an amorphous agglomerate of symptoms, but a person with a specific, meaningful and (to a certain extent) coherent "form of life".

Obviously, psychopathology helps to rehumanize psychiatry, but this does not mean that it stands against science. Psychopathology, being the science of human abnormal subjectivity, is a peculiar kind of discipline characterized by an and-and agenda: it brings into a clear epistemic focus the fact that psychiatry is based on two main, complementary methodological approaches: explaining and understanding. We causally explain a phenomenon when we find, by repeated experience, that this phenomenon is regularly linked to a number of other phenomena. This allows us to formulate general rules and to establish causal connections with subpersonal causes. The third reason to teach psychopathology derives from this: it helps to causally explain a given abnormal phenomenon, or a set of abnormal phenomena, since it helps characterizing them. Any phenomenon, in order to be explained, must first of all be described in the greatest detail.

The fourth reason for teaching psychopathology is that mental symptoms do not simply have subpersonal causes, but also have a personal feel and meaning. Psychopathology is a method for grasping the personal feel and meaning of an experience or set of experiences. Understanding is not the effect of a generalized knowledge, but is achieved by sinking ourselves in a singular situation. Thus, psychopathology preserves the individuality and uniqueness of the suffering person.

Psychopathology can operate in parallel with a traditional biomedical approach, since it does not exclude seeing abnormal phenomena as symptoms caused by a dysfunction to be treated, but additionally includes the exploration of personal meanings (9). The sick person, as a self-interpreting agent, plays an active role in trying to cope with and make sense of his/her aberrant experiences. Psychopathology conceptualizes mental symptoms as the outcome of a mediation between the person and his/her abnormal phenomena (10).

The fifth reason for teaching psychopathology is that the personal background, as a pre-reflective context of meaning and significance within which and against which persons construe the significance of their abnormal phenomena, should be part and piece of a thorough psychiatric assessment.

Psychopathology, as the discipline that assesses and makes sense of abnormal human subjectivity, should be at

the heart of training in psychiatry, and a key element of the shared intellectual identity of clinicians and researchers in this field (11).

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The achievements of the WPA Scientific Publications Program – 2011-2014

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WPA Secretary for Publications

At the World Congress of Psychiatry held in Madrid in September 2014, the WPA General Assembly was provided with a report on the fulfillment of the goals of the triennium 2011-2014 under the Presidency of P. Ruiz. Included in this report was a briefing I presented on the scientific publications of the WPA. Highlights of this presentation are provided below.

For the period 2011-2014, members of the WPA Operational Committee on Scientific Publications included M.B. Riba, Chair (USA), C. Leal, Co-Chair (Spain), A. Cia (Argentina), L. Lam (China), and Z. Zemishlany (Israel). The Committee met once a year over the triennium to develop an agenda, goals and deliverables. The principal goals of the WPA Publications Program have been to disseminate information about clinical care, services, and research developments in mental health care throughout the world, and to promote and give strong visibility to high quality research and practice, involving psychiatrists from all WPA zones.

A major achievement of the WPA has been to produce the acclaimed journal *World Psychiatry*, whose editor in chief is M. Maj. This esteemed journal is published by Wiley-Blackwell, and has reached now an impact factor of 12.846, ranking number 4 among psychiatry journals worldwide. It is translated into such languages as Russian, French, Arabic, Turkish, Spanish, Chinese, and Romanian. It is indexed in PubMed, Current Contents/Clinical Medicine, Current Contents/Social and Behavioral Sciences, Science Citation Index, and EMBASE.

In addition, the WPA has developed and supported publications from WPA Sections and Committees, proceedings from WPA meetings, newsletters, publications from Member Societies and books. A new relationship has just been announced between the WPA Section on Education, chaired by A. Tasman, and the journal *Academic Psychiatry*, Springer, whose editor in chief is L. Roberts.

We continue to publish the highly successful series *Evidence and Experience in Psychiatry*, which compares research evidence and clinical experiences concerning the diagnosis and management of the most common mental disorders.

Members of the WPA are very active in authoring books on a wide range of important psychiatric topics (see Table 1). In addition, many of the very active and productive WPA Scientific Sections have officially linked journals (see Table 2).

The Secretary for Publications has given presentations at national and international meetings on how to bring ideas and work to publication. These

Table 1 Selection of recent books authored by WPA members

Baron D, Reardon C, Baron S (eds). Clinical sports psychiatry: an international perspective. Oxford: Wiley-Blackwell, 2013.

Bhugra D, Ruiz P (eds). Leadership in psychiatry. Oxford: Wiley-Blackwell, 2013.

Bloch S, Green SA, Holmes J (eds). Psychiatry: past, present and prospect. Oxford: Oxford University Press, 2014.

Callard F, Sartorius N, Arboleda-Florez J et al (eds). Mental illness, discrimination and the law; fighting for social justice. Oxford: Wiley-Blackwell, 2012.

Cooper JE, Sartorius N. A companion to the classification of mental disorders. Oxford: Oxford University Press, 2013.

Grassi L, Riba M (eds). Clinical psycho-oncology: an international perspective. Chichester: Wiley, 2012.

Grassi L, Riba M (eds). Psychopharmacology in oncology and palliative care. Berlin: Springer, 2014.

Joska J, Stein D, Grant I (eds). HIV and psychiatry. Oxford: Wiley-Blackwell, 2014.

Koslow SH, Ruiz P, Nemeroff CB (eds). A concise guide to understanding suicide. Cambridge: Cambridge University Press, 2014.

Patel V, Minas H, Cohen A et al (eds). Global mental health: principles and practice. New York: Oxford University Press, 2013.

Riba M, Rubenfire M, Wulsin L et al (eds). Psychiatry and heart disease. Oxford: Wiley-Blackwell, 2012.

Soldatos C, Ruiz P, Dikeos D et al (eds). Pluralism in psychiatry. Bologna: Medimond International Proceedings, 2014.

Tasman A, Kay J, Ursano R (eds). The psychiatric interview. Oxford: Wiley-Blackwell, 2013.

Thornicroft G, Patel V (eds). Global mental health trials. Oxford: Oxford University Press, 2014.

Table 2 Journals with linkages to WPA Sections

Affective Disorders – *Journal of Affective Disorders*

Classification, Diagnostic Assessment and Nomenclature – *Psychopathology*

Clinical Psychopathology – *Psychopathology*

Disaster Psychiatry – *Revue Francophone du Stress et du Trauma; Revista de Psicotrauma*

Ecology, Psychiatry and Mental Health – *Idee in Psichiatria*

Education – *Academic Psychiatry*

History of Psychiatry – *History of Psychiatry*

Mental Health Economics – *Journal of Mental Health Policy and Economics*

Personality Disorders – *Personality and Mental Health*

Psychiatric Rehabilitation – *International Journal of Mental Health*

Psychiatry of Intellectual Disability – *Journal of Intellectual Disability Research*

Psychophysiology in Psychiatry – *Activitas Nervosa Superior*

Rural Mental Health – *Psychiatry in General Practice*

Transcultural Psychiatry – *Transcultural Psychiatry*

Women's Mental Health – *Archives of Women's Mental Health*

presentations have been helpful, especially to trainees and junior members of the WPA, and we hope to continue these types of presentations at future WPA regional and thematic meetings.

Future goals of the Publications Program will include helping the Scientific Sections and other WPA groups to develop innovative ideas that can be brought to publication; more use of technology; enhancement of linkages to developing countries in terms of access and development of journals and publications; and new partnerships with publishing companies which would like to work with WPA members, Member Societies, Scientific Sections, Committees and other components. We also welcome opportunities to work with patients and families in identifying ways to provide information in a timely and useful way.

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ICD-11 symposia at the World Congress of Psychiatry

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Within the 16th World Congress of Psychiatry, held in Madrid from 14 to 18 September 2014, a series of symposia took place, providing information on the ongoing development of the chapter on mental disorders of the ICD-11.

The symposia summarized the proposals for the various sections of the chapter, which are being produced by the fourteen working groups appointed by the World Health Organization (WHO) in consultation with relevant stakeholders, including WHO's member countries, several professional groups, and users of mental health services and their families. A list of scientific papers presenting and discussing these proposals, and of other relevant publications, is provided at the end of this article (1-99).

The symposia also presented the field studies for the development of the ICD-11 chapter on mental disorders, which can be subdivided into three groups: formative field studies, Internet-based field studies, and clinic-based field studies.

Formative field studies aimed to guide decisions about the basic structure and content of the classification, exploring clinicians' conceptualizations of the interrelationships among categories of mental disorders.

In the first study (100), 1,371 psychiatrists and psychologists from 64 countries rated the similarity between mental disorders presented as paired comparisons. The results indicated that the participants' mapping of mental disorders was remarkably consistent across professions, languages and WHO regions. The degree of similarity between clinicians' views and the structures provided by the DSM-IV and ICD-10 was moderate (kappa = .42). The proposed structure for ICD-11 was found to more closely align with clinicians' understanding of the relationships among disorders (kappa = .51).

In the second study (101), 517 mental health professionals recruited by field study centres in eight countries were asked to sort a set of 60 cards containing the names of mental disorders, based on their own clinical experience, and then to form a hierarchical structure by aggregating and disaggregating these groupings. The hierarchical organizations produced by clinicians were remarkably consistent across countries, diagnostic systems currently used and professions. Clinicians' consensus classification structure was different from ICD-10 and DSM-IV and in several respects consistent with proposals for ICD-11.

Internet-based field studies are being implemented through the Global Clinical Practice Network, which currently includes about 12,000 practitioners from all regions of the world. Physicians, primarily psychiatrists, represent 59% of the Network, and psychologists 30%. All other mental health disciplines (e.g., nursing, social work and occupational therapy) are also represented. One third of the members are from Asia, one third from Europe, and 20% from the Americas, equally divided between Latin and North America. About 41% come from low- or middle-income countries. Members have registered through nine languages (Arabic, Chinese, English, French, German, Japanese, Portuguese, Spanish and Russian).

These Internet-based studies are using vignette methodologies to examine clinical decision-making in relationship to the proposed ICD-11 diagnostic categories and guidelines. Data collection has been completed for the first study, dealing with disorders specifically associated with stress, which has been conducted in English, Japanese and Spanish with the participation of 1,738 Network registrants.

Clinic-based studies will assess the clinical utility of proposed ICD-11 diagnostic guidelines in real-life settings, with a special focus on low- and middle-income countries. More specifically, the studies will assess: the ability of the diagnostic categories to aid clinicians' understanding of the person's condition; how well the guidelines fit the presentation of actual clinical cases; the feasibility of using the guidelines in regular clinical interactions; and the adequacy of the guidelines for assessing individuals' conditions.

A major multi-country study has also been conducted concerning the utility and reliability of key changes being recommended for the primary health care version of the ICD-11 chapter on mental disorders. This study focused on the most common mental disorders seen in primary care settings (in particular, depression, anxiety and somatic symptoms).

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