World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 13, Number 3 *October 2014*

WILEY Blackwell

NEW IMPACT FACTOR: 12.846

ISSN 1723-8617

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EDITORIAL

Technical and non-technical aspects of psychiatric care: the need for a balanced view

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The role of empathic communication and therapeutic alliance in psychiatric practice has been underappreciated in the past few decades. A de-contextualized and objectifying approach has been promoted in some quarters, ignoring that without a communicative interaction no person will allow any professional to genuinely access his/her personal world (thus rendering spurious and clinically insignificant any superficial degree of diagnostic reliability which may be achieved), that the person's narratives of psychopathological experiences and their origins should be actively encouraged and worked on, and that relationship and context variables have a major impact on the outcome of all mental health interventions.

In part as a consequence of the above attitude, several persons with mental disorders have been complaining of not being listened to, or taken seriously, by mental health professionals, or of being treated in ways which hampered, rather than fostering, their journey to recovery (e.g., 1).

It is also to be acknowledged that the boundary between genuine psychopathology and ordinary mental distress is difficult to draw, and that the added value of clustering psychopathological phenomena into diagnostic categories is at present a matter of debate.

It is finally true that a reductionistic view of mental disorders, regarding them merely as brain diseases, has been endorsed in several (although certainly not the majority of) academic settings, just at a time when neuroscience was acknowledging the complex interrelationships between brain processes and social context, and the rest of medicine was recognizing the impact of relationship variables on the determination, manifestation, course and response to treatment of a variety of physical diseases.

Several papers in this issue of the journal (2-4) highlight the above points, and we should fully assimilate these messages, become aware of the empirical evidence supporting them, and acknowledge their implications for our practice and training.

Does all this imply that the "dominant psychopathological framework" or "technical idiom", and "the way it defines users' problems through an expert vocabulary and logic" (5) should be rejected as useless, obsolete and even harmful? That "interpretation and search for meanings" of users' "mental distress" should replace the above "technology" (e.g., 4,5)? That our current pharmacotherapies and psychotherapies work only, or primarily, through their "non-technical" components (e.g., 5)? That the efficacy of their "technical" (or "specific") elements is just an illusion (fueled, in the case of pharmacotherapies, by the financial conflicts of interests of researchers and clinicians) (e.g., 6)? And that a non-technical approach should be given predominance in ordinary psychiatric practice (e.g., 4)? In all these respects, I would be much more cautious.

True, each individual is unique, and an attention to what renders him/her unique, in terms of meanings, relationships and values, is crucial for an in-depth understanding of his/her problems. However, it is a fact that persons with genuine psychopathology have several features in common with other persons with genuine psychopathology, and that a typification and an assessment of these features is also essential for a thorough understanding of the individual case and, if appropriate, for the planning of management. Such a typification and assessment does require a technical expertise. If the above typification were not possible, we would not have much to learn from our professional education and personal clinical experience, and clinical trials would be useless. We would have to start from zero with each new service user. Fortunately, this is not the case.

At the same time, we should acknowledge that: a) we cannot impose our predefined psychopathological patterns on the individual cases – we should draw hypotheses on the basis of the actual evidence, we should then test these hypotheses by collecting further evidence, and modify them if needed; and we should be open to the possibility that our conclusions be challenged by new evidence; b) our psychopathological patterns may not apply to several people we encounter in our practice, especially in community settings – in these cases, we should accept this reality and its implications for management; we should also be open, however, to the possibility that further evidence, again, will challenge our conclusion; c) our current psychopathological patterns are far from perfect, and we must keep on refining them on the basis of research evidence – nonetheless, the limitations of our current patterns is not a good reason to conclude that any psychopathological typification is useless or harmful.

The search for meanings in the individual case is, as we acknowledged, essential. However, also this search should be guided by a scientific attitude. We should not forget that an uncontrolled, acritical search for meanings has led in the past to conceptualizations such as that of the "schizophrenogenic mother" which have proven incorrect and harmful. Bracken's example of Picasso's *Guernica* (4) is well taken, but, while the variety of discrepant meanings ascribed to that painting along the years has produced no harm to anybody, it is well documented (e.g., 7) that a wrong attribution of

meanings to psychopathological phenomena by parents, friends and not rarely professionals (e.g., interpreting them as "a normal experience of adolescence" or the expression of "an introverted personality") may be, in a young person with a first psychotic episode, a powerful factor leading to treatment delay and sometimes tragic consequences.

True, relationship and context variables have a significant impact on the outcome of pharmacotherapies, as well as psychotherapies. However, the argument that pharmacotherapies work primarily (or even exclusively) through non-technical elements leaves me suspicious, and several papers putting forward that argument give me the impression of a bias related to the authors' ideological conflicts of interests. Actually, a recent review of meta-analyses (8) documented that antipsychotics, antidepressants and mood stabilizers are at least as efficacious (on their target conditions) as many drugs used by the other branches of medicine, when the reference measure is the standardized mean difference from placebo. On the basis of that measure, antipsychotics turn out to be as efficacious in the acute treatment of schizophrenia as antihypertensives in the treatment of hypertension and corticosteroids in the treatment of asthma. Furthermore, the efficacy of long-term antipsychotic treatment in preventing relapses in schizophrenia is almost six times higher than the efficacy of angiotensing-converting enzyme (ACE) inhibitors in preventing major cardiovascular events in people with hypertension. True, the benefits of second-generation antipsychotics with respect to first-generation drugs have been oversold (e.g., 9), but it is a fact that both groups of drugs are very efficacious. True, the difference between antidepressants and placebo has been declining in recent decades (e.g., 10), but a major explanation of this is likely to be the overextension of the concept of depression.

Certainly, our current pharmacotherapies and psychotherapies have limitations, and it is appropriate to highlight them. However, it impresses me that the detailed account of these limitations is never followed by an equally careful delineation of the alternatives. Again, we should learn from the past. I have witnessed in some contexts in my country what the consequences of an indiscriminate denigration of our therapeutic techniques can be. I have seen the gradual deprofessionalization of care. I have seen the therapeutic vacuum filled with a myriad of "experimental" interventions, actually "experimented" without any protocol, any approval by an ethics committee and any informed consent by the users involved, and automatically labelled as "good practices", often with the support of politicians sharing the ideological orientation of the professionals involved, without any kind of formal outcome assessment. I have seen the initial enthusiasm of professionals turning into demotivation, leading to the early retirement of several generations of clinicians. I have seen the initial hope of parents turning into rebellion. I have seen some tragic suicides of young persons with bipolar disorder who had had their mood stabilizers discontinued and "replaced" by involvement in a social cooperative, because the "analysis of needs" dictated so. I have seen the irrational use of antipsychotics at high doses and in cases in which they were not indicated, by professionals who did not feel the obligation to learn to utilize them appropriately, because they regarded them as just a marginal element of care. I have seen the consequent development of serious side effects being exploited to reinforce the ideological prejudice against those medications.

I would not like to see all this at the international level. I would like to see a psychiatric practice in which *both* technical and non-technical elements of care are valued, in which the limitations of our current knowledge concerning both these elements are acknowledged, and in which further empirical evidence on the impact of both elements is collected, driven by a genuine scientific motivation and without being biased by conflicts of interests of any kind.

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DOI 10.1002/wps.20168

SPECIAL ARTICLE

Biomarkers and clinical staging in psychiatry

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Personalized medicine is rapidly becoming a reality in today's physical medicine. However, as yet this is largely an aspirational goal in psychiatry, despite significant advances in our understanding of the biochemical, genetic and neurobiological processes underlying major mental disorders. Preventive medicine relies on the availability of predictive tools; in psychiatry we still largely lack these. Furthermore, our current diagnostic systems, with their focus on well-established, largely chronic illness, do not support a pre-emptive, let alone a preventive, approach, since it is during the early stages of a disorder that interventions have the potential to offer the greatest benefit. Here, we present a clinical staging model for severe mental disorders and discuss examples of biological markers that have already undergone some systematic evaluation and that could be integrated into such a framework. The advantage of this model is that it explicitly considers the evolution of psychopathology during the development of a mental illness and emphasizes that progression of illness is by no means inevitable, but can be altered by providing appropriate interventions that target individual modifiable risk and protective factors. The specific goals of therapeutic intervention are therefore broadened to include the prevention of illness onset or progression, and to minimize the risk of harm associated with more complex treatment regimens. The staging model also facilitates the integration of new data on the biological, social and environmental factors that influence mental illness into our clinical and diagnostic infrastructure, which will provide a major step forward in the development of a truly pre-emptive psychiatry.

Key words: Biomarkers, clinical staging, diagnostic reform, early intervention, personalized medicine, pre-emptive psychiatry, youth mental health

(World Psychiatry 2014;13:211–223)

As many areas of clinical medicine move towards the introduction of more personalized or stratified treatment selection (1), linked to the stage of illness at which one presents for care, we are still early in the process of evaluation of the relevance of clinical staging for major psychiatric disorders (2-4).

Clinical staging in psychiatry builds on strong epidemiological evidence indicating that what we regard as major mental illnesses evolve over time in terms of clarity and severity. The staging model aims to differentiate earlier and milder clinical phenomena from those that mark illness progression and extension, moving outside the traditional diagnostic boundaries to place strong emphasis on where a person sits within the evolution or resolution of his/her illness.

Advances in research, particularly in the area of early psychosis, have shown that treatment in the very early stages of illness can produce significantly better clinical and functional outcomes for patients (3,5-7). This research has opened the way for a paradigm shift in psychiatry: the movement towards a pre-emptive, rather than largely palliative, psychiatry (8).

Preventive medicine, including pre-emptive psychiatry, requires predictive tools. Predicting who is at risk of developing an illness allows for the possibility of preventive interventions, while predicting an individual's response to the different treatment options available allows for a more personalized therapeutic approach.

While this has become a reality in key areas of physical medicine today, in psychiatry we still largely lack the ideographic tools that would support a profiling strategy to complement the nomothetic staging approach described below (9). At the most basic level, the clinical and trait/state risk factors that form the basis of our current predictive criteria are relatively crude and non-specific.

Despite the lack of detailed knowledge of the risk factors for the onset of mental illness, authors such as Eaton et al (10) have proposed that sub-threshold syndromes may be regarded as risk factors for full-threshold disorders such as schizophrenia and major depression, and could become the relevant targets for preventive interventions.

So far no biomarkers (measurable biological characteristics that index pathogenic processes or treatment responses (11)) or other risk markers are available to create profiles to enhance prediction and therapeutic selection in psychiatry. Stratified or personalized interventions remain aspirational, yet potentially within reach.

The concept of clinical staging is based on the notion of underlying pathophysiology that has, at some point along its course, the capacity to result in persistent or progressive illness. To test the concept, there is a clear need to develop illness markers that are directly linked to pathophysiology and, further, have the capacity to track the extent of the disease process. By examining the relationship between various biomarkers and both syndrome and stage, it may be possible to distinguish between those biomarkers that possess a degree of syndromal specificity from those that do not, and furthermore, to distinguish disease markers, vulnerability markers and risk factors across stages, markers of disease progression, and epiphenomena.

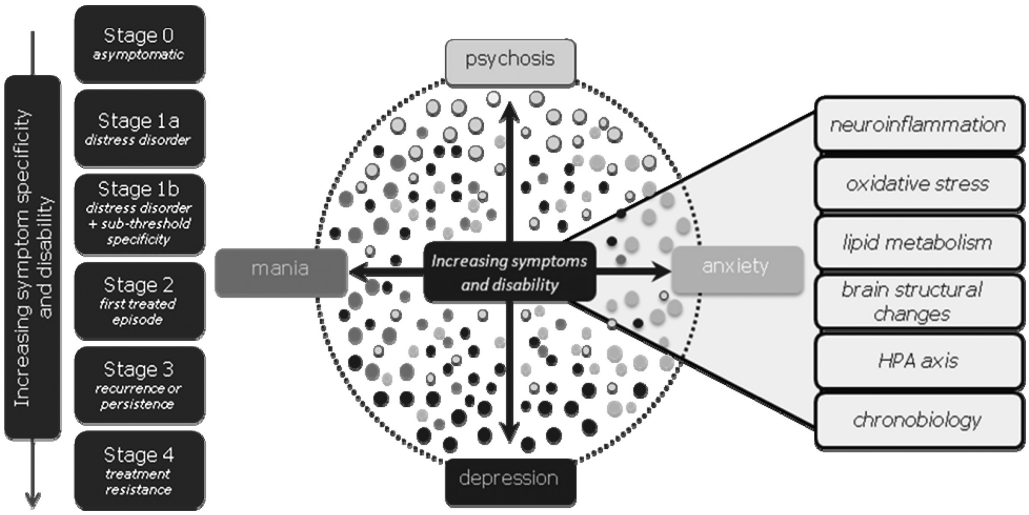

Figure 1 Clinical staging model for mental disorders and putative biomarkers. HPA – hypothalamic-pituitary-adrenal

Despite our current lack of detailed knowledge linking clinical phenotypes to specific pathophysiologies, it is possible to outline the framework of a useful staging model based on presenting clinical features (Figure 1). We propose that major mental illnesses develop from an "at-risk" but asymptomatic state (stage 0), through an initial stage of undifferentiated general symptoms such as mild anxiety, depressive and somatic symptoms, followed by a worsening of these existing symptoms and the acquisition of new ones, associated clinically with hints of greater syndromal specificity, and with behavioural and functional decline (stage 1). Personality development and functioning are typically affected in young people, and this dimension should be incorporated in staging definitions rather than split off in another axis. Further progression of illness may then take place, resulting in the occurrence of a first episode of a full-threshold syndrome(s) (stage 2), which may be followed by the development of persistent symptoms, frequent relapses and ongoing impairment (stage 3), or even severe, unremitting illness (stage 4) (2-4). Remission and amelioration is possible at every stage, though it is less likely with advancing stage (Figure 1).

Within this model, there is an implied "step function", rather than a simple severity gradient, between the "attenuated syndromes" (of psychosis or severe mood disorder) in stage 1 and the onset and persistence of full-blown syndromes in stage 2 and beyond. The risk of progression and of persistence and recurrence are proposed to increase with each stage. However, this is only part of the justification for what is primarily a heuristic strategy of imposing a categorical framework upon what otherwise is likely dimensional in nature. Hence the notion of a "step" or discontinuity remains a hypothesis, since each stage may merely represent an arbitrary boundary rather than carving nature at a biologically or therapeutically relevant "joint".

Underlying this framework (at least when applied to youth-onset disorders) is the assumption that the emergence and persistence of mental illness is driven by risk factors, some of which are earlier vulnerability factors or trait markers (e.g., genotype, intrauterine infection, adverse childhood experiences, childhood-onset learning, developmental or behavioural disorders), while others operate later, notably in the peri- or post-pubertal periods (e.g., developmental and life stress, illicit drug use, etc.). Presumably, at least some of these later factors, which may not only affect onset but also the risk of persistence and progression, are potentially modifiable (e.g., alcohol, cannabis or other substance misuse, adverse social environments, social isolation).

Within the model, the actual persistence and progression of illness over time is presumed to be determined by a gene-environment interaction between the underlying pathophysiology, influenced by genetic, epigenetic and other factors, and the balance of other risk or protective factors. Within this framework, these modifiable factors, as well as the underling pathophysiology, become major targets for preventive intervention.

This model has an explicitly preventive stance, emphasizing that progression of illness or "transition" from one stage to the next is by no means inevitable. The specific goals of therapeutic interventions are therefore broadened to include the prevention of illness onset or progression, and to minimize the risk of harm associated with more complex treatment regimens that are typically provided to those with more severe, persistent or recurrent disorders. Ensuring that early stage treatment is demonstrably safer is a key principle underpinning preventive medicine and early intervention. A further advantage of this model is that it facilitates the integration of new data on the biological, social, and environmental factors that influence mental illness into our clinical and diagnostic infrastructure. Ultimately, we seek to replace our prototypical clinical staging model with the development of a more robust clinico-pathological framework.

Clearly, the identification of cross-sectional and longitudinal biomarkers that provide accurate assessments of risk

and illness progression is of crucial importance. Ideally, these markers should link to relevant pathophysiology and enhance our understanding of the biological mechanisms that underlie the onset and progression of illness. Here, we discuss examples of how certain biological markers that have already undergone some systematic evaluation could be integrated into a clinical staging framework. We review some of the well-replicated risk factors for the early stages of psychiatric disorders within the neurobiological and other biomarker domains. These biomarkers may reflect causal mechanisms (such as genetic and oxidative stress markers) or consequences of the pathophysiology (such as cognitive, structural and physiological alterations). Some may reflect both (e.g., inflammation). Some biomarkers (e.g., imaging findings) may have potential predictive and/or diagnostic value (12), while others may suggest novel therapeutic interventions (e.g., N-acetylcysteine and omega-3 fatty acids for oxidative stress and anti-inflammatory agents for inflammation (13,14)).

COGNITIVE MARKERS

Examination of cognitive factors in major psychiatric disorders has primarily focused on neurocognition – mental operations underlying goal-directed behaviour such as attention, working memory, processing speed, learning and memory, executive functions, and global intellectual functions, including IQ. However, social cognition, a related but independent construct involving the perception, interpretation and processing of social information, has also received increasing investigation. It includes the domains of emotion recognition, theory of mind, social perception/knowledge and attributional style.

Neurocognition and social cognition are potentially highly valuable markers within the staging model. They may provide clues regarding underlying pathophysiology and/or genetic etiology (i.e., endophenotypes). They are also strongly related to functioning and disability across a range of psychiatric disorders (which form a key element of defining the stage of illness) independently of symptoms (15,16), can be relatively easily assessed within the clinical setting, and are amenable to intervention (17).

There is extensive evidence of neurocognitive, and increasingly, social cognitive deficits across all putative clinical stages of psychosis relative to healthy controls. Mild significant premorbid neurocognitive deficits are found in asymptomatic at-risk and ultra-high risk individuals. Deficits around 0.5 standard deviations below healthy controls are seen in global indices such as IQ (18-20), as well as specific accentuated deficits, particularly in verbal and visual memory, working memory, olfactory identification and social cognition (18,21,22). A recent meta-analysis found that deficits are greater in high-risk individuals who later develop full-threshold schizophrenia-spectrum disorders relative to those who do not (21).

In patients with first-episode psychosis, significant medium to large impairments (0.64-1.20 SDs below healthy controls) are present across all neurocognitive domains, including IQ and social cognition, with the most severe deficits observed in immediate verbal memory and information processing speed (23). The pattern and magnitude of these deficits are remarkably similar to those reported in meta-analyses of older, more chronic patients (0.46-1.57 SDs below healthy controls) (24). Furthermore, longitudinal studies indicate that the profile and severity of neurocognitive impairments tend to be stable for up to the first 10 years of illness (25) and over periods of up to 6 years in older people with chronic schizophrenia (24-26). Preliminary findings also point to relative stability in social cognition from early through to later stages of psychosis (27).

A cautionary note regarding the heterogeneity of psychotic disorders is important, as there is evidence that specific subgroups (i.e., those with unremitting symptoms and poorer functioning) may experience a more deteriorating cognitive course (24). Collectively, however, findings indicate that both cognitive lag (failure to develop normally) and progressive decline occurring primarily somewhere between premorbid and first-episode psychosis phases may be present, and followed by relative stability of deficits.

Medium to large neurocognitive impairments are also well documented in stable euthymic bipolar I disorder (28,29). Verbal learning and memory, executive functioning, attention and processing speed are most consistently impaired, with relative preservation of verbal abilities and intelligence (28). Similar milder impairments are also observed in bipolar II disorder (30). These neurocognitive deficits are evident early in the course of bipolar disorder (stage 2), but are less severe than in later illness stages (31-33). Specifically, cross-sectional studies have demonstrated a relationship between the degree of neurocognitive dysfunction and number of mood episodes, as well as illness duration (31,32). In general, neurocognitive deficits in bipolar disorder are not as severe as those observed in psychotic disorders (29,34).

Contrary to psychotic disorders, the presence of neurocognitive deficits prior to the onset of first-episode mania (stages 0-1) remains less clear, mostly because few studies have been conducted. Relatively intact or even higher global intellectual function (e.g., IQ) was found in children and adolescents who later developed bipolar disorder (19,35). However, there is preliminary evidence for specific neurocognitive deficits compared to healthy controls in at-risk young people who later developed a bipolar spectrum disorder (36,37). Milder neurocognitive deficits are found in healthy first-degree relatives, although the specific domains implicated have been inconsistent (28,29,38). Together these findings suggest that neurocognitive deficits are present after the onset of full-threshold bipolar illness and may progressively worsen with illness chronicity, but their role as a specific early risk marker remains undetermined, since few studies have focused on the premorbid and subthreshold stages.

While neurocognitive deficits are also common in unipolar depression, the evidence for staging is less clear, largely due to limited pre-diagnosis and longitudinal studies. In adolescents, young adults and older adults with depression, evidence exists for deficits in several neurocognitive domains, with executive functioning abilities (particularly in set-shifting), psychomotor speed and verbal and visual explicit memory most consistently impaired (39-45). Deficits are observed in mild, moderate and severe depression, with an apparent relationship between depression severity and neurocognitive impairment (39,43,45,46). Moreover, endogenous (melancholic) relative to non-endogenous depression seems to be associated with greater neurocognitive decrement (39,43,46).

Together, these findings tend to suggest that neurocognitive impairment is state-dependent. Nevertheless, it remains undetermined whether the neurocognitive deficits in depression may also reflect trait-based phenomena (41,47). Two studies of offspring at genetic risk for depression found no significant impairment in neurocognitive function relative to healthy controls (48,49). Mild premorbid deficits in psychomotor speed and attention were reported in one population study of children who later developed unipolar depression (50). Furthermore, mild residual deficits have been reported in older remitted patients, particularly in executive functions (41,42), but studies of remitted patients are sparse and the relationship of neurocognitive dysfunction with factors such as age, age of onset, duration of illness and number of episodes is equivocal (43,46,51). One study reported a relationship between neurocognitive dysfunction and recurrent episodes (52), suggesting a possible progressive course, while others have found no relationship (43). Much more work is needed to characterize cognitive dysfunction in terms of trait, state and progressive manifestations of depressive illness.

In summary, there has been a paucity of longitudinal studies examining cognition from premorbid to first-episode and more chronic illness phases, particularly in unipolar and bipolar illness. Nevertheless, the pattern of cognition according to stages of illness suggests that neurocognitive impairment may reflect both neurodevelopmental trait vulnerabilities and progressive illness-related deficits in major psychiatric illness. The evidence for social cognition is less advanced, but is beginning to parallel the neurocognitive findings, at least in psychotic disorders.

Points of difference between psychotic and bipolar disorder appear to be in severity and pattern of progression. Cognitive deficits are more broad and severe across all stages of illness in psychotic relative to bipolar disorder. In psychosis the greatest progression of cognitive dysfunction occurs between the sub-threshold and full-threshold stages, whereas cognitive decline is more evident after the onset of bipolar disorder and with increasing episodes. Although state-related neurocognitive deficits are clearly evident in depression, research is much less advanced, precluding any firm assertions regards to vulnerability and progression.

To exactly determine the timing and pattern of cognitive deterioration, more longitudinal studies are required to serially compare cognitive functioning of the same at-risk samples before and after development of full-threshold psychiatric disorders.

BRAIN STRUCTURAL MARKERS

Neuroimaging evidence for clinical staging in psychotic disorders has been reviewed recently (53), and space permits merely a summary here. A substantive body of literature has accumulated showing subtle structural brain changes in non-symptomatic relatives at risk for schizophrenia. A meta-analysis by Boos et al (54) showed modest reductions in gray matter volume, notably in the hippocampus, but also more widely spread. Such changes may tend towards normalization in relatives that do not show emergent psychopathology (55), but seem to be more prominent in those who already manifest schizotypal (56), cognitive (57) or early prodromal symptoms (58).

The brain region most commonly shown to be abnormal in chronic schizophrenia, the lateral ventricles, is less affected in first-episode patients (59), and unaffected in ultra-high risk individuals (60). A recent study has shown that gray matter decreases, predominantly in the frontal cortex, are far more pronounced in chronic schizophrenia than in first-episode psychosis patients (61), while other work has extended this evidence to ultra-high risk subjects (62). We have found similar patterns in the superior temporal gyri (63) and insular cortex (64,65), with clear evidence for increasing abnormality across the stages of illness (66). Similarly, marked reductions in hippocampal volume have been noted in chronic schizophrenia patients, while this is less clear in first-episode patients (67), and non-significant in ultra-high risk subjects (68-70). Meta-analyses confirm progression of ventricular enlargement and gray and white matter reductions (71), and these changes have been associated with poor outcome (72).

A key issue that has arisen recently is the role of antipsychotic medication in these progressive brain changes, given that illness duration and treatment intensity have been shown to be predictive of brain tissue loss, with illness severity having a smaller effect (73,74). Relapse duration and antipsychotic treatment intensity have both been shown to contribute to this tissue loss, although their effects are relatively small (74). These findings have important implications and indicate that, while relapse prevention is a key therapeutic strategy, the lowest possible doses of antipsychotic medications should be used.

Structural brain abnormalities have also been widely investigated in patients with both unipolar and bipolar affective disorders (75-77). Typically, the degree of gray matter loss reported appears to be correlated with the duration of illness and lack of exposure to antidepressant therapies. White matter changes have also been documented,

particularly among those who develop depression for the first time in later life, which appear to be secondary to micro-vascular pathology (78). For depressive disorders, therefore, it is particularly important to differentiate early-onset disorders (typically post-puberty) from those that develop in mid- or later life.

For depressive disorders, it has been assumed that the observed structural abnormalities – even in young people – are a consequence rather than a risk factor for illness. This assumption is now being challenged by studies focusing on young people, particularly those who go on to develop more severe bipolar or psychotic disorders. An accelerated loss in ventral and rostral prefrontal cortex volume in adolescents/young adults with bipolar disorder has been found in a longitudinal study (79). To date, there has been a major lack of longitudinal studies comparing findings prior to onset, early or later in the course of illness, or the effects of exposure to the range of treatments employed in those with early-onset disorders.

Affective symptoms, in particular depression, are common in the early phases of schizophrenia, and the emergence of psychosis is often the harbinger of what might later evolve as a non-affective psychosis. Of relevance in this context are imaging studies across the psychotic spectrum which can inform whether patients with psychotic versus non-psychotic affective disorders might have qualitative and quantitative differences in brain structure. There is evidence that, compared to psychotic depression, non-psychotic depression may be associated with preserved ventricular and white matter volumes (80). Brain structural differences are also seen between psychotic and non-psychotic bipolar disorder, supporting the categorical distinction between these entities (81). Strasser et al (82) have also observed smaller ventricular volumes in non-psychotic versus psychotic bipolar subjects. Recent meta-analyses have shown that gray matter reductions and ventricular enlargement may be more common in schizophrenia, while white matter volume reductions (83) and amygdala volume increases (75) may be more likely in bipolar disorder. In general, structural changes appear to be more confined to regions involving affect regulation in bipolar disorder, while the alterations are more pervasive in schizophrenia (84). Thus, it is likely that differential structural brain changes might become more prominent as syndromal specificity increases, such as may be seen with the emergence of psychotic or affective symptoms.

Taken together, these observations support the view that progressive brain structural changes in schizophrenia clearly involve a linear gradient of change, though a non-linear step function is also possible. Thus, it is likely that hippocampal alterations are subtle or absent in the early stages of psychotic disorders, but may appear and progress during the prodromal phase before reaching a plateau. Gray and white matter losses might, however, progress over time, and prominent ventriculomegaly might characterize chronic, poor outcome cases of schizophrenia, while more focal alterations in brain regions involved in affect regulation might signify affective psychoses. Such progressive evolution and differentiation of neuroanatomical changes may be paralleled by changes in function, connectivity and neurochemical integrity in these circuits, and will need systematic research.

A key issue is to clarify the role of antipsychotic medication in progressive brain changes. There is an association that could prove to be causal or turn out to be merely an epiphenomenon, but this requires urgent investigation (73). For now, structural magnetic resonance imaging (MRI) measures are a valuable first step towards the neurobiological characterization of staging across clinical phenotypes and syndromes.

MISMATCH NEGATIVITY AS A MARKER OF BRAIN FUNCTION

Several electroencephalographic properties have been studied in psychotic and mood disorders. Mismatch negativity (MMN) is a change in the activity of the brain induced by the occurrence of novel stimuli, leading to a switch of attention in the subject. MMN amplitude is thought to reflect the functioning of N-methyl-D-aspartate (NMDA) receptors, and impaired MMN generation has been associated with poor social and global functioning. Classically, this event-related potential is induced by the occurrence of a deviant sound in an otherwise contiguous stream of events, and it can be measured with electroencephalography.

A meta-analysis of 32 studies reports that a decrease in the amplitude of the MMN has been consistently replicated in schizophrenia (85). Very few data on the amplitude of MMN in people suffering from major depressive disorder are available, and the studies on this topic have all been conducted in stages 3 or 4 of the illness. One study showed no difference in the MMN amplitude between patients with major depression and controls (86), while others showed either an increase (87,88) or a decrease (89,90). Of the two studies that showed a decrease, one used a visual paradigm and the other measured MMN with magnetoencephalography, making it difficult to compare the results to those obtained with schizophrenia patients. Research into the MMN deficit in individuals with bipolar disorder has also been conducted during the later stages of the illness. Only two of six studies have shown impairment in MMN generation, with an MMN amplitude lying between that of controls and schizophrenia patients (see 91). Thus, the impairment in the generation of MMN appears to have some specificity for schizophrenia.

Umbricht and Krljes' meta-analysis (85) also revealed that the effect sizes of MMN induced by pitch-deviant sounds were significantly correlated with duration of illness, indicating that the pitch-deviant MMN amplitude attenuation could reflect disease progression. Results of MMN studies in people at ultra-high risk for psychosis are in line with

this proposition. Indeed, the generation of pitch-deviant MMN was shown to be intact in first-degree relatives (92,93) and in individuals with sub-threshold psychotic symptoms (94). Furthermore, the amplitude of the pitch-deviant MMN was intact in patients with first-episode psychosis (93,95-100), with a subsequent significant decrease in the same patients in the post-acute phase (95), or one year after their first psychotic experience (97). In the later follow-up study, deterioration in MMN generation was correlated with gray matter volume reduction in the primary auditory cortex, a correlation that was also observed in chronic schizophrenia (101). Two studies showed contradictory results on pitch-deviant MMN in first-episode psychosis, but both groups recruited individuals presenting with a first episode of schizophrenia specifically, rather than a first episode of psychosis more broadly (94,102).

On the other hand, MMN induced by a duration-deviant sound seems to behave like a trait marker of psychosis. Indeed, in all four studies conducted in ultra-high risk individuals, i.e., those with sub-threshold psychotic symptoms and/or genetic vulnerability, a decrease in duration-deviant MMN amplitude was observed compared to controls (91,94,103,104). Most interestingly, this decrease in amplitude was significant only in ultra-high risk participants who later transitioned to psychosis, suggesting that this impairment in duration-deviant MMN could be used as a predictor of illness (94,103). The amplitude of the MMN for a change in the duration of the sound was equally attenuated in schizophrenia and first-episode psychosis (94,102,105), but this was not reported in all studies (93,99).

In summary, while the attenuation of frequency-deviant MMN seems to follow the staging model, the duration-deviant MMN deficit appears to be more closely related to the genetic disposition of the patient.

SLEEP AND CHRONOBIOLOGICAL MARKERS

A ubiquitous characteristic of the onset period of most major psychiatric disorders is disruption of sleep, which is often accompanied by specific shifts in the sleep-wake cycle. While there is a normal tendency in adolescence for later onset of sleep, prolonged sleep and later daytime rising compared with younger children, those experiencing their first major onset of depression are particularly prone to further changes in this key homeostatic and developmental function. Shortened sleep duration appears to be a risk factor to the onset of common forms of psychological distress, and their persistence over 12 months, in late adolescence (106).

Among those with first-onset depressive syndromes, a significant sub-population develop "atypical" syndromes characterized by over-sleeping (and over-eating) and reduced daytime activity. In more severe cases, this phenotype may be characterized by distinct phase-delay in circadian timing, with shifting to later times of sleep onset and sleep offset, as well as increased total sleep time (107). In the most extreme forms, there may be a loss of normal circadian synchronization of mood, energy, cognitive performance and neurohormonal parameters, as well as the development of more somatically-focused "prolonged" or "chronic fatigue" syndromes. Those with more severe somatic syndromes, accompanied by persistent mood disturbance, appear to be at increased risk of later development of bipolar spectrum disorders (108).

A large body of data have accumulated since the 1980s on alterations in sleep architecture. Polysomnographic studies have received relatively little attention in recent years, perhaps because of lack of diagnostic specificity (109). However, there appear to be distinct sleep "signatures", with consistent reductions in slow wave sleep (SWS) in schizophrenia, and shortened rapid eye movement (REM) latency and increases in REM density in depression. These alterations may precede the emergence of full-blown disorder; for example, shortened REM latency can predict emergence of depression in at-risk adolescents (110). On the other hand, SWS reductions are seen in asymptomatic relatives of schizophrenia patients (111,112). Sleep disturbances are also predictive of psychosis in prodromal cases at clinical high risk for schizophrenia (113). Sleep alterations may possibly be stage-specific and vary with the course of illness, with acute symptoms being associated with REM density and latency (114), while chronicity, poor outcome and cognitive deficits are associated with SWS alterations (115,116).

Sleep disturbances are treatable, though it is not known whether such interventions can potentially prevent the emergence of psychopathology in individuals at high risk. Clearly, sleep studies may offer an early marker that is treatable, with likely preventive value.

NEUROENDOCRINE MARKERS

An impaired ability to cope with stress, both at the psychological and biological level, is thought to play a key role in the development and maintenance of psychiatric disorders (117). The hypothalamic-pituitary-adrenal (HPA) axis is the main biological mediator of the stress response, and its function is often altered in psychiatric disorders, with early life stress or trauma being an important moderating factor in determining the level of stress reactivity later in life (118).

Hyperactivity of the HPA axis, characterized by elevated cortisol secretion, an enlarged pituitary gland volume and impaired negative feedback of the HPA system, has been observed in affective (119) and psychotic disorders (120,121). Patients with psychosis also exhibit increased reactivity to daily minor stressors and this in turn correlates with greater negative affect and psychotic symptoms (122).

It is hypothesized that HPA axis abnormalities are involved in the genesis of psychopathology and cognitive deficits via the neurotoxic effects of elevated cortisol in brain regions such as the hippocampus and prefrontal cortex (117), and via interactions with the dopaminergic and

other neurotransmitter systems (117). Elevated cortisol secretion is linked with greater severity of positive and negative symptoms in patients with schizophrenia (123) and first-episode psychosis (124). Furthermore, decreases in cortisol and the cortisol/dehydroepiandrosterone sulfate (DHEAS) ratio during the initial three months of treatment in first-episode psychosis were directly related to an improvement in depression, negative and psychotic symptoms (124). Cortisol hypersecretion has also been associated with smaller left hippocampal volume in patients with first-episode psychosis (125), and an abnormal cortisol awakening response has been associated with greater cognitive deficits (126).

Atypical antipsychotics have been shown to dampen HPA axis activity (127) and reduce pituitary volume in a dose-dependent manner (128), providing further support for the stress-vulnerability model. These medication effects may also partly explain the discrepancies in HPA axis findings in patients with differing length of illness. Further longitudinal studies are urgently needed to better understand the role of the HPA axis in progressive brain change and cognitive decline associated with illness progression.

A recent body of literature has demonstrated that HPA axis abnormalities are evident prior to illness onset and in unaffected relatives of patients. An enlarged pituitary (a marker of HPA activation) was found to predict the subsequent transition to psychosis in ultra-high risk individuals (129). Consistent with this, a later study conducted in young at-risk individuals found that increased cortisol secretion was predictive of later transition to psychosis (130). Circulating cortisol was also positively associated with depressive and anxiety symptoms in ultra-high risk individuals (131). Healthy first-degree relatives of patients with a psychotic disorder have been shown to have increased stress reactivity, elevated cortisol levels (132) and an enlarged pituitary (133). The study by Collip et al (132) also reported an association between cortisol secretion and intensity of psychotic-like experiences and negative emotions, similar to that observed in patients with psychosis.

Taken together, these findings suggest that stress/HPA axis activity may be an important biological marker for vulnerability to develop psychopathology. It is important to note that distinct patterns of HPA axis dysfunction may occur within and across psychiatric diagnoses, and HPA activity may also change as a function of illness duration.

INFLAMMATORY AND OXIDATIVE STRESS MARKERS

There is increasing evidence to implicate inflammatory processes in the pathophysiology of major psychiatric disorders. Elevated levels of cytokines are a well-replicated finding in most major mental illnesses. Infusion of pro-inflammatory cytokines and interferon is perhaps the best experimental human model of depression (134), and elevated levels of cytokines are known to be associated with psychosis, depression and mania (135-137).

In parallel, there is a consistent body of evidence for an increase in oxidative stress in mood and psychotic disorders, including reduction in brain glutathione levels, changes in antioxidant enzymes, lipid peroxidation, protein carbonylation and DNA damage, as well as progressive structural changes consistent with oxidative damage (13,14,138).

Elevated levels of pro-inflammatory cytokines appear to precede the development of *de novo* disorder, suggesting that they play a role in its genesis (139). Inflammatory mediators have been thought to be related to processes underpinning stage-related structural and cognitive decline (140) and may be relevant to acute relapse and associated brain structural changes. The first data to support this hypothesis is the finding that the pro-inflammatory cytokines IL-6 and TNF-α were elevated in both early and late stage disorder, whereas the anti-inflammatory cytokine IL-10 was increased only in the early stage of the disorder (141). Additionally, TNF-α, while elevated throughout the course, was higher in later stages, suggesting that the inflammatory state is more perturbed later in the course of the disorder.

There are similar stage-dependent changes in oxidative parameters. In late stage patients, the activity of key enzymes in the glutathione pathway, glutathione peroxidase and glutathione-S-transferase, are increased compared to early stage patients and controls (142). Akin to the pattern seen with inflammatory markers, this stage-related change in oxidative biology may form part of the progressive failure of compensatory mechanisms over time, and may in part underlie the phenomenology of disease progression (143,144).

Consistent with a role for these pathways, there is evidence that most established psychotropic agents, including mood stabilizers and atypical antipsychotics, have substantive impacts on oxidative and inflammatory pathways (145,146). The selective COX-2 blocker celecoxib displays potential efficacy in the treatment of bipolar disorder (147) and schizophrenia (148). The use of statins, which have intrinsic anti-inflammatory and antioxidant properties, appears to be associated with lowered risks of mood disorders in community studies and in cohorts of individuals with cardiac disorders (139,149). N-acetylcysteine, which has core antioxidant and anti-inflammatory properties, shows preclinical and clinical efficacy in bipolar disorder and schizophrenia (13), and is a potential neuroprotective candidate (150). Aspirin appeared to reduce the symptoms of schizophrenia in a placebo-controlled trial (151), and was linked to less progression of disease in bipolar disorder in a pharmaco-epidemiological study (152). Minocycline, which has antioxidant and anti-inflammatory properties, has potential in diverse illness models (153).

FATTY ACID MARKERS

Phospholipids are the main structural elements of all cell membranes, and make up around 60% of the dry weight of the brain. The polyunsaturated fatty acids (PUFAs) play

central roles in a broad range of physiological functions. For example, two particularly important PUFAs are eicosapentaenoic acid (EPA) and arachidonic acid (AA), which are key players in signal transduction, ion transport and receptor sensitivity (e.g., for serotonin, dopamine, endocannabinoids), as well as precursors in the biosynthesis of the eicosanoids (prostaglandins, leukotrienes, thromboxanes), which mediate the inflammatory response. Another key PUFA, docosahexaenoic acid (DHA), serves as a precursor for the docosanoids (resolvins, neuroprotectins), which have a neuroprotective effect.

PUFAs are essential fatty acids, and since humans are unable to synthesize them *de novo*, they must be sourced in the diet. The typical Western diet contains relatively low levels of anti-inflammatory omega-3 fatty acids (e.g., EPA) and high levels of pro-inflammatory omega-6 fatty acids (e.g., AA) and saturated fatty acids, leading to increased production of pro-inflammatory eicosanoids. This imbalance has numerous pathological consequences, and is a potent promoter of chronic disease (154).

In relation to mental health, the omega-3 PUFAs may play a role in the pathogenesis of major affective (155,156) and psychotic disorders (157). Alterations in fatty acids in major depression include a decrease in omega-3 PUFAs and increased omega-6/omega-3 PUFA ratios in plasma, erythrocytes, adipose tissue and post-mortem brain tissue (156,158,159). The patterns of these fatty acid alterations are not specific to depression, but are also found in other conditions accompanied by increased oxidative stress, such as Alzheimer's disease, bipolar disorder and schizophrenia, and during normal ageing (160). A recent meta-analysis of 18 studies in schizophrenia examining the four most frequently explored PUFAs (DHA, AA, docosapentaenoic acid, linoleic acid) concluded that decreased levels of DHA and AA were present in antipsychotic-naïve patients. Furthermore, antipsychotic medication may (partially) normalize PUFA measures (161). The reasons for these membrane PUFA deficits are not completely known, but the available data suggests that increased oxidative stress may be one of the mechanisms underlying the reduced levels of omega-3 PUFAs in people with major depressive or psychotic disorder (162,163).

Alterations in membrane PUFAs may be present before the manifestation of stage 2 disorders. A study in a cohort of 33,000 women from the general population found a relationship between the dietary intake of fish (the richest dietary source of PUFAs) and vitamin D and psychotic-like symptoms (164). There is also preliminary evidence that fatty acid deficits may be present during the early stages (stage 1b) of psychotic disorders. For instance, we have shown that supplementation with long-chain omega-3 fatty acids can reduce the risk of progression to psychotic disorder in individuals at ultra-high risk of psychosis (165). In addition, we have found that lower levels of omega-3 PUFAs correlated with more severe negative symptoms in ultra-high risk subjects (166). Together, these findings imply that omega-3 PUFA deficits may be present before the onset of schizophrenia. In fact, omega-3 fatty acids are the only treatment superior to placebo in preventing conversion from stage 1b to stage 2 psychosis (167). On the other hand, PUFA supplementation may have relatively less benefit in patients with established schizophrenia (168). As omega-3 PUFAs are potent anti-inflammatory agents, this suggests that neuroinflammation could be a stage-specific phenomenon that may precede the dopamine overactivity associated with a first psychotic episode (stage 2).

There is also evidence that nervonic acid (NA), a monounsaturated omega-9 fatty acid that has been reported to be decreased in people with schizophrenia (169), may serve as a biomarker to differentiate truly prodromal people who are at immediate risk of transition to psychosis from those who do not progress to stage 2 (166). As NA is the major constituent of the sphingolipids in myelin membranes, decreased levels of NA could reflect the suboptimal myelination status seen in ultra-high risk individuals who progress to a psychotic disorder. This view is supported by a recent diffusion tensor imaging study in people with recent-onset psychotic disorders, showing that a lower total PUFA concentration was associated with lower fractional anisotropy in the corpus callosum and bilateral parietal, occipital, temporal and frontal white matter (170).

Finally, increased activity of phospholipase A2, a family of enzymes that catalyze the cleavage of PUFAs from the sn-2 position of phospholipids, is a robust biological finding in schizophrenia (171). Consistent with the staging model, phospholipase A2 activity appears to be higher in first-episode psychosis (stage 2), but not in multi-episode chronic schizophrenia (stages 3-5) (172). Our own research on the role of intracellular phospholipase A2 (inPLA2) in ultra-high risk subjects has shown that levels of membrane omega-3 and omega-6 PUFAs and inPLA2 activity were strongly correlated. However, some of the significant associations were in opposite directions in individuals who did (a positive correlation) and who did not (a negative correlation) transition to psychosis (173). These findings are suggestive of ongoing changes in the interactions of membrane metabolic markers during the course of the ultra-high risk phase of illness (stage 1b).

Thus, there is accumulating evidence that cell membrane PUFAs are involved in the pathophysiology of major mood and psychotic disorders. Lipid metabolism could provide a stage-specific phenomenon that is particularly relevant in the early stages of illness, and should be further investigated and considered for preventive interventions.

CONCLUSIONS

In summary, a large body of data already exists that may offer predictive and early diagnostic markers, as well as indicators of pathophysiological processes that may vary across the stages of the evolution of major psychiatric disorders. We have attempted to bring together evidence from several

lines of neurobiological work to address problems of the complex overlaps and heterogeneity of course and outcome across psychiatric disorders. A neurobiologically-informed staging approach that crosses current diagnostic silos may bring clarity to such complexity. What we have proposed is a framework for the next steps in research, and we suggest that some caveats are worth considering as this field moves forward.

First, it is important for staging approaches to be agnostic to traditional symptom-based nosological boundaries. These may not respect the true biological boundaries of disease entities, and therefore may have low utility for predicting outcome or selecting specific interventions. It is perhaps more useful to examine specific neurobiological domains that cut across diagnoses, e.g., working memory, negative salience etc., an approach central to the recent concept of Research Domain Criteria (174). Such an approach is likely to help characterize differential predictors of outcome based on cross-cutting dimensions rather than categorical distinctions.

Second, research needs to address ways to anchor the staging scheme to optimum stage-specific interventions. Available data already suggest certain common pathophysiological mechanisms that could be targeted with benign interventions: e.g., oxidative/inflammatory changes may respond to N-acetylcysteine or fish oil; disturbances in the HPA axis to stress management or cognitive-behavioral therapy; and chronobiological changes to sleep hygiene, simple lifestyle interventions or melatonin. Evidently, for the very early stages, the "do no harm" imperative is critical.

Other biomarkers implicate a developmental component – particularly the structural/functional changes in the brain and neurocognitive impairments – and may respond to more specific treatments such as antidepressants, mood stabilizers, second generation antipsychotics or cognitive remediation.

Third, a staging approach would do well to distinguish pathophysiology from etiological factors. As in the rest of medicine, disease staging based on clinical/biomarker measures may not necessarily map onto etiologically-based classifications. Genetic risk should also be interpreted agnostically, as it is unlikely to provide diagnostic specificity, but may be useful as a guide to disturbances in neurodevelopmental trajectories or aspects of neurobiological functioning.

Fourth, a useful point of departure in staging across diagnoses might be a shift from the broad, non-specific presentation to the evolution of more specific syndromal pictures. Such an evolution may not only involve the emergence of new symptoms or the evolving syndromal coherence of symptom clusters, but also the development (or lack thereof) of disability and functional and social impacts.

Overall, there is a critical need for longitudinal studies of biology and clinical manifestations, agnostic to the traditional diagnoses, to chart the evolution of distinct trajectories. This will inform not only our treatment choices, but also our understanding of the pathophysiology of these complex illnesses. Elaborating the complex linkages between the disturbances in basic neurobiology and the symptomatology that we see in clinical psychiatry will be a major step forward in the development of a truly pre-emptive psychiatry.

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DOI 10.1002/wps.20144

SPECIAL ARTICLE

Cognitive impairments in psychotic disorders: common mechanisms and measurement

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Decades of research have provided robust evidence of cognitive impairments in psychotic disorders. Individuals with schizophrenia appear to be impaired on the majority of neuropsychological tasks, leading some researchers to argue for a "generalized deficit", in which the multitude of cognitive impairments are the result of a common neurobiological source. One such common mechanism may be an inability to actively represent goal information in working memory as a means to guide behavior, with the associated neurobiological impairment being a disturbance in the function of the dorsolateral prefrontal cortex. Here, we provide a discussion of the evidence for such impairment in schizophrenia, and how it manifests in domains typically referred to as cognitive control, working memory and episodic memory. We also briefly discuss cognitive impairment in affective psychoses, reporting that the degree of impairment is worse in schizophrenia than in bipolar disorder and psychotic major depression, but the profile of impairment is similar, possibly reflecting common mechanisms at the neural level. Given the recent release of the DSM-5, we end with a brief discussion on assessing cognition in the context of diagnosis and treatment planning in psychotic disorders.

Key words: Cognitive control, working memory, episodic memory, cognitive deficits, schizophrenia, psychotic disorders, generalized deficit, DSM-5

(World Psychiatry 2014;13:224–232)

The last four decades have produced an impressive body of research on cognition in schizophrenia, in part prompted by the evidence that cognitive function is a critical determinant of quality of life and everyday functioning in people with this disorder, potentially more so than the severity of symptoms such as hallucinations and delusions (1-3).

A strikingly consistent finding within the cognitive neuroscience literature is that patients with schizophrenia display deficits on a huge variety of neuropsychological tasks (4,5). Historically, researchers had hypothesized impairments in specific cognitive domains with pockets of intact functioning in these patients, but there has been a recent push to re-conceptualize the range of deficits in schizophrenia as reflecting a "generalized" or "global" cognitive deficit, implying that cognitive impairments across domains share a common neurobiological source (6-10).

One such common mechanism may be an inability to actively represent goal information in working memory as a means to guide behavior, with the associated neurobiological impairment being a disturbance in the function of the dorsolateral prefrontal cortex (DLPFC) and its interactions with other brain regions such as the parietal cortex, the thalamus, and the striatum, and the influence of neurotransmitter systems such as dopamine, GABA and glutamate (11-13).

In this paper, we provide a discussion of the evidence for such impairment in schizophrenia, and how it manifests in domains typically referred to as cognitive control, working memory (WM) and episodic memory (EM). We also briefly discuss how cognitive impairments manifest across psychotic disorders in both the non-affective and affective psychosis domains. We end with an overview of the assessment of cognition in the DSM-5.

COGNITIVE CONTROL AND GOAL REPRESENTATIONS IN SCHIZOPHRENIA

In recent years, cognitive impairment in schizophrenia has been conceptualized as a deficit in the function of proactive cognitive control (12,14-16), or the ability to proactively maintain goal representations that can be used to guide ongoing behavior.

This conceptualization builds upon earlier ideas on the use of context information in psychosis (e.g., 17-19), to argue for flexible mechanisms of cognitive control that allow humans to deal with the diversity of challenges they face in everyday life. In this theory, termed dual mechanisms of control (12,14,15), a distinction is made between proactive and reactive modes of cognitive control.

The proactive control mode can be thought of as a form of "early selection", in which goal-relevant information is actively maintained in a sustained or anticipatory manner, before the occurrence of cognitively demanding events. This allows for the biasing of attention, perception, and action systems in a goal-driven manner. Goal information refers to information about what one needs to accomplish in a particular task or situation, or the intended outcome of a series of actions or mental operations. In real life, such goals may include the need to avoid eating a piece of cake while on a diet, maintaining points one wishes to communicate in a conversation, or overriding habits (e.g., driving straight home) to accomplish a specific goal (pick up one's dry cleaning).

In contrast, in the reactive mode, attentional control is recruited as a "late correction" mechanism that is mobilized only when needed, such as after a high-interference event is detected. For example, such a reactive control mechanism

might be engaged if you encounter an unexpected distracting stimulus and need to retrieve the topic of your conversation, or if your mind wanders and you suddenly find yourself at a critical intersection, where one direction leads home and the other leads to the dry cleaners. Thus, proactive control relies on the anticipation and prevention of interference before it occurs, whereas reactive control relies on the detection and resolution of interference after its onset.

This dual mechanisms of control theory, similar to other theories about cognitive control, suggests that proactive control depends on actively representing information in lateral prefrontal cortex (20), using this information to coordinate activity with other psychological and neural systems (21,22), and that the updating and maintenance of such information depends on precise inputs from neurotransmitter systems such as dopamine into prefrontal cortex (20). As such, proactive control may be particularly vulnerable to disruption, since it is resource demanding, and dependent upon precise dopamine-prefrontal interactions. Thus, we have suggested that populations characterized by disordered prefrontal and dopamine function (such as people with schizophrenia) may rely more heavily on reactive control, as it may be more robust in the face of such dysfunction (12).

There is convincing evidence for an association between impairments in DLPFC activity and deficits of proactive control in schizophrenia (23-26), for both medicated (27) and unmedicated patients (17,28), as well as those at risk for the development of the disorder (29,30). These findings were strengthened by a meta-analysis of imaging studies of executive control and proactive control, which demonstrated reduced activity in DLPFC in schizophrenia (25). Further, growing evidence suggests a critical role for impaired connectivity between the DLPFC and other cognitive control related brain regions (31-36), as well as for GABAergicly mediated (37) impairments in neural oscillations that may support representations in DLPFC (38,39). A relationship between dopaminergic function and DLPFC activity in schizophrenia (40), and a positive impact of dopamine enhancement on cognitive control in psychosis (41,42), have also been documented.

WORKING MEMORY IN SCHIZOPHRENIA

Although many studies have focused on understanding cognitive control deficits in schizophrenia, an even larger amount of research has been devoted to the cognitive neuroscience of WM (43), leading to an overwhelming amount of evidence in support of WM impairments in schizophrenia (e.g., 5,44).

WM traditionally refers to temporary storage and manipulating information "on-line", typically in the service of some goal (45), but it is not a unitary construct. For example, Baddeley's model of WM suggests that it is comprised of a central executive resource system, two slave subsidiary systems (the phonological loop and the visuo-spatial sketchpad), and an episodic buffer (45).

There is relatively little evidence that WM deficits can be unambiguously attributed to dysfunction in either the verbal or visual-spatial buffer systems, as individuals with schizophrenia exhibit abnormalities on WM tasks with many different material types, with relatively little evidence for selective deficits for one material type over another (5,44). This has led to the suggestion that WM deficits in schizophrenia might primarily reflect deficits in the central executive resource system, or the active maintenance and manipulation of information over time, an interpretation consistent with a central role for deficits in the proactive control of behavior.

However, there is debate about the degree to which WM impairments in schizophrenia really reflect deficits in the maintenance of information, versus the initial encoding or representation of information. For example, in one meta-analysis (44), the effect sizes of WM impairment across studies did not change as a function of the delay period used, implying that deficits in the initial generation of representations could impact the stability of such representations, and therefore the ability to accurately maintain them over time. Consistent with this hypothesis, studies examining encoding deficits have demonstrated that patients with schizophrenia exhibit deficits even in the absence of a delay (e.g., 46). At the same time, a number of studies have provided evidence for deficits in the ability to maintain information across time in schizophrenia, even after controlling for encoding differences (e.g., 46,47).

Prefrontal recruitment during working memory in schizophrenia

Similar to the literature on cognitive control and DLPFC function, there is a robust functional neuroimaging literature demonstrating the presence of abnormalities in prefrontal cortex recruitment associated with WM dysfunction in schizophrenia.

The majority of findings suggest that regions comprising the dorsal frontal-parietal network are affected in patients and may be contributing to WM abnormalities. Specifically, reductions in DLPFC (Brodmann's area 9/46) activation have been documented while patients perform WM tasks, suggesting that patients exhibit task-related "hypofrontality" (17,48). These findings have also been confirmed through quantitative meta-analytic studies (49,50). Such DLPFC deficits are present even in medication naïve individuals (17), and also occur, albeit to a lesser extent, in the first-degree relatives of individuals with schizophrenia (e.g., 29), suggesting a potential role as an endophenotypic marker.

Further, as with proactive cognitive control, there is evidence suggesting a key role for impaired connectivity between DLPFC and other WM related regions (e.g., parietal cortex, thalamus and striatum) in explaining WM impairments in

schizophrenia (51-55), as well as evidence for altered gamma and theta oscillatory activity in prefrontal regions associated with WM impairments in this disorder (e.g., 56-58).

The above discussion focused on decreased DLPFC activity associated with proactive control and WM. However, there have been discrepant findings with regard to whether individuals with schizophrenia show decreased or increased DLPFC activity during WM (59-61). To explain this, some work has focused on the idea that WM capacity may be dependent on the level of recruitment of DLPFC, which is thought to operate according to an inverted U model (62). Such a model suggests that, with increasing WM demands, there is a concomitant parametric DLPFC signal increase. However, as WM load demands reach and exceed capacity limitations, DLPFC signals begin to drop, presumably due to information load exceeding available computational resources (62).

In line with this hypothesis, evidence suggests that patients with schizophrenia may exhibit a shifted inverted U function, such that capacity limitations are reached faster (i.e., with lower WM load levels), which may result in over- or under-recruitment when compared to healthy controls, depending on the level of WM load at which the groups are compared (63-65). In other words, at low difficulty levels, patients may find performance more effortful and may have to recruit more prefrontal cortex resources than healthy controls to accomplish the same task, leading to findings of "hyperactivity" in prefrontal cortex. Consistent with this model, a meta-analysis (50) demonstrated that the magnitude of WM performance differences between patients and healthy controls was positively correlated with the magnitude of activation differences in dorsallateral prefrontal regions.

Another way to understand the mixed directions of WM related DLPFC activation in schizophrenia is to think about the temporal course of WM. If WM impairments in schizophrenia also reflect impairments in proactive control and DLPFC mediated function, then more specific predictions can be made about the timing of altered brain activation in WM tasks in schizophrenia. A failure to use proactive control would suggest that patients may show reduced activity during encoding and/or maintenance in lateral prefrontal regions. When a response is needed, they may need to try to retrieve the memoranda, potentially resulting in increased activation in brain regions associated with memory retrieval or response selection.

A number of studies that examined the time course of activity during WM trials have shown evidence for reduced activity during encoding and maintenance periods in DLPFC, as well as other WM related brain regions (12,66-69). Further, studies that have specifically examined retrieval related activity have found evidence for increased activation among individuals with schizophrenia in either the same or different regions that showed reduced encoding/maintenance related activation (12,65). Thus, it may be useful in future research to more specifically tease apart the components of WM, as well as to examine the role of overall level of performance.

EPISODIC MEMORY IN SCHIZOPHRENIA

Similarly to WM, EM is not a unitary construct, but instead involves a number of different functional components and associated neural systems. The current literature on EM posits critical roles for both the medial temporal lobe, with a particular focus on the hippocampus, and prefrontal regions.

A common theme in theories regarding the role of the hippocampus in EM is the idea that it is critical for the rapid binding of novel configurations of information (e.g., 70,71). Consistent with such theories, numerous imaging studies have shown activation of the hippocampus during the encoding or retrieval of novel relational information (e.g., 72), and have shown that enhanced hippocampal/parahippocampal activity at the time of encoding predicts subsequent successful retrieval of that information (e.g., 73,74). Furthermore, work in amnestic patients demonstrates the importance of hippocampal structures in relational processing (e.g., 75).

More recent models of EM also suggest differential roles for hippocampal versus perirhinal regions of the medial temporal lobes in encoding of item versus relational memory (76). At the same time, there are also clearly important contributions from prefrontal regions. Damage to the prefrontal cortex can lead to EM deficits, among other cognitive impairments (e.g., 77,78). Further, activity during encoding in a number of prefrontal regions (e.g., Brodmann's areas 45 and 47) predicts subsequent memory when participants are asked to process verbal information using semantic elaboration strategies (79,80). In addition, there is work suggesting that DLPFC may contribute specifically to successful relational memory formation and retrieval (81-83).

As discussed above, much of the EM literature has argued that the hippocampus is critical for binding information in memory. A number of studies have examined whether individuals with schizophrenia have binding deficits by exploring whether they are more impaired on memory for associative information (e.g., the association of previously unrelated words or items) as compared to memory for individual items. For example, Achim and Lepage (84) conducted a meta-analysis comparing performance on associative and item memory tests in individuals with schizophrenia, and concluded that there was evidence for a 20% greater impairment in associative as compared to item memory. However, a number of the associative memory studies included in this meta-analysis were tests of source memory (i.e., memory for the time and place in which an event occurred) rather than associations of novel pairs of items, and the human neuropsychological and imaging literatures suggests that PFC function may make an important contribution to source memory (85).

More recently, clinical researchers have begun to use tasks derived from the animal literature on hippocampal function, such as the transitive interference test, which measures the ability to learn the relationships among hierarchically arranged stimulus pairs, as well as the transitive patterning test, in which individuals have to learn about relationships between items for correct selection. Individuals with schizophrenia are impaired on critical conditions of these tasks requiring relational processing, but not on conditions that require simpler associative reinforcement mappings (86-88), though not in all studies (89).

Other work has used eye-movement measures of relational memory, shown to be impaired in patients with hippocampal lesions (e.g., 90), to identify relational memory impairments in schizophrenia (e.g., 91,92). There is also work indicating impairments in both item and relational retrieval for information that was relationally encoded in schizophrenia (93). Still other work has provided evidence for greater deficits in recollection than familiarity in schizophrenia, which have also been interpreted as reflecting relational memory impairments (e.g., 94). It is certainly possible that this pattern of EM deficits in schizophrenia suggest hippocampally mediated impairments (95). However, as noted above, prefrontal structures also contribute to EM, and this may be particularly important for control functions, such as the ability to generate and apply effective memory strategies that help bind novel information into memory. Accordingly, a number of studies suggest that individuals with schizophrenia are impaired in their ability to generate effective mnemonic strategies, and that providing people with schizophrenia with effective memory strategies enhances EM function (for a review, see 96).

Importantly, a meta-analysis of brain activity alterations during EM performance in schizophrenia showed consistent evidence for reduced activation in both ventrolateral prefrontal cortex and DLPFC, but did not find consistent evidence for altered hippocampal activity (97). Recent work on relational memory encoding and retrieval has shown evidence for impaired DLPFC function associated with impaired relational memory function (98) and autobiographical memory (99) in schizophrenia, though other recent work has also implicated hippocampal function (100).

Taken together, these findings suggest potential roles for both hippocampal and prefrontal function in EM, and also suggest the possibility that cognitive control deficits may contribute to EM deficits in schizophrenia.

COGNITION ACROSS PSYCHOTIC DISORDERS

A key question is whether the nature and/or severity of cognitive impairment found in affective psychoses is similar or different to that found in schizophrenia. If qualitatively different, this would argue for a fundamentally different role for cognition in those psychoses. However, if the pattern or profile of cognitive impairment is similar, such a result would be consistent with the hypothesis that there are common dimensions of psychopathology across the affective and non-affective psychoses (101).

Both empirical and meta-analytic studies have fairly consistently shown that the degree of cognitive impairment in schizophrenia is worse than in bipolar disorder (for a review, see 102) and psychotic major depression (103), with an effect size typically in the range of 0.3 to 0.5 (103-107). The literature on the comparison of schizoaffective disorder to schizophrenia is mixed, with some studies finding very similar magnitudes of cognitive impairments in these two disorders (108-110) and others reporting worse impairment in schizophrenia (107,111).

Despite the evidence of a larger magnitude of cognitive impairment in schizophrenia as compared to affective psychoses, the literature is fairly consistent in demonstrating that the profile of cognitive impairment is similar across schizophrenia and affective psychoses (112,113). In other words, the relative severity of impairments across different cognitive domains tends to be very similar in bipolar disorder, psychotic major depression and schizoaffective disorders as compared to schizophrenia (e.g., 104,105,109,114).

Perhaps one of the clearest examples of such a result was provided by Reichenberg et al (114). These researchers compared individuals with consensus research diagnoses of schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, and bipolar disorder with psychotic features. The individuals with schizophrenia and schizoaffective disorder were overall more impaired than the individuals with psychotic affective disorders, and the prevalence of cognitive impairment was higher in schizophrenia and schizoaffective disorder. However, the individuals within all four groups showed the same relative pattern of impairment across cognitive domains, with the greatest impairment in verbal memory, and the least impairment in visual processing and general verbal ability.

Depp et al (104) provided another compelling example in their study comparing patients with schizophrenia or bipolar disorder and healthy controls. The profile of impairment was very similar in the two patient groups, with the most impairment in information processing speed and the least in crystallized IQ. In addition, there is evidence that the factor structure of cognition is very similar across schizophrenia and bipolar disorder (115,116). There are, however, some exceptions to these results, and some studies that have shown differences across psychotic disorders in the pattern of cognitive impairment (e.g., 111).

Thus, the bulk of the evidence suggests that all psychoses (affective and non-affective) are associated with some level of cognitive impairment. This impairment may be equally severe in schizophrenia and schizoaffective disorder, but less severe in individuals with psychotic bipolar disorder and psychotic major depression. However, the profile or pattern of cognitive impairment across affective psychoses is very similar to that seen in schizophrenia. This finding is consistent with the idea that there are common mechanisms

that lead to cognitive dysfunction across psychotic disorders and with a growing emphasis on identifying core neural systems that contribute to impairments cutting across traditional diagnostic boundaries (117).

MEASURING COGNITION IN THE DSM-5

As reviewed above, there is ample evidence that a large percentage of individuals with schizophrenia and other psychotic disorders suffer from impairments in a range of cognitive domains (e.g., 114), and growing evidence that the level of cognitive impairment predicts functional abilities (social, occupational, living status) (e.g., 118,119-121).

Despite the importance of cognition in understanding function in schizophrenia and other psychotic disorders, the DSM-5 psychosis committee did not propose to include cognitive deficits as a criterion A symptom of schizophrenia or any other psychotic disorder. This is because cognition may not be useful as a differential diagnosis tool. As described above, the profile of cognitive impairments is similar across the non-affective and affective psychoses (103-105,109,114,122), though the level of impairment may be greater in non-affective psychoses (103-106). However, the wealth of data suggests that this separation is not sufficient to justify inclusion of cognition as a criterion A symptom of schizophrenia.

Nonetheless, it remains clear that cognitive function is important for understanding functional status in schizophrenia (121,123,124), as well as other psychotic disorders, including bipolar disorder (125-128), and that cognitive deficits are not well treated by current antipsychotic medications (e.g., 129). Thus, the DSM-5 psychosis committee included a dimensional assessment of cognition, in order to highlight the potential need for additional treatments specifically targeting cognitive remediation in schizophrenia and other psychotic disorders (e.g., 130,131).

This assessment is a single dimension that collapses across all potential aspects of cognitive impairment. Ideally, one might have a separate dimensional rating of most major domains of cognitive impairment in psychosis separately, as it is possible to see dissociations across the level of impairment in one domain versus another within an individual (e.g., relatively impaired in WM, more so than in EM). However, this is not feasible from a practical standpoint, and the pretense of at least a single global dimension serves to highlight the need to attend to cognitive impairment when conceptualizing treatment and prognosis for an individual with psychosis.

Information about cognitive function is not something that is typically possible to assess as part of the standard psychiatric interview. Ideally, one would obtain a formal clinical neuropsychological assessment in individuals with psychosis to fully understand the nature and severity of their cognitive impairments. Such assessment may be of particular value early in the course of illness, when considering plans for further education and vocational functioning. If it is not possible to obtain a full neuropsychological evaluation, a number of studies have shown that several different brief assessment approaches provide clinically useful information concerning a patient's general level of cognitive impairment (7,8,132-136). However, brief screening instruments developed for use in the detection of frank dementia, such as the Mini-Mental Status Exam, are not sensitive to the types of impairments that are typically observed in patients with schizophrenia and therefore their use is discouraged in this context.

The growing research on other methods for assessing cognitive function (e.g., self-report, clinician interview) suggests that they have limited correlation with objective measures of cognitive performance (137), though they may still have utility in predicting functional status (137-144). If a formal assessment of cognition is not possible, it is still important for the clinician to use the best available information to make a judgment about the individual's cognitive function, including the clinician's interactions with the patient and/or reports of family members or clinical staff. However, it is likely that, without objective assessments, such ratings may have less than optimal reliability and validity, though hopefully they will still serve to highlight the critical need for treatments that address this debilitating aspect of psychotic disorders.

CONCLUSIONS

Individuals with schizophrenia show significant deficits in a number of different cognitive domains, including cognitive control, WM and EM, and the pattern of deficits is similar to those observed in affective psychotic disorders. Given the emerging re-conceptualization of cognition in schizophrenia (or all psychotic disorders) as reflecting a core neurobiological abnormality, we suggest that an impairment in proactive control can influence performance in a wide variety of cognitive domains, and therefore may represent a common mechanism contributing to these deficits.

Further, we suggest that, at the neural level, a common denominator to such deficits may be an impaired function of DLPFC, its connectivity with other brain regions, and the neurotransmitter systems that support precise updating and maintenance of goal representations which enable proactive control.

We do not mean to imply that all aspects of cognitive impairment in schizophrenia can be fully explained by these mechanisms. Schizophrenia is a complex disorder, and it is clear that it would be an oversimplification to suggest that a single mechanism could explain the diversity of impairments found in this illness. Nonetheless, we think it important to raise the possibility that there is a common core mechanism that can help explain at least a subset of impairments, and which may serve as a target for therapeutic interventions that could broadly enhance cognitive function and outcome in this illness.

Acknowledgement

Both authors contributed equally to the work presented here.

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DOI 10.1002/wps.20145

A social neuroscience perspective on clinical empathy

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Clinical empathy is an important element of quality health care. Empathic communication is associated with improved patient satisfaction, increased adherence to treatment, and fewer malpractice complaints (1). Patients' perceptions of their physicians' empathy are positively related to more favorable health outcomes (2-4).

In addition to improving patient outcomes, clinical empathy is associated with increased overall well-being for the physician (5). High levels of practitioner empathy have been associated with decreased burnout, personal distress, depression and anxiety, along with increased life satisfaction and psychological well-being (6,7).

Despite increasing appreciation of the value of empathy, medical educators continue to struggle with how best to educate students and residents on empathy maintenance. There have been several promising creative approaches that have shown demonstrable short-term success (8). However, there is a lack of evidence for enduring success, that is, for interventions during medical education that will enable physicians to sustain empathy throughout their careers. A more comprehensive and precise understanding of the subcomponents of empathy and how they are influenced by stress and anxiety is needed in order to design targeted interventions.

CLINICAL EMPATHY AND DETACHED CONCERN

Empathy is difficult to define, and an operational definition remains elusive. In medicine, empathy has often been conceptualized as consisting of two primary features: *cognitive empathy*, defined as the ability to recognize and understand another's experience, to communicate and confirm that understanding with the other person, and to take effective action to then act appropriately in a helpful manner (9), and *affective empathy*, defined as emotional resonance with the patient (10).

Cognitive empathy has been singled out as beneficial in the clinical relationship, while affective empathy has been viewed as interfering with the physician's ability to make effective diagnoses and facilitate better outcomes. This has resulted in the teaching and practice of "detached concern", a process where physicians establish a certain emotional distance from their patients in order to maintain objectivity and limit exposure to the negative emotions routinely experienced by those patients (11).

However, recent research has demonstrated that the underlying rationale for implementing a "detached concern" approach is no longer tenable. First, affective engagement contributes to empathy, improving cognitive accuracy as well as affective understanding (12). Second, patients respond differently to emotionally engaged physicians. Patients who perceive their physicians as emotionally attuned or genuinely concerned disclose more, are more adherent to treatment, and show greater agency in addressing serious health problems such as cancer (11). Furthermore, there is now convincing empirical evidence that cognitive and affective aspects interact in the experience of empathy (13). Finally, the primary motivation behind the "detached concern" approach, that emotional connection will necessarily lead individuals into emotional turmoil, is not supported by the literature (14).

LACK OF EMPATHIC COMMUNICATION IN CLINICAL PRACTICE

Despite the clear importance of empathy in clinical settings, many physicians experience difficulty empathizing with their patients. For instance, a study which coded interviews between physicians and lung cancer patients found that, out of 384 empathic opportunities – defined as patients' statements including an explicit description of emotion or patients' statements or clues that indicated an underlying emotion – physicians responded empathically to only 39 (10%), most often reacting with little emotional support and shifting to biomedical questions and statements (15).

Using patient-physician interaction videos where students are taught to identify and code these types of empathic opportunities, as well as what would be appropriate empathic responses, could help them more effectively address those opportunities. Additionally, sustaining empathy during distressing moments begins with doctors learning to take their own emotional temperatures, so that they can notice when they are anxious and take a deep breath or count to ten before responding to the patient.

Both implementing mindfulness skills (16) and learning to return focus on the patient by becoming curious about what the patient is most concerned about at that moment can help physicians maintain empathy (11). Intensive training in mindful communication has been shown to reduce psychological distress and burnout, and increase empathy (17).

The vast majority of individuals have the capacity for empathy, and research suggests that medical students start school with similar or higher levels of empathy compared to an age-matched control group (18). However, empathy significantly declines over the course of medical school (10). The precise underlying causes of this decline are not well understood, and multiple factors likely play a role. The decrease has been attributed to a curriculum that promotes the objectification of the patient (19), increasing workload, mistreatment by supervisors, and lack of emotional support (6,20). High levels of burnout, personal distress, depression and anxiety have also been found to contribute to the erosion of empathy in medical school (7,20).

Notably, the decline in empathy is not consistent across students. A longitudinal study of 446 medical students found two distinct groups, with 70% showing a significant decline on the Jefferson Scale of Physician Empathy, and 30% seeming to have protective factors that neutralize the erosion of empathy (10). This study demonstrated that individuals in patient oriented specialties showed less decline in empathy than those in technology oriented specialties, and suggested that students with individual traits that protect against empathy erosion self-select into the more patient focused specialties (10). This could be the case, or it could be that training for patient focused areas places more emphasis on skills such as listening to the patient and how to counteract objectification of the patient, important to maintaining empathy in a patient-physician interaction.

Additionally, greater perceived social support from faculty and greater satisfaction with the learning quality of the environment have been associated with increased resilience to burnout, and high levels of stress and fatigue have been associated with decreased resilience to burnout (21). As increased burnout has previously been associated with decreased empathy in medical students (22), it is possible that these protective factors might also contribute to maintaining empathy.

A SOCIAL NEUROSCIENCE APPROACH TO EMPATHY

Empathy is a natural socio-emotional competency that has evolved with the mammalian brain to form and maintain social bonds, and which encompasses different components (13). Affective sharing, the first element of empathy to appear during ontogeny, refers to the unconscious sharing of the affective state of another, which can be assessed by measures of concordance of skin conductance (an index of autonomic arousal) between two individuals (23). Empathic understanding entails the conscious awareness of the emotional state of another person. Empathic concern refers to a motivation to care for someone in need. Successful emotion regulation enables the control of emotion, drive and motivation in the service of adaptive behavior. Even though these components are intertwined and not independent of one another, it is helpful to consider them separately, as each contributes to various aspects of the experience of empathy, and could be the target of specific interventions to promote clinical empathy in medical students (24).

Recent work in social neuroscience using functional neuroimaging demonstrates that the affective, cognitive and regulatory components of empathy involve interacting neural circuits (25). Empathic arousal is mediated by strong bidirectional connections between the brainstem, amygdala and sensory cortices, as well as connections with the hypothalamus, insula and somatosensory cortex (13,24). The cognitive aspects of empathy, such as emotion understanding and emotion regulation, are closely related to processes involved in perspective taking, self-regulation, and executive attention subserved by the medial prefrontal cortex, dorsolateral prefrontal cortex and temporo-parietal junction. Finally, the ability to feel concern and care for others has deep evolutionary roots that likely evolved in the context of parental care (26). Its neural underpinnings are found in subcortical neural systems similar to those known to regulate maternal behavior, especially the hypothalamus and orbitofrontal cortex (27).

These components differently contribute to the experience of clinical empathy. Affective sharing may act as a gain antecedent to empathic understanding, while cognitive components are important for representing the mental states of self and other, necessary to make decisions in a medical context (24). Importantly, the type of emotion regulation an individual employs largely determines whether cognitive resources are drained or primed (28). Specifically, research shows that a detached perspective can quickly dampen emotional reactions or filter out emotional information. This can be adaptive to a surgeon while operating on his anesthetized patient, but maladaptive when the same physician interacts with his patient after the surgery (28). This example illustrates the flexibility of emotion regulation in clinical settings, depending on both the physician's goals and the patient's needs.

The perception of pain in others acts as an empathic signal, alerting individuals that another person is at risk, attracting their attention and motivating social behaviors. The neural response to the pain and distress of others, a situation familiar to physicians, has been used in social neuroscience research as a window into the neurobiological underpinnings of empathy. Several regions involved in the experience of physical pain, including the anterior cingulate cortex, insula, periaqueductal gray, orbitofrontal cortex and amygdala, are activated by the perception or even the imagination of another individual in pain (29). Importantly, the pattern of neural response is highly flexible and can be modulated by a number of contextual, cognitive, social and interpersonal factors (25).

In the context of medicine, two neuroimaging experiments examined the neurophysiological response to the perception of pain in physicians (30,31). Physicians as well as matched non-physician controls underwent functional magnetic resonance imaging while watching videos of needles

being inserted into another person's body parts (face, hands and feet), as well as videos of the same areas being touched by a cotton bud (30). Physicians showed significantly less activation in brain areas involved in empathy for pain (anterior cingulate cortex, insula) than did non-physicians. In addition, physicians showed significantly greater activation in areas involved in executive control, self-regulation, and mental states understanding.

These findings suggest less empathic arousal and greater cognitive regulation of an emotional response among the physicians, and indicate that physicians' down-regulation of the pain response dampens their negative arousal to the pain of others. This may have beneficial consequences by freeing up cognitive resources necessary for being of assistance and perhaps even for expressing empathic concern.

These results may also inform individual differences in empathic decline and professional distress. Meta-analyses show that clinicians' distress is a key determinant of empathy decline (6). Medical students who are most vulnerable to professional distress, which may lead to emotional exhaustion, detachment and a low sense of accomplishment, may be those who have difficulties regulating their negative emotions. On the other hand, students with overly suppressed pain responses and insufficient negative arousal will also have problems with empathy. Some modicum empathic arousal (or affective sharing) may be necessary to help physicians attune to and empathically understand patients' emotions. A positive emotional reappraisal requires emotional content from the patient to be reinterpreted, molding potentially important information once it is available (28).

INDIVIDUAL DIFFERENCES IN EMPATHIC RESPONDING

Empathic disposition varies across individuals, and these differences are likely in part accounted for by interactions between an individual's life history, psychological traits and genetic makeup. Attachment is one construct, first proposed by Bowlby (32), which appears to reside at the interface of all three of these determinants. Attachment theory offers a compelling framework for understanding one's capacity to connect with others and develop supportive relationships as coping resources, and predicts individual differences in empathy (33). Security of attachment correlates with the individual degree of empathy and successful emotion regulation, and is inversely related to pain report and emotional distress (34). Empirical research also indicates that attachment security provides a foundation for empathic concern and caregiving (35). Importantly, these attachment styles are relatively stable across the lifespan.

In recent years, a great deal of work has begun to reveal some of the underlying neuroanatomical and neurochemical foundations of attachment-related processes and the variance in such attributes both between and within species (36). Such research has identified a number of neuropeptides that are clearly involved in an array of attachment-related social behaviors, including opioids, vasopressin and oxytocin.

Oxytocin, for example, has been demonstrated to play a central role in the initiation of maternal behaviors, social recognition and pair bonding in rodents (37). Studies in humans have demonstrated that oxytocin infusion can modulate a number of attachment-related behaviors, including trust, generosity, empathic concern, and empathic accuracy (38). Oxytocin administration selectively reduces emotional arousal to threatening social images (39) and differentially modulates visual attention toward social signals of positive approach (40). Moreover, it appears that individuals lacking high quality social connections show significantly reduced responses to oxytocin administration (39), which may reflect reduced receptor sensitivity.

Research into the influence of genetic variation within the oxytocin receptor has provided converging evidence of the role that oxytocin plays in human social behavior. Polymorphisms within the oxytocin receptor have been shown to be related to affiliative behavior, behavioral and dispositional empathy, and perceived social connectedness (41). Similarly, genetic variation in the oxytocin receptor is related to decreased neuroendocrine and autonomic reactivity to social stress and interacts with perceived social support to dampen physiological reactivity to social-evaluative threat (41).

Importantly, this does not suggest that empathy-related behaviors are genetically determined. Particular alleles in the oxytocin receptor system (or vasopressin or opioid systems) previously considered "vulnerability genes" can actually be viewed as "plasticity genes" in that they allow some individuals to be more sensitive to the social environment in general (42). This is consistent with the observation of large individual differences in what can be viewed as a "biological sensitivity to context", in which people are especially interpersonally adept in socially supportive environments and especially anxious and withdrawn in noxious environments (43).

CLINICAL EMPATHY AND PATIENT HEALTH: POTENTIAL MECHANISMS

A meta-analysis of studies that evaluated various contextual influences on patient outcomes found that physicians who adopted a reassuring warm and friendly approach were more effective than those employing detached concern (44). Empathic medical care may provide patients with a sense of personal connection and perceived control over their health that results in more effective coping strategies, influencing health outcomes through chronic modulation of physiological stress responses. In fact, a quarter century of research in neuroendocrinology and stress physiology has clearly demonstrated that the perception of social support and stressor controllability can have profound influences on the hormonal, cardiovascular and immunological response to a

broad array of physiological responses in both humans and non-human animal models (45).

Indeed, perceived controllability over a stressor is associated with prefrontal cortex mediated regulation of limbic (amygdala and hypothalamus) and brainstem (dorsal raphe nucleus) structures associated with neuroendocrine and autonomic nervous system reactivity (45). This provides a direct pathway through which the perception of one's ability to control aspects of his/her disease is capable of regulating physiological processes ranging from glucose metabolism and blood pressure to immunomodulation and neurogenesis (46).

Physicians routinely present information to their patients capable of generating substantial physiological stress responses. In many such cases, the physician-patient relationship represents the front line in the battle against disease, as it has the potential to shape the endogenous responses to illness-related stress that, in some cases, can have effects similar to pharmacological interventions (3). Empathic concern, as opposed to detached concern, allows physicians to better understand their patients and modify their approach to fit the individuals they are attempting to treat. Given the past quarter century of work showing that quality emotional connection has comparable influences on health outcomes as obesity and hypertension (47), it is clear that empathic approaches are needed for patient care.

CONCLUSIONS

The current view of empathy in clinical practice is limited and focused primarily on self-reports of physicians, with little understanding of the mechanisms which contribute to declining empathy during medical school and a lack of empathy generally within the medical field. A better scientific understanding of the connections between the mechanisms involved in interpersonal sensitivity, empathy, and care-giving behavior is needed to help physicians maintain high levels of empathy in clinical practice while limiting burnout and personal distress (48). This understanding should be incorporated into research on the organizational and contextual factors that shape medical professionalization.

It is now possible to bring to the study of clinical empathy a risk-vulnerability approach that promises to be both more precise and more comprehensive than previous research. This approach will increase our capacity to design better institutions and educational interventions to support empathy within clinical practice and to protect against its decline. Some interventions to improve empathy and communication between physicians and patients have already shown positive effects on both physicians' professional satisfaction and well-being. There is a need, however, for dedicated research to respond to the vital call for empathy enhancement in medicine with programs using social neuroscience-based knowledge.

Acknowledgements

The writing of this paper was supported by grants from the John Templeton Foundation (The Science of Philanthropy Initiative and Wisdom Research at the University of Chicago) and from National Institutes of Health (R01MH087525; R01MH084934) to J. Decety.

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DOI 10.1002/wps.20146

Harnessing the potential of the therapeutic alliance

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Originally developed within psychoanalytic psychotherapy, the therapeutic alliance has emerged as a widely studied pantheoretical change variable. In fact, a Google Scholar search for "therapeutic alliance" and "outcome" returns roughly 135,000 hits. The vast majority of these studies have reported on the relationship between the alliance and psychotherapy outcome. However, a smaller but growing literature has also examined the relationship between the therapeutic alliance and pharmacotherapy adherence and outcome.

The therapeutic or working alliance involves an ongoing collaboration between patient and provider encompassing both task- and affectively-oriented features of their relationship. Specifically, it is often defined as: a) the extent of patient-provider agreement on treatment goals; b) collaboration on treatment tasks necessary for goal attainment; and c) the affective bond (e.g., caring, liking, trust) between patient and provider (1). Patient and provider-rated, as well as observer-rated instruments are represented in the alliance-outcome literature.

THE ALLIANCE AND PSYCHOTHERAPY OUTCOME

Consistent with previous findings, a recent meta-analysis (2) involving 190 studies reported a significant relationship between the therapeutic alliance and psychotherapy outcome (weighted $r=.28$, $p<0.0001$). Overall, meta-analytic findings reveal that the magnitude of the alliance-outcome relationship is modest, accounting for 5-8% of the variance in outcome. However, the relationship is consistent, having been demonstrated across a variety of populations and treatments, including individual, couples/family as well as child and adolescent psychotherapy.

Although the literature linking the therapeutic alliance and psychotherapy outcome is robust, it is characterized by methodological shortcomings that have raised questions about the causal relationship between the alliance and symptom outcomes. Extant findings are observational rather than experimental. Inferring a causal relationship between alliance and outcome in such studies requires temporal precedence (3). That is, the alliance must predict subsequent outcome, while accounting for change that occurred prior to the alliance assessment (3). Many studies in this literature have not ruled out the possibilities that the alliance is "predicting" change that has already occurred or that symptom change is bringing about an improved alliance, rather than the reverse.

A recent review which examined eleven studies that met one or both of the criteria suggested by Feeley et al (3) – i.e., alliance predicting subsequent outcome and/or accounting for change that occurred prior to the alliance assessment – reported a median correlation between alliance and outcome of .24, with a mean of .19 (4). Although there was some variability in the findings, they supported the conclusion that therapeutic alliance is a key contributor to psychotherapy outcome. However, even such well-controlled studies may underestimate the magnitude of the alliance-outcome relationship. Crits-Christoph et al (5) reported that the use of multiple early alliance assessments, as opposed to just one, revealed a stronger alliance-outcome relationship than is characteristic of current meta-analytic findings; one alliance score accounted for 4.7% of outcome variance, while the average of six early sessions accounted for nearly 15% (5).

Patient diagnosis may play an important role in the alliance-outcome relationship. Among well-controlled studies that failed to find a significant relationship between the therapeutic alliance and outcome was one that examined three treatments for cocaine dependence (6). Although absolute alliance levels in this study were reportedly high, it is possible that the "chaotic" nature of the illness in these patients was responsible for the lack of relationship with outcome (6).

THE ALLIANCE IN PHARMACOTHERAPY

More recently, researchers have begun to examine the relationship between alliance, pharmacotherapy adherence and outcome. Initial studies suggest that the relationship between alliance quality and symptom outcome is also present in pharmacotherapy. For example, a study controlling for prior symptom change found that early alliance predicted subsequent change in depressive symptoms among those receiving antidepressant medication (7). A probable mechanism for improved outcomes is medication adherence. Indeed, alliance quality has been associated with treatment adherence among those with bipolar disorder (8) and first-episode psychosis, although only provider-rated alliance was predictive in psychosis (9). A smaller literature has examined the relationship between alliance and medication adherence outside the domain of psychiatric prescribing. For example, in patients with systemic lupus erythematosus, higher levels of working alliance were associated with greater medication adherence (10).

PATIENT AND THERAPIST VARIABLES RELATED TO THE ALLIANCE

The relationship between alliance and treatment outcome has stimulated efforts to identify predictors of alliance

quality. Few patient-related predictors have been identified. Patient demographic characteristics have not demonstrated consistent relationships with alliance quality. One of the few reliable predictors of high-quality alliances in psychotherapy is a secure patient attachment style (11), which is theorized to develop from predictable and caring interactions with caregivers early in life, eventually manifesting as an enduring relationship pattern.

Therapist variability in alliance development appears to have a greater impact on the alliance-outcome relationship than patient variability (12). Therapist attributes such as confidence, warmth, patience and flexibility have been shown to be positively associated with the development of high-quality therapeutic alliances (13).

Although the alliance is related to nonspecific therapist attributes and skills, it arises in a context in which technical interventions associated with specific forms of treatment are implemented. Considering that the alliance involves agreement on the goals and tasks of treatment, as well as the emotional bond, the contribution of specific techniques to the alliance is not surprising. In a comparison of the relationship between alliance and outcome in a structured form of cognitive therapy versus brief supportive therapy (in which therapists relied primarily on nonspecific elements of treatment), the magnitude of the alliance-outcome relationship was greater in the more structured therapy (14). Additionally, while there were no between-treatment differences in patient ratings of the emotional bond, participants in the more structured treatment rated agreement on tasks and goals more highly than did those in the brief support therapy condition. Thus, different models of intervention are likely to promote the alliance in distinct ways.

ALLIANCE DEVELOPMENT AND REPAIR

Data on how to train providers in promoting high-quality therapeutic alliances are few. In one study, trainees were taught specific alliance-promoting procedures including regular collaborative review of goals and therapeutic tasks, and high frequency intentional demonstrations of empathy as well as attention to use of the term "we" during sessions. While the sample was small and the results were not statistically significant, patient-rated alliance from pre- to post-training revealed moderate to large effect sizes (15).

The alliance is an ongoing interpersonal process that unfolds over the course of treatment. Some investigators have reported that the alliance manifests a U-shaped or V-shaped course, although the evidence is not consistent. Nonetheless, dealing constructively with alliance perturbations and ruptures is a critical therapeutic task. Recommendations for dealing with such ruptures include openness to criticism, validation of the patient's negative experience, and accepting responsibility for mistakes and empathic failures. Unrepaired ruptures have been shown to predict poor treatment outcome (16).

CONCLUSIONS AND FUTURE DIRECTIONS

Despite justifiable reservations about methodological flaws in the alliance-psychotherapy outcome relationship, well-controlled studies reveal that alliance is a consistent predictor of outcome. Moreover, the most common alliance measurement approach, the use of single session snapshots, as opposed to multiple early assessments, may underestimate the magnitude of the relationship (5). A nascent literature suggests that the therapeutic alliance is also related to pharmacotherapy adherence and outcome.

Despite its consistent relationship with therapeutic outcome, the potential of the alliance has not yet been fully harnessed. Clinicians and those who train them have few guidelines regarding how to create high-quality alliances, and more research is needed in this critical area. Furthermore, although a number of intuitive suggestions for addressing ruptures currently exist, empirical examination of these and other strategies is needed to derive data-based recommendations for responding constructively to alliance perturbations.

Finally, given the relationship between alliance and outcome in psychotherapy and more recent similar findings in pharmacotherapy, such research should be extended to areas beyond mental health settings. Although the therapeutic alliance is associated with medication adherence, the potential for employing the alliance to enhance medication adherence outside the domain of psychiatric prescribing has been understudied. Furthermore, treatment approaches for many chronic medical conditions include recommending behavior changes such as exercise or smoking cessation. The role that the patient-provider alliance may play in facilitating changes in these areas has rarely been investigated, but a few studies suggest the patent-rated alliance is related to adherence to treatment recommendations, patient satisfaction, quality of life and self-efficacy for health-related behavior change (17).

Hence, re-conceptualizing therapeutic alliance more broadly and studying the impacts of the provider-patient alliance across health care domains may yield insights that improve outcomes for many of the world's most pressing health conditions.

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DOI 10.1002/wps.20147

Towards a hermeneutic shift in psychiatry

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Psychiatry is currently going through a crisis of confidence (1). Some medical commentators have even questioned the very credibility of the profession (2). There are many indicators of this crisis. For example, leading up to the launch of DSM-5 by the American Psychiatric Association last year, the chairperson of the DSM-IV task force raised serious questions about the validity of the whole DSM process (3), echoing earlier criticisms by the chairperson of the DSM-III (4). It is clear that psychiatry has been a particular target of the marketing strategies of the pharmaceutical industry (5), strategies that have led to the corruption of evidence-based medicine in general (6). Much-heralded advances in antipsychotic psychopharmacology are now revealed as "spurious" (7). Academic psychiatry's attempt to transform itself into a sort of "applied neuroscience" (8) has consumed enormous resources but delivered very little for patients. A. Kleinman has called it an "extraordinary failure" and stated that "academic psychiatry has become more or less irrelevant to clinical practice" (9). In the U.S., where the practice of psychiatry has been most dominated by the DSM, neuroscience and the pharmaceutical industry, clinical work has become equated with the prescription of drugs. The *New York Times* carried a story in 2011 in which a psychiatrist spoke of having to train himself not to get too close to his patients and "not to get too interested in their problems" (10). Our discipline is in trouble.

There are several dimensions to the current crisis, but one of the most important difficulties is around the perennial question of what is an appropriate epistemology for psychiatry. What sort of knowledge can we have with regard to mental illness and what sort of expertise is possible? The current technological paradigm that dominates psychiatric thought (11) is based on the idea that episodes of mental illness arise from abnormalities in specific neural, or psychological, pathways or processes. Furthermore, it assumes that these can be grasped with the same sort of de-contextualized, causal logic that is used to explain problems of the liver or lungs. The authority of psychiatry and the power invested in it are often justified on the basis that it possesses, or is on the way to possess, a science that can predict outcomes, based on an accurate map of the underlying processes (12).

Therefore, debates about epistemology are not simply an intellectual exercise. Many psychiatrists feel that they cannot be "real doctors" unless their discipline is grounded in the natural science epistemology that guides the rest of medicine. In this short discussion, I do not intend to engage with the wider ethical and political dimensions of the current crisis; rather I simply wish to make the case that natural science methods reach their limits in the territory of mental health and illness. This is largely a territory of meanings, values and relationships, an assertion now supported by a large body of empirical evidence about how psychiatric interventions actually work (11). I argue that, if we are to be truly "evidence-based" in our discipline, we need a radical rethinking of our guiding epistemology: a move from reductionism to hermeneutics.

MEANING, CONTEXT AND PRACTICE

Many people still believe that answers to the current crisis will emerge from an ever greater focus on neuroscience. The Research Domain Criteria (RDoC) project, a quintessentially technological view of the future, is being promoted as the way forward. It conceptualizes mental illnesses as brain disorders: "in contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits" (13). Furthermore, it assumes that "the dysfunction in neural circuits can be identified with the tools of clinical neuroscience". However, others argue that there is also a need for "higher order" cognitive and computational approaches in addition to genetics and neuroscience in our attempts to map the mind and its disorders (14).

Central to all these approaches is the assumption that the mind is simply another organ of the body, or that it can be equated with the brain. In this understanding, "meaning" is generated *internally*, within "the brain" or "the mind" (15). It is viewed as something that emerges from a series of underlying neurological and/or cognitive processes, processes that are open to scientific investigation and explanation. Meaning, therefore, is something that can be explained fully in the terms of neuroscience or cognitive science models. This is what is meant by the term "reductionism".

I believe that these approaches are simply inadequate. One of the major insights of 20th century philosophers such as Wittgenstein, Heidegger and Merleau-Ponty was the realization that meaning is not something that happens inside an individual mind or brain, but instead comes into our lives from the social practices that shape the world around us. It is in and through this world that we grow into human beings and come to know ourselves and others. Social practices generate a context in which our words, our experiences, indeed our lives, have a meaning. For example, the man or woman being tortured faces physical pain, the tearing of flesh and screams of agony; so too does a mother in childbirth. A pain questionnaire administered in both scenarios will record similar scores. And yet there is a major

difference. The *context* of motherhood is usually rich with love and hope; the suffering of childbirth has a positive meaning and can be integrated into the mother's life. This is seldom the case for those who endure torture. The context of their suffering is very different, despite the fact that in both cases the physical pain will have been mediated through similar centres in the brain and similar neurotransmitters will have been released. Even the most sophisticated neuroscience will not help us to understand the *meaning* of pain in the life of any particular person. And it is the meaning of the experience that will determine the longer-term outcome.

This is also true of most of the experiences with which our patients struggle. As psychiatrists, our work is about "making sense" of experiences such as low mood, suicidality, voices and paranoia. This requires attention to contexts and the use of empathy. With the tools available to us (listening, coupled with the specific insights of phenomenology, psychology, neuroscience and the social sciences, and the specialized insights given to us through our medical training), we can sometimes begin to grasp "what is going on" for our patients. This is rarely definitive and all psychiatrists have to live with ambiguity and uncertainty.

TOWARDS HERMENEUTICS

I contend that good psychiatry involves a *primary* focus on meanings, values and relationships, both in terms of how we help patients as well as identifying from whence their problems arise (11). This is not to deny that psychiatry should be a branch of medicine, or that other doctors sometimes deal with problems of meaning. However, interpretation and "making sense" of the personal struggles of our patients are to psychiatry what operating skills and techniques are to the surgeon. This is what makes psychiatry different from neurology. When we put the word "mental" in front of the word "illness", we are demarcating a territory of human suffering that has issues of meaning at its core. This simply *demands* an interpretive response from us. I think that many psychiatrists would recoil from the idea that they should train themselves to be *uninterested* in the problems of their patients, as the *New York Times* interviewee described (10).

Hermeneutics is based on the idea that the meaning of any particular experience can only be grasped through an understanding of the context (including the temporal context) in which a person lives and through which that particular experience has significance. It is a dialectical process whereby we move towards an understanding of the whole picture by understanding the parts. However, we cannot fully understand the parts without understanding the whole. The German philosopher H.-G. Gadamer suggested that the idea of hermeneutics is particularly relevant to the work of the psychiatrist (16).

By adopting a hermeneutic approach to epistemology, we can attempt to understand the struggles of our patients in much the same way as we attempt to understand great works of art. To grasp the meaning of Picasso's *Guernica*, for example, we need to understand what is happening on the canvas, how the artist manages to create a sense of tension and horror through the way he uses line, colour and form. We also need to understand where this painting fits in relation to Picasso's artistic career, how his work relates to the history of Western art and the political realities of his day that he was responding to in the painting. The meaning of the work emerges in the dialectical interplay of all these levels and also in the response of the viewer. The actual physical painting is a necessary, but not a *sufficient,* factor in generating a meaningful work of art. A reductionist approach to art appreciation would involve the unlikely idea that we could reach the meaning of a painting through a chemical analysis of the various pigments involved.

CONCLUSION

I do not believe that we will ever be able to explain the meaningful world of human thought, emotion and behaviour reductively, using the "tools of clinical neuroscience". This world is simply not located inside the brain. Neuroscience offers us powerful insights, but it will never be able to *ground* a psychiatry that is focused on interpretation and meaning. Indeed, it is clear that there is a major hermeneutic dimension to neuroscience itself (17). A mature psychiatry will embrace neuroscience but it will also accept that "the neurobiological project in psychiatry finds its limit in the simple and often repeated fact: mental disorders are problems of persons, not of brains. Mental disorders are not problems of brains in labs, but of human beings in time, space, culture, and history" (18).

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DOI 10.1002/wps.20148

The promise of cognitive behavior therapy for treatment of severe mental disorders: a review of recent developments

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Cognitive behavior therapy (CBT), as exemplified by the model of psychotherapy developed and refined over the past 40 years by A.T. Beck and colleagues, is one of the treatments of first choice for ambulatory depressive and anxiety disorders. Over the past several decades, there have been vigorous efforts to adapt CBT for treatment of more severe mental disorders, including schizophrenia and the more chronic and/or treatment refractory mood disorders. These efforts have primarily studied CBT as an adjunctive therapy, i.e., in combination with pharmacotherapy. Given the several limitations of state-of-the-art pharmacotherapies for these severe mental disorders, demonstration of clinically meaningful additive effects for CBT would have important implications for improving public health. This paper reviews the key developments in this important area of therapeutics, providing a summary of the current state of the art and suggesting directions for future research.

Key words: Cognitive behavior therapy, adjunctive therapy, severe mental disorders, schizophrenia, major depressive disorders, treatment refractory depression, bipolar disorder

(World Psychiatry 2014;13:244–250)

Despite both steady advances in neuroscience and the introduction of newer generations of medications for treatment of schizophrenia and severe mood disorders, there remain many unmet needs in the therapeutics of these disorders. Worldwide, millions of people who are treated for those conditions do not obtain adequate responses to pharmacotherapy and, collectively, major depressive disorder, bipolar disorder and schizophrenia constitute the world's greatest public health problem (1), costing billions of dollars of lost human capital.

Although ongoing efforts to develop novel pharmacologic treatments will probably help to address these staggering unmet needs, at present the best strategy to improve outcomes is to combine therapies that are thought to have complementary mechanisms of action. Among the myriad of potentially adjuncts to pharmacotherapy that might be considered, cognitive behavior therapy (CBT) is arguably the most promising.

As exemplified by the model of therapy developed and refined over the last 40 years by Aaron T. Beck and colleagues, CBT is a treatment of first choice for outpatients with depressive and anxiety disorders (2,3). Beyond efficacy as a stand-alone treatment for less severe mental disorders, there have been vigorous efforts over the past 30 years to adapt CBT for treatment of more severe mental disorders. In this paper we examine the evidence pertaining to the utility of CBT for treatment of schizophrenia and the more severe, chronic or treatment resistant mood disorders. We also suggest areas where additional research would be helpful to further clarify the role of CBT for improving the lives of people with these potentially ruinous illnesses.

SCHIZOPHRENIA AND RELATED PSYCHOTIC DISORDERS

By the 1970s it was evident that, although many patients with schizophrenia obtained some symptomatic benefit from antipsychotic medications, relatively few actually fully recovered and the psychosocial functioning of many who obtained symptomatic relief left much room for improvement. The adjunctive use of psychosocial therapies, including more rehabilitative interventions and individual psychotherapies, represented one of the most obvious strategies to try to broaden the benefits of treatment and improve the quality of outcomes.

Whereas many psychosocial approaches to psychotic disorders side stepped delusions and hallucinations as appropriate targets for intervention, CBT did not, and promising findings from the first generation of randomized controlled trials (RCTs) began to emerge in the 1990s. There have been more than fifty RCTs, which have informed a number of meta-analyses and narrative reviews. These have generally been positive, and guidelines internationally have recommended the use of CBT in people with psychosis, especially medication-resistant cases (4,5). Typically, effect sizes ranging between 0.3 and 0.5 have been found (6,7).

In one of the most influential meta-analyses, Wykes et al (6) found an average effect size for target symptom (33 studies) of 0.40 (95% CI: 0.25-0.55), and significant effects (ranging from 0.35 to 0.44) for positive symptoms (32 studies), negative symptoms (23 studies), functioning (15 studies), mood (13 studies) and social anxiety (2 studies). They noted that these effect sizes were somewhat smaller in the

twelve studies that used the most rigorous methodologies – for example, a target symptom effect of 0.22 (95% CI: 0.02-0.43).

In the most recent meta-analysis, Turner et al (7) considered forty-eight RCTs examining psychological interventions for psychosis, including 3,295 participants. They concluded that CBT was significantly more efficacious than other interventions pooled in reducing positive symptoms (g=0.16). Of note, CBT was also significantly more efficacious when compared directly with befriending for overall symptoms (g=0.42) and supportive counseling for positive symptoms (g=0.23).

One limitation revealed in these meta-analyses has been a high degree of heterogeneity: the studies have been diverse and have included differing patient groups and different models of CBT of different levels of intensity. Nevertheless, even critics of CBT agree that there is a real, albeit small effect size advantage for CBT over and above medication alone (8). Notably, the investigators found no evidence of publication bias in these studies (8).

One persisting question has been the utility of CBT for the patients who may need the greatest amount of help, namely those who are resistant to multiple courses of therapy with antipsychotics. The meta-analysis of Burns et al (9) directly addressed this issue, examining the adjunctive benefit of CBT in patients with medication resistant syndromes both on completion of treatment and at follow-up. Twelve randomized controlled trials, with 639 participants, were included. Of these, 552 completed the post-treatment assessment (drop-out rate of 14%). An overall benefit for adjunctive CBT was found at post-treatment on both positive symptoms (Hedges' g=0.47) and global symptomatic status (g=0.52), and these effects were maintained at follow-up (g=0.41 and 0.40, respectively, for positive and general symptoms).

Where specific symptoms, such as command hallucinations (10), have been targeted, meta-analyses have also given positive results. A recent study focusing specifically on negative symptoms (11) likewise demonstrated a statistically significant and clinically meaningful benefit for adjunctive CBT. There have also been successful studies in early psychosis (12), patients with a history of aggressive behavior (13) and patients who have refused to take antipsychotics (14). In one study of CBT in patients with psychosis who were abusing substances (15), adjunctive CBT significantly improved outcomes, although in a second study the combination of motivational interviewing and CBT failed to demonstrate a positive effect (16).

There has been some dissent about the degree of effect overall and in comparison with supportive therapies (8,17), although the audience at a recent debate held at the Institute of Psychiatry in London rejected the contention that CBT for psychosis had been "oversold" (18).

There is also a substantial body of psychological and social evidence underpinning the practical research into "salience" (19), which is a very useful concept in describing deficits addressed by medication and CBT. The influence of trauma and social factors, such as poverty or immigration status, have been demonstrated to be relevant to psychosis (20) and these are key foci in CBT (21), with success shown in cultural adaptations (22).

However, implementation of CBT, even in countries where guidelines have strongly advocated its use, such as the UK, has been slow. Estimates suggest that up to 90% of eligible patients are not being offered adjunctive therapy in that country. A program of work with pilot sites and outcome metrics has been commenced to address this problem with dissemination.

CBT for psychosis has developed from Beck's original work in depression, which linked thoughts, feelings and behavior and broadened our biopsychosocial perspectives on psychopathology (23). However, the use of CBT in psychosis requires a primary focus on engaging people who may not recognize and indeed may actively dispute that they have mental health problems. There is, therefore, a need to develop a shared formulation of the problems that is acceptable to the individual from the narrative that he/she can provide. This allows increasing understanding and ability to cope with hallucinations, delusions and negative symptoms as well as anxiety and depression. The aim is to reduce distress and disability by working with these experiences and symptoms. The evidence shows that symptoms such as hearing voices and the intensity of delusional beliefs may recede, but this is a subsidiary goal.

Work with delusions involves exploration of their narrative – what led up to the beliefs emerging – and then further elaboration of the feelings and behaviors that accompany these beliefs. A reasoning approach is helpful in re-examining the basis for beliefs or at least sewing doubt sufficient for behavior to shift from often quite extreme avoidance or self-defeating behaviors to more constructive actions.

Beliefs about hallucinations can be elicited – these tend to involve externalization, omnipotence and omniscience. Each can be explored and alternative explanations arrived at, often using normalizing information – e.g., discussing effects of sleep deprivation and similarities of voices with dreams may be helpful. The content of voices may be commanding and abusive – work countering voices can begin to undermine underlying beliefs of shame, guilt and general negativity. Reduction in anxiety and depression can contribute to improvements in general wellbeing. Traumatic events commonly precede onset of abusive voices and work with these directly or by cognitive restructuring of negative beliefs about the self can be very successful.

Negative symptoms often arise through demoralization, but may also protect against distress and recrudescence of positive symptoms. Social avoidance reduces stress but causes major functional disability – work in finding alternative ways of coping with distress including behavioral activation can provide positive reinforcing experiences. Understanding beliefs like delusions of reference and thought broadcasting can provide the confidence and

resilience to release motivation and combat social inactivity and isolation.

In summary, CBT for psychosis is a very promising and evolving development (24). The evidence is clear that it reduces suffering, but it is offered to very few people in very few countries. Psychiatrists (25), mental health nurses (26) and case managers (27) have all been demonstrated to be able to effectively and safely use CBT in working with their patients with schizophrenia. Training is available, and there are many mental health workers – and their patients – who could benefit from using more effective and acceptable recovery-focused ways of working. National psychiatric associations and governments need to address problems with dissemination of CBT as a matter of urgency.

MAJOR DEPRESSIVE DISORDERS

CBT is by far the best-studied form of psychotherapy for treatment of major depressive disorders (28). It is also the best studied form of adjunctive psychotherapy for use in combination with antidepressants. For ambulatory treatment of non-psychotic episodes of major depressive disorder across the severity continuum, the combination of CBT and antidepressant medication has been shown in meta-analyses to convey an about 10-20% advantage in response or remission rates (29,30).

Given the large contribution of non-specific therapeutic effects in milder depressions (see, for example, 31), it has been suggested that the cost-effectiveness of combined treatment would be greater if it were used preferentially with patients with more severe, chronic or treatment resistant depressive disorders, i.e., those who are less likely to remit with one or the other monotherapy (28).

To date, no large scale studies or meta-analyses have confirmed the hypothesis that the advantage of combining CBT and pharmacotherapy is larger for more severe depressions. However, in a meta-analysis of individual patient data from studies of major depressive disorder that utilized either CBT or interpersonal psychotherapy (IPT), either singly or in combination with antidepressants, Thase et al (32) found a modest overall advantage for combined therapy, which was moderated by a significant interaction between severity and treatment strategy. Specifically, the advantage of combined treatment over psychotherapy alone was about three fold larger for the patients with recurrent major depressive disorder and more severe depressive symptoms than for the remainder of the patients.

There have been two major studies of CBT for patients who have not responded to antidepressants. The first was conducted as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project, a large multicenter trial carried out in the U.S. (33). This particular component of the multi-stage study enrolled 304 outpatients with major depressive disorder who had not remitted after a 12-14 week trial of citalopram therapy. Patients were allocated to receive either CBT or a change in pharmacotherapy, either alone or in addition to ongoing citalopram therapy. About 40% of the participants were treated in primary care practices, with the remainder treated in ambulatory psychiatric clinics.

The statistical power of the randomized components of STAR*D was unintentionally, but adversely affected by the decision to use an equipoise stratified randomization strategy. This was a paradoxical observation, as equipoise stratified randomization was intended to minimize attrition by maximizing patient choice. As only about 30% of the eligible patients consented to the randomization strata that offered CBT, the study had much less statistical power than planned and, as a result, could only detect large group differences as statistically significant. Some have suggested that the fact that so many patients opted out of the psychotherapy arms indicates that CBT has relatively low acceptability in "real world" settings. This interpretation, while understandable, is incorrect, as comparable proportions of patients were likewise unwilling to accept randomization to either the augmentation or switch options within the pharmacotherapy alone strata.

Among those who consented to randomization, the 12-week outcomes of the patients who received CBT (either alone or in combination with ongoing citalopram therapy) were generally similar to those who received pharmacotherapy alone. There were, in fact, no statistically significant differences in symptom reduction or response/remission rates. Not surprisingly, the patients who received CBT alone had fewer side effects than those who received pharmacotherapy alone, and those who received CBT as an adjunct to ongoing citalopram therapy had a significantly longer time to remission than those who received pharmacologic adjuncts.

The second study of antidepressant non-responders, known as CoBalT, was conducted in England (34). This study, which was carried out in primary care clinics, randomly assigned 469 patients with major depressive disorder who had not responded to at least one prospective, adequate antidepressant trial in the current episode to either CBT plus "usual care" (UC) or UC alone. Importantly, the design of CoBalT differed from that of STAR*D in that no effort was made in UC to ensure that patients received adequate courses of pharmacotherapy. CoBalT also differed from STAR*D in that the primary outcome was assessed six months after randomization, rather than after three months. Thus, CoBalT studied about seven times more CBT-treated patients than STAR*D and provided a longer course of therapy in comparison to a less rigorous specified pharmacotherapy condition.

With these design differences in mind, it may not be surprising that the CoBalT trial found a strong difference favoring the group that received CBT plus UC as compared to the group that received UC alone. For example, 46% of the CBT-treated patients met the response definition after 6 months, as compared to only 22% of the group that received UC alone. Significant

differences were also found on several secondary outcomes, including measures of depressive and anxiety symptoms.

A third study evaluated the utility of CBT for relapse prevention following successful treatment with electroconvulsive therapy (ECT) (35). This is a potentially important application of CBT because, despite being the most effective intervention for severe depression, longer term outcomes following ECT are typically worse than desired because of a high rate of relapse.

In this multicenter trial conducted in Germany, 90 patients with major depressive disorder who received an in-hospital course of right unilateral ECT began a 6-month course of guideline-guided antidepressant medication and were randomly assigned to one of three conditions: one third received adjunctive CBT, one third received adjunctive ECT, and one third received no adjunctive therapy (i.e., medication alone).

Although this preliminary study only had the statistical power to detect extremely large effects, trends strongly favored the patients who received CBT. For example, after 6 months of continuation treatment, 77% of the CBT-treated group met criteria for a sustained response, as compared to 40% and 44% of the patients in the groups that did not receive adjunctive psychotherapy. After 12 months, 65% of the patients who received CBT, as compared to only 28% and 33% of those in the ECT and pharmacotherapy continuation arms, had sustained responses.

These results suggest that, among a group of patients that was prone to relapse despite continuation treatment with antidepressants and/or ECT, a relatively large proportion obtained sustained responses with CBT. Moreover, given the problem with relapse following ECT, these results suggest that the potential value of CBT as an alternate means to improve longer term outcomes warrants further study.

The large, multi-center study of Keller et al (36) evaluated the utility of an intervention called cognitive behavioral analysis system of psychotherapy (CBASP) in more than 600 outpatients with chronic forms of major depressive disorder. This multi-stage RCT compared outcomes of a group treated with CBASP alone and the antidepressant nefazodone alone versus a group treated with the combination of both therapies. The results at the end of the 12 week acute phase strongly favored the combination strategy, within an advantage in intent-to-treat response and remission rates of approximately 20% (36).

A more detailed secondary analysis of the temporal sequence of symptom change demonstrated that the overall advantage of the combined group was attributable to sharing both the earlier onset of benefit seen in the nefazodone alone group and the later-emerging benefit seen in the CBASP alone group (37). Combined treatment was particularly more effective than pharmacotherapy alone for patients with a developmental history of physical or sexual abuse (38) and, as compared to CBASP alone, among the subset of patients with severe sleep disturbances (39). In a crossover phase that was delimited to patients who did not respond to an initial course of treatment with either of the monotherapies (40), sequential delivery of the alternate modality resulted in eventual outcomes that, at 24 weeks, matched those of the combined group at 12 weeks.

The value of sequential combined treatment of chronic forms of major depressive disorder was not confirmed in a subsequent multicenter trial (41). In this study, 491 outpatients with chronic forms of major depressive disorder who had not remitted following a prospective trial of antidepressant medication (primarily sertraline) received a second course of antidepressant medication and, in addition, were randomly assigned to receive 12 weeks of adjunctive CBASP, adjunctive supportive therapy (i.e., a "warm" contact/expectancy control condition), or no psychotherapy. No significant advantages – neither specific nor non-specific – were observed for the groups receiving adjunctive psychotherapy (41). To date, the investigators have not been able to identify any factors to explain the discrepancy in findings between this negative study and the much more positive first study of CBASP.

In summary, the promise of CBT to improve upon the outcomes of pharmacotherapy for patients with more difficult to treat depressive disorders has been partly supported by controlled studies conducted over the past decade. Although the evidence is generally supportive, there are several studies in which the predicted additive benefits of CBT were not observed (e.g., 33,41).

BIPOLAR DISORDER

Given the unmet need for better rates of sustained recovery in patients with bipolar depression who do respond to pharmacotherapy, the field has witnessed new interest in the possible role of CBT as an adjunctive treatment in bipolar disorder.

To date, six RCTs have tested the efficacy of adjunctive CBT. They included three studies that evaluated acute phase therapy of depressive episodes (42-44) and three studies that focused on relapse/recurrence prevention as the outcome of greatest interest (45-47).

In the initial study, which was a relatively small (n=52) single site trial conducted in Australia (42), the patients who received adjunctive CBT obtained a significantly greater reduction in depressive symptoms at the 6-month assessment (the primary endpoint) than did the patients who received pharmacotherapy alone. The advantage of CBT was not statistically significant at the one-year follow-up, although the trend continuing to favor the CBT group was large enough to be clinically meaningful if confirmed in a larger study.

The study of Miklowitz et al (43), which was a large, multicenter trial conducted as part of the Systematic Treatment Evaluation Program for Bipolar Disorder (STEP-BD), randomly assigned 293 depressed patients to receive either an intensive psychosocial intervention or three sessions of

psychoeducation. All participants were taking a mood stabilizer and/or a second generation antipsychotic, and most were also treated with an antidepressant. In addition to studying CBT, the STEP-BD investigators studied family focused therapy (FFT) and an alternate individual therapy, interpersonal-social rhythms therapy (IPSRT). The study consisted of a 6-month acute phase and a one-year follow-up. At the end of the acute phase, results strongly favored the group receiving adjunctive psychotherapy, both in terms of symptom reduction and remission rates: the group that received adjunctive psychotherapy was about 15% more likely to remit/recover than the one who received pharmacotherapy alone. Benefits were also sustained during follow-up. The outcome of the patients who received adjunctive CBT was similar to those who received IPSRT or FFT.

A third study, which was carried out in Spain (44), enrolled 40 patients with bipolar depression who had not responded to mood stabilizers and antidepressants. The CBT protocol lasted 6 months; the durability of treatment effects was assessed across a 5-year follow-up. Although the study was small, the results were clear: patients who received adjunctive CBT obtained significantly greater improvements in depressive symptoms at the end of the acute treatment protocol. At the 5-year follow-up, 89% of the patients who had received adjunctive CBT were recovered, as compared to only 20% of the group that had received pharmacotherapy alone.

The three RCTs that have examined the utility of adjunctive CBT for prevention of relapse/recurrence in bipolar disorder have produced more conflicting results. In the first trial, Lam et al (45) found a very strong effect favoring adjunctive CBT during the first year of follow-up, with the risk of relapse or recurrence reduced by about 50%. However, subsequent larger, multicenter trials found no advantage for adjunctive CBT as compared to either pharmacotherapy alone (46) or a briefer psychoeducational intervention (47).

A secondary analysis of the study of Scott et al (46) yielded an unexpected result that, if replicated, might explain the discrepancy in findings. Specifically, Scott et al found that patients who had suffered relatively few lifetime illness episodes (e.g., roughly 5 or fewer prior episodes) benefited from adjunctive CBT, whereas those who had experienced more numerous episodes (roughly 10 or more prior episodes) actually did worse when therapy was added to their treatment regimen.

As the value of routinely treating episodes of bipolar depression with antidepressant medications has still not been established definitively, the promising – albeit preliminary – findings about the use of CBT as a focused acute phase therapy for bipolar depressive episodes certainly engender optimism and suggest an important avenue for further research. It would be particularly worthwhile to examine the effectiveness of CBT – both alone and as a monotherapy – for patients with bipolar disorder II, for whom mood stabilizers have uncertain benefit, and only one medication – the second generation antipsychotic quetiapine – has received Food and Drug Administration approval.

CONCLUSIONS

Although many important questions still remain to be answered, the current state of the evidence suggests that adjunctive CBT conveys a clinically and statistically significant benefit for patients with schizophrenia and severe and/or treatment resistant mood disorders. Overall, these effects tend to be modest in grouped data – on the order of 10-20% increases in response or remission rates as compared to pharmacotherapy alone.

Such findings underpin the arguments of some who continue to assert that the additive effect of CBT for patients with severe mental disorders has been "oversold". To this we reply that we agree that there is much work to still be done and that we need other strategies to help those who do not respond to pharmacotherapy and CBT. We also note, however, that the effects of CBT in RCTs are comparable to the drug-placebo differences observed in contemporary RCTs of new generation pharmacotherapies for the same conditions. Thus, whereas there is room for further improvement, we are glad to be able to offer our patients a non-pharmacologic adjunct that may indeed help to reduce their symptoms, improve the quality of their response, or increase the amount of well time after achieving a response to treatment.

In an era of scarce resources, it cannot be said that all patients with severe mental disorders should receive adjunctive CBT. In fact, if replicated, the findings of Scott et al (46) might point to some subgroups who should not receive this type of adjunctive intervention.

Changes in the delivery of CBT are reducing the cost and slowly increasing the accessibility of treatment, which will eventually shift the cost-effectiveness equation such that combined treatment may be recommended for "most patients" who do not rapidly respond to first-line interventions. In the future, it may be possible to further refine the selection of patients who are likely to benefit from adjunctive CBT by use of neuroimaging techniques to gauge the activity of relevant circuits, as suggested by some recent findings (48-51).

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DOI 10.1002/wps.20149

Off label CBT: a promising therapy or an adjunctive pluralistic therapeutic ingredient?

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It is a truth universally acknowledged that any treatment developed in psychiatry for a specific target condition will be progressively judged as having therapeutic propensities above its station, whether it be a medication tested "off label" or a psychotherapy developed for specific scenarios and repositioned as having broader if not universal application.

Such a diffusion effect is neither to be disparaged nor commended – resolution should weight empirical evaluation. Astute clinical observations of such "secondary" targets leading to formal efficacy studies can provide breakthrough therapeutic advances. A simple exemplar is the progressive extension of use of the atypical antipsychotic drugs for managing schizophrenia to their use as augmenting antidepressant medications and in managing bipolar disorders.

Thase et al (1) detail such a diffusion effect for cognitive behavior therapy (CBT), with their title raising some questions for pondering. Are we simply observing CBT expansionism? Is CBT *truly* of value in managing "severe mental disorders" and what does "severe" mean? If of value, does CBT have a primary role or only an adjunctive one? Does it offer substantive or skimpy add-on benefits? What mechanisms are involved – a specific or non-specific therapeutic effect? And does the word "promise" in the title imply potential or a distillation of empirical evidence? Importantly, their paper answers many of these first-phase questions.

But not the issue of expansionism. Beck wrote (2) that he first commenced to formulate CBT in the fifties for the management of depression. His theory weighted a "cognitive triad" – with depressed patients viewing themselves, their future and their experiences negatively – and thus provided a therapeutic paradigm (i.e., redress the faulty dysfunctional attitudes held by those with depressive disorders). What remained unclear from that 1967 monograph (2) was whether such cognitive distortions were antecedent causal factors and/or "state" consequences of a depressed mood. If causal, then their correction did offer a logical therapeutic paradigm for those possessing a predisposing personality style, and might therefore not only be salient to acute management but of prophylactic benefit in averting future episodes by modulating the causal factor. If cognitive distortions were simply an epiphenomenon of a depressed mood, CBT would appear to lack a logic. For example, if an individual evidenced depressive cognitive distortions solely during an episode of melancholic depression and with both the depression and faulty attributions lifting after two weeks of receiving antidepressant medication, why might CBT be contemplated or initiated?

That exemplar suggests that CBT may be of no direct benefit when the psychiatric condition is quintessentially a "disease" with primary biological determinants and requiring a medication to address the biological perturbations – essentially the territory where Thase et al boldly choose to go in focusing on schizophrenia, related psychoses, bipolar disorder and severe, protracted and treatment-resistant depressive disorders.

But, while Beck focused on depressive disorders, he also articulated a broader "cognitive model", quoting Epictetus: "Men are disturbed not by things but by the views which they take of them" (2). Patients seeking clinical assistance not only have a disease or a disorder but psychological perturbations and distress accompanying that condition, its concomitants and its consequences. As Montgomery observed (3), "patients want to know what is wrong, if it's serious, how long it will last, whether it will alter their life plans". Even if they have a primary psychiatric disease responsive to medication, such non-disease concomitants have the potential to benefit from the therapist's interpersonal interactions – whether provided informally or as a formal psychotherapy – disallowing any parsimonious view that diseases require physical treatments only.

We recently demonstrated (4) superiority of antidepressant medication to CBT in a 12-week study of patients with melancholia – a putative depressive "disease". However, while we quantified absolutely no benefit from CBT over the first four weeks, we did observe some improvement over the next eight weeks. This perplexing pattern was clarified by several subjects stating (5) that, while CBT did nothing for their depressive condition, it progressively assisted in dealing with illness concomitants (e.g., anxiety) and in addressing depressive meta-cognitions – such as despair and demoralization about having such a condition. In essence, CBT was seemingly ineffective as a treatment for melancholia but it did assist people with such a disease to adjust to it and its consequences – an adjunctive but nevertheless important therapeutic component.

It is known that psychotherapy benefits accrue from both the specific technical nuances integral to its theoretical model (e.g., CBT can redress dysfunctional attitudes) and from non-specific therapeutic ingredients (including empathy, a clear rationale, a therapeutic relationship), and with the specific ingredients seemingly making the minority contribution. For example, Lambert's review of empirical studies (6) quantified that only 15% of improvement during psychotherapy was attributable to specific techniques – as against 30% to the therapeutic relationship, 15% to

expectancy effects and 40% to client and extra-therapy factors. Such non-specific (but potentially beneficial) factors are likely to be equally salient for those with the conditions considered by Thase et al, and again argue for a pluralistic therapeutic paradigm.

In their review, Thase et al provide a rich set of studies quantifying the benefits of CBT for psychotic and other "severe" mental disorders, but clearly position it as having an adjunctive role and avoid proselytizing. Several secondary questions can now be put. Are such benefits unique to CBT as against any other psychotherapy, or is that CBT is the "in vogue" psychotherapy or did it out-punch the other psychotherapies simply by having an evidence base? Does adjunctive CBT have specific (as against non-specific) benefits in such disease groups, and if so, where does it provide an impact? Is adjunctive CBT superior to non-drug adjunctive options (e.g., exercise, counselling, mindfulness)? If CBT is provided, when: as a combination package, or as a sequencing model after the impact of medication has been determined?

In the paper, as would be anticipated of these authors, understated wisdom weaves data about efficacy with the nuances of "real world" effectiveness. The authors' balanced appraisal allows us to conclude that findings, though promising, do not position adjunctive CBT as a therapeutic panacea to be mandated in a formulaic way.

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DOI 10.1002/wps.20158

CBT for severe mental disorder: a good product that is in danger of being over-extended

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There often comes a time in the history of every successful treatment in psychiatry when the notion of diagnosis seems to evaporate and the treatment seems to be a universal panacea. This happened in the past when, in the heady days after the introduction of antidepressants, these drugs were not only alleged to be effective in the treatment of depression, anxiety and somatic disorders, but also in "depressio sine depressione". Cognitive behavior therapy (CBT) is getting closer to this dangerous milestone, dangerous because it can lead to disillusion, so it is worth examining this in the new treatment areas described in the paper by Thase et al (1).

Improvement in schizophrenia may be only a consequence of improvement in depression, anxiety and related symptoms. When training medical students I advise them that, if they are stuck when asked for a named treatment for any psychiatric disorder, they should reply "CBT". When asked for the rationale for this, I suggest they reply: "because mood, symptoms, behavior and thinking are all closely inter-related and in (X) disorder mood and all other symptoms are made worse by cognitive distortion". This comment is relevant to the use of psychological treatments in schizophrenia. Although some of the trials of CBT in schizophrenia have been carried out without antipsychotic drugs being included, most, as Thase et al indicate, have used the psychological therapy as an adjunctive one. This is not ideal, as schizophrenia is a heterogeneous condition associated with considerable mood disturbance. There is also evidence that those who have relatively "pure" schizophrenia have a much better outcome than those who have comorbid mood or substance use disorders (2). Anxiety in particular is a very prominent symptom in schizophrenia (3). It is therefore quite possible that the benefits of CBT in schizophrenia are dependent entirely on the mood component, and although target symptoms of schizophrenia such as command hallucinations may be improved, this is not necessarily an anti-schizophrenic effect, as it could be secondary to the effects of treatment on mood. It is perhaps worth reminding ourselves that a similar adjunctive therapy for schizophrenia proposed 35 years ago, beta-blockade in the form of propranolol, was similarly found to be effective as an adjunctive treatment to antipsychotic drugs (4), but not when compared directly with chlorpromazine (5), and we know now that beta-blocking drugs have very little role to play in the treatment of schizophrenia apart from their possible value in treating abnormal movements.

A collaborative relationship may be therapeutic and independent of CBT. In chronic schizophrenia, where

negative symptoms are prominent, a great deal can be achieved by establishing a good collaborative relationship with patients. This is one of the important aspects of the recovery model (6), but is not specifically linked to CBT. It is also an important component of systematic environmental adjustment, or nidotherapy, in the treatment of schizophrenia (7,8). In further studies in this population, CBT should be compared with these other collaborative treatments.

The evidence base is subject to publication bias. There has been a great deal of concern in recent years about unpublished trials of drug treatment creating bias and distorting subsequent systematic reviews and meta-analyses. We all need to be reminded that psychological treatments in general are subject to publication bias, very clearly shown in respect of studies in depression (9). This is partly because single-blind methodology is less rigorous than double-blind methodology, and we need to be cautious when enthusiastic investigators are comparing a psychological treatment with a pharmacological one. Although Thase et al have claimed publication bias is not present in studies of CBT in schizophrenia, that bias is highly likely to be present. One of the major problems with complex psychological treatments is that adequate numbers to test hypotheses in trials are relatively rare, and encouraging results with small trials are often not replicated in large ones with much more rigorous methodology, and better independent assessment (10,11).

Early results promising but must work harder. It is possible to summarize the position of CBT in the management of severe mental disorder in the same language as a school report on a precocious, talented, but somewhat self-satisfied adolescent: "C. Beatty has impressed everybody with his ability and flair, but in recent months has become a bit of a dilettante. He needs to knuckle down and concentrate on his core work a little more assiduously. We are sure he can do this, but he must not be distracted and needs to avoid spending too much time with his less critical friends".

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DOI 10.1002/wps.20159

Have the potential benefits of CBT for severe mental disorders been undersold?

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Thase et al's useful review and update on cognitive behavior therapy (CBT) for severe mental disorders (1) highlights the recurrent debate about the magnitude of the impact of CBT on persons with psychosis, including the question raised by some as to whether the effectiveness of CBT for this population has been "oversold" (2,3). We would like to take this opportunity to adopt the opposite position, and to suggest that rather than the benefits of CBT being oversold, the potential benefits have actually been undersold. We argue our point by discussing three issues related to the evaluation and application of CBT for persons with severe mental disorders, including inattention in meta-analyses to critical study variables, over-emphasis on comparing CBT to so-called non-specific therapy controls, and the relative lack of use of CBT in persons with psychosis to address the most conventional treatment targets for which CBT has been established in the general population.

The conclusions drawn by meta-analyses are only as accurate as the variables summarized from the original

studies. Researchers who conduct meta-analyses go to great lengths to measure a broad range of study characteristics, such as using standardized approaches to quantify methodological rigor, publication bias, and the outcomes themselves, and this has been true in work evaluating the outcomes from CBT for psychosis (2,4,5). However, despite this laudable attention to capturing study details, meta-analyses of research on CBT typically ignore the unique outcomes targeted by specific studies, and combine all available studies when evaluating the impact of CBT on symptom and functional domains (2). Because of the breadth of potential targets of CBT for psychosis, these procedures may inadvertently lead to drawing inaccurate conclusions.

CBT comprises a broad range of treatment elements that can be adapted and applied to a wide variety of symptoms and impairments, and the specific treatment target in any one study has important implications for interpreting the results of meta-analyses which include that study. Studies may target positive symptoms, negative symptoms, relapse, and/or functional impairments. Combining studies that target different outcome domains is like "comparing apples to oranges", and can lead to an underestimation of the effects of CBT when the results of studies that did not target a specific domain are combined with those that did. For example, Sensky et al (6) evaluated the impact of CBT for psychosis on stable outpatients with persistent positive psychotic symptoms, Garety et al (7) focused on relapse prevention and psychotic symptoms in individuals who had recently experienced a relapse of psychosis, and Granholm et al (8) targeted defeatist attitudes and functional impairment in persons with schizophrenia. However, the results of all three studies were pooled in a recent meta-analysis examining the effects of CBT on psychotic symptoms (2), which likely obscured the results.

In a related fashion, inattention to critical population characteristics or contextual factors related to with whom and where the study was conducted can lead to results that are biased against CBT. For example, Lewis and colleagues (9,10) evaluated the impact of adding CBT for psychosis to inpatient treatment for people recently hospitalized for a first or second episode of psychosis. Psychosis severity decreased dramatically for the CBT, the supportive therapy, and routine treatment groups from baseline to post-treatment and follow-up, with the CBT group showing slightly more rapid improvement, but no differences between the groups at follow-up. The study appears to be a failure of CBT. However, what does it teach us about the effects of CBT in the sizable population of people with schizophrenia-spectrum disorders who experience persistent psychotic symptoms and are the typical recipient of the treatment? Very little. And yet in a recent meta-analysis (2) this study was included along with other studies of CBT for psychosis conducted in very different settings, such as studies focusing on stabilized outpatients with psychotic symptoms.

Meta-analyses are a powerful tool for evaluating the impact of an intervention by combining the results of multiple studies. However, the choice of which studies to include is not a trivial one, and needs to be made with an understanding of the nature of the intervention and target population. In the case of CBT, the penchant for meta-analyses to indiscriminately combine the results of studies targeting different outcomes in different populations or contexts has likely led to an underestimation of the true impact of CBT on selected targeted outcomes.

In most treatment systems for people with a serious mental disorder, resources to provide psychotherapy are limited. The primary question facing clinicians and policy makers is whether adding a particular form of treatment will significantly improve symptoms or functioning compared to the often-constrained services as usual. This question is particularly apt when discussing the inclusion of psychotherapy, which tends to be labor-intensive and not routinely provided to this population, even when evidence supports it, in contrast to pharmacological treatment, which is often the standard of care even in the absence of compelling evidence to support the specific intervention (e.g., off label use, polypharmacy). Unfortunately, most of the controlled research evaluating the effects of CBT has not been designed to address this most basic question facing clinicians and policy makers: does CBT for psychosis added to customary care confer more benefits than customary care alone?

In the field of mental health, researchers usually think about the utility of interventions in very different ways from clinicians. In their zeal to prove that psychotherapy can be studied just as rigorously as medication, psychotherapy researchers have typically adopted a "gold standard" control group modeled after the placebo used in randomized pharmacological studies. The rationale for using a control psychotherapy intervention is not based on the presumed inertness of the intervention, but rather that it controls for "non-specific treatment factors" common across all psychotherapies. Psychotherapy researchers are under tremendous pressure to adopt research designs that compare a specific psychotherapy model (e.g., CBT) with a potentially active control psychotherapy (e.g., supportive therapy, befriending), rather than treatment as usual, because such designs are considered to be more "rigorous" or elucidating of the mechanisms underlying the experimental treatment by reviewers. However, the answers obtained using this research design typically have limited practical utility to settings where supportive therapy or befriending are not the standard of care. Comparing a psychotherapeutic intervention to another "control" psychotherapy is informative about the relative benefits of one intervention over the other, but not about the absolute benefit of the experimental intervention when added to usual services, the primary question at stake. Research (including meta-analyses) that concludes that CBT offers little more

than a control condition such as supportive therapy inadvertently misses the critical issue for most clinicians: is there a strong probability that this intervention will improve outcomes for the individuals with serious psychiatric illnesses with whom I work?

Aside from the fact that studies comparing CBT to a control psychotherapy do not provide a direct test of the added benefit of CBT in a typical clinical setting, there are at least two other problems with such research designs. First, designs that evaluate the relative benefit of CBT vs. another psychotherapy approach provide no reasonable basis for even *inferring* the degree of improvement provided by CBT over usual care. Unlike medication placebos, the effects of non-specific psychotherapeutic interventions for people with severe mental disorders are not well understood, hence even when CBT outperforms a control psychotherapy, the absolute benefit of CBT remains unclear. Second, there is modest evidence suggesting that supportive psychotherapy may be beneficial for people with schizophrenia (11). To the extent that "non-specific treatment factors" in psychotherapy *do* contribute to improved outcomes in people with severe psychiatric disorders, research designs that compare CBT with a control psychotherapy will underestimate the effects of CBT over usual care in a typical clinical setting, where even supportive therapy may be a rare commodity.

Although the primary evidence base for CBT lies in decades of research on its effects on depression and anxiety, somewhat surprisingly these two symptom domains have not been the focus of extensive CBT research in people with schizophrenia and other disorders with psychotic features. Depression frequently antedates the onset of schizophrenia, and is one of the most consistent and impairing clinical syndromes in the illness (12). Research trials of CBT for psychosis often target depression related to psychotic symptoms, and demonstrate positive effects in reducing depression. However, very limited research has evaluated the effects of CBT on depression as the primary target symptom in this population (13,14), suggesting that CBT may be underutilized, and its effects under-appreciated in people with psychotic disorders.

Similar to depression, anxiety and anxiety disorders are also common in people with schizophrenia and related disorders, but have not been the focus of extensive CBT research. Some research does suggest that CBT is effective for anxiety disorders such as post-traumatic stress disorder (15) and social phobia (16) in people with severe psychiatric disorders. If CBT produces similar or even attenuated effects on anxiety in people with schizophrenia and other severe mental disorders as those reported in the general population, it would be an important tool for clinicians to alleviate much of the suffering caused by these disorders.

In conclusion, a growing body of research supports the efficacy of CBT for severe psychiatric disorders, but, as Thase et al note, access to CBT remains limited for most people with these conditions. While there has been an ongoing debate as to the magnitude of the impact of CBT, there are strong reasons to suggest that reviews of the research literature and commonly employed research designs have led to a systematic underestimation of the benefits of adding CBT to usual services. Specifically, meta-analyses that have failed to take into account the treatment targets, study populations, and contexts of different studies of CBT may underestimate treatment effects by combining the results of studies focusing on very different outcomes. Research designs that compare CBT with another active psychotherapeutic intervention in order to control for "non-specific treatment factors" will underestimate the incremental benefit of adding CBT to usual services to the extent that such control treatments produce some clinical benefit. Last, CBT has had only limited application to the problems of depression and anxiety as a primary treatment focus for people with schizophrenia and related disorders, despite the preponderance of evidence supporting the effects of CBT for these symptoms in the general population. This suggests that CBT may have untapped potential for addressing these problems in people with severe mental disorders. The confluence of these factors, combined with the lack of access to CBT for most people with severe mental disorders, suggest that the true benefits of CBT have been undersold, not oversold, to clinicians, researchers, policy makers, consumers of mental health services, their families, and the public at large.

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DOI 10.1002/wps.20160

CBT for psychosis: effectiveness, diversity, dissemination, politics, the future and technology

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Cognitive behavior therapy for psychosis (CBTp) was always going to be controversial, given the backwash in the US from the failure of psychoanalysis, the influence of biological psychiatry and neuroscience, and the globalization of the pharmaceutical industry. Talking therapies will attract criticism in spite of the evidence for their efficacy, a consistent albeit small effect. The evidence is summarized in the paper by Thase et al (1), but a number of points are worth making.

There is considerable heterogeneity in the CBTp studies, in the nature of the treatment and in the populations recruited, which may well result in some confusion.

CBTp has developed mainly in the UK, with different centres proposing their own theoretical models and array of clinical techniques. There were a number of reasons for this. The British tradition of social psychiatry and the work of the Medical Research Council Social Psychiatry Unit over five decades or more in investigating the importance of social factors in the course of psychosis was a significant challenge to purely biological explanations. Associated with this was the development of stress-vulnerability models of psychosis. Later, family intervention studies demonstrated that psychosocial interventions could reduce relapse rates in schizophrenia.

The second important factor was the expansion of CBT in the treatment of anxiety and depression. This provided the diversity of techniques, theoretical development and skills base that allowed expansion into the treatment of psychosis. As well as approaches to cognitive therapy developed by Beck, other cognitive and behavioral approaches were also influential, such as self-management, rational emotive therapy and applied behavioral analysis. In a systematic review (2), we classified the treatments used in 34 trials depending on the cognitive or behavioral focus of the intervention, and found that larger effect sizes were associated with more behavioral techniques. Cognitive therapy could, perhaps unkindly, be considered "the bastard child of the medical model", and the importance of social, familial and environmental factors emphasized in earlier more behavioral formulations were sidelined with the increased interest in internal (thinking) processes.

Finally, the expansion of clinical psychology in the UK National Health Service (NHS) resulted in a workforce, skills base and clinical and research opportunity that provided fertile ground for CBTp to develop. The NHS provided the infrastructure, opportunity and ideology for innovation.

Thus, there has been considerable variation in the theoretical and clinical developments of CBTp, which makes comparisons across trials problematic. It must also be accepted that trials are limited by practical, temporal and financial considerations, which means that questions such as the necessity or benefit of long-term and continuing treatment with CBTp are rarely answerable.

In addition, there is variation in the stage of illness, with inevitable confusion concerning therapeutic goals. Although the majority of studies have investigated drug resistant community based chronic patients, with a view to further reducing symptoms, and this was clearly the initial driver of CBTp, other later trials have had other goals. For example, attempting to speed recovery and influence course in acute recent onset patients, reduce relapse, prevent the development of psychosis in high risk patients, reduce substance abuse in dual diagnosis, treat the effects of trauma/post-traumatic stress disorder. All this has resulted in different patient populations, theoretical models, treatment approaches and therapeutic goals, making aggregated comparisons difficult.

It is worth noting that Wykes et al (2) found that generic CBTp did not reduce feelings of hopelessness, a risk factor for suicide, while a recent study with a theoretically based intervention was successful in reducing suicide behavior (3), indicating that specialist interventions are required for specific clinical problems. This has clearly become the focus of the second wave of studies, increasing the diversity of both cohorts and interventions, and increasing the difficulty in across study comparisons.

A related issue is the appropriateness of various outcome measures. Outcomes used by researchers are not necessarily those most important to patients. Thus, aggregation or single symptom measures in meta-analyses may miss important treatment effects or inflate them. One

example of this was the finding that CBTp did not perform significantly better than a control treatment of supportive counselling, although both did better than routine care, in the treatment of delusions. However, supportive counselling appeared to worsen auditory hallucinations, whilst CBTp resulted in their reduction (4).

Accepting that CBTp has a beneficial effect, how then to increase availability? The apparently simple solution to this is to train the workforce in these treatment techniques, thus an increasingly skilled workforce will increase access and availability of CBTp. This is based upon a number of assumptions which may not be accurate. First, it assumes that training is available. This is not always true. In the US there is a lack of training opportunities (5). In the UK, where training may be available, it is not clear to what level of training, experience or skills clinicians need to be able to deliver CBTp.

With the heterogeneity and variation in CBTp, it is not clear what should be taught. What are the necessary techniques and competencies, assuming it is possible to try and define these, a difficult task at the best. Given that psychotic disorders are notoriously difficult to treat, it might be expected that the most qualified and experienced practitioners would provide treatment, as would be the case, say, with complex heart surgery. But this is rarely the case in mental health services, where costs are the main driver. Thus, there is frequently a move to employ the cheapest staff and provide the minimum training necessary when rolling out new treatments, which could dilute treatment effects and be poor value for money.

Once trained staff return to their work place, they do not necessarily receive the management support and have the time to implement their training. Furthermore, having received training, staff may no longer be willing to work on the front line and, having become more qualified, they may prefer to take up teaching or research posts. Thus, training has the unanticipated effect of depleting the skilled workforce rather than enhancing it.

Lastly, what of the future? I would like to raise a few possibilities. First, an integration with neuroscience, so that investigations on brain plasticity effects of cognitive, behavioral and social interventions can be undertaken. Second, a greater focus on positive emotions and clinical methods which elicit and encourage these as part of a treatment strategy, from both a theoretical and clinical perspective. For example, broaden-and-build theories (6) and broad minded affective coping intervention (7,8). Third, the potential for the use of new technologies as a delivery platform for psychological interventions (9). This would include the use of mobile phone technology for real time assessment and interventions and the use of intelligent systems to individualize interventions and identify critical time points (10). The possibilities here for the widespread application of CBT in the developing world, where mobile phones are ubiquitous but health system infrastructure is undeveloped and prohibitively expensive, by "leap frogging" the normal pedestrian development (or lack of it) of mental health care, are exciting.

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DOI 10.1002/wps.20161

The efficacy of CBT for severe mental illness and the challenge of dissemination in routine care

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Cognitive behavior therapy (CBT) for severe mental illness has acquired a solid scientific status. Although the effect sizes are small to moderate, they are also quite robust and re-established in many meta-analyses over the last decade. Small to moderate effect sizes are common in adjunctive therapies, since the adjunctive intervention has to add further effects to a treatment which is already efficacious.

The conclusion at this moment is that monotherapy with pharmacological agents such as antipsychotic medication and antidepressants does not constitute optimal treatment for severe

mental illness. CBT can add to that with improved symptom reduction and fewer relapses in cases of depression (1). In children and adolescents, early intervention services for psychosis, delivering CBT and other interventions, are cost-effective (2). CBT has been found to be effective in the prevention of a first episode of psychosis in meta-analyses (3), and also cost-effective (4,5). So, CBT adds health gains for lower costs. Why not implement CBT in routine services?

Here we meet the biggest challenge for CBT in severe mental illness. Although CBT for schizophrenia has been recommended in several guidelines (e.g., 6) for over a decade, the accessibility in routine services even in England, where CBT for psychosis is most promoted and researched, is dramatically low (7).

The pharmaceutical industry has built an implementation infrastructure that is missing in psychosocial and psychological interventions. Whenever a new drug is released on the market, a substantial marketing budget is used on merchandising. Hundreds of salesmen will then visit doctors with brochures, free specimens and small gifts. In this way, the medication is successfully disseminated in the routine practices of the prescribers in a relatively short time. The challenge for CBT is that the professionals who will deliver the intervention first have to be trained and employed by the services, while a marketing budget is completely lacking. Training takes several years, and vacancies are not automatically open after training. This slows down the process enormously.

The caseload for a CBT therapist is much lower than for a medication-prescribing psychiatrist. Many more CBT therapists are needed to guarantee an access to CBT comparable to the access to drug treatment. Several therapists have been training nurses in CBT, but these nurses in general have too little knowledge of general psychopathology to develop adequate individually tailored case formulations, and permanent supervision is often needed.

Training of nurses and low-intensity therapists in CBT interventions directed at accomplishing a patient's personal goal has been successful. These interventions are more broadly accessible to service users, but the need for more specialized CBT for complex cases is not diminished (8). At some places in the Netherlands, CBT therapists work in teams with nurses, where the CBT therapist develops the individually tailored case formulation and the nurse is conducting parts of the therapy such as exposure exercises, self-esteem protocols, relaxation exercises. In this way, the shortage of CBT therapists working with patients with severe mental illness can partly be overcome.

On the other hand, CBT is a transdiagnostic intervention, successfully applied to almost all psychiatric conditions. The underlying mechanisms of (for instance) selective attention and avoidance behavior are common to several anxiety disorders, depression, eating disorders and also paranoid delusions. This is certainly an advantage. A therapist can use the principles of CBT in several kinds of disorders, and comorbid disorders as well. Training can be limited to the universal principles, and only small adjustments are needed for each disorder, such as different assessment instruments, a different speed of progress through the protocol, and different attitudes in case formulation dependent on the patient's illness insight. Because of the universal nature of generic CBT, therapists working in other psychiatric domains could easily enter the field of severe mental illness with little extra training.

This advantage of universality is, however, a disadvantage as well. Generic therapy might not be targeted enough for the specific problems of some patients. In recent years, more specific variants of CBT have been developed and successfully tested for psychotic symptoms, command hallucinations, and negative symptoms. Dissemination is not the dissemination of a final intervention. The intervention is at the same time improved and differentiated to address more specific problems with improved efficacy.

In conclusion, we can state that CBT has reached such a level of adjunctive effectiveness in severe mental illness that pharmacological monotherapy is not the optimal treatment anymore. CBT must be made available and accessible in routine psychiatric practice. This can only be accomplished if budgets are reallocated from clinical services with high 24-hour staffing needs to less labour-intensive outpatient services with more specialized interventions directed at symptomatic and social remission. The era of implementation has a slow start, but there is progress.

At the same time, there is room for improvement of CBT protocols by more specific and symptom-tailored interventions. The era of research has just begun for psychological treatments such as CBT in severe mental illness.

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DOI 10.1002/wps.20162

The usefulness for indicated prevention of severe mental disorders should play a central part in the further development of CBT

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Schizophrenic, severe major depressive and bipolar disorders often do not respond sufficiently to the usual pharmacotherapy and therefore constitute the world's greatest public health problem (1). Thus, we have every reason to be happy that we can offer cognitive behavior therapy (CBT) as an effective non-pharmacological adjunct to the millions of people who are treated for those conditions worldwide.

Obviously there are methodological problems as well as discrepant and negative results in numerous studies and meta-analyses on the effectiveness of complementary CBT in the above disease groups. Overall, however, the evidence speaks much more for than against the assumption that CBT or CBT-oriented strategies may improve the outcome of pharmacological treatment and prophylaxis, especially for treatment-resistant or chronic patients.

On the other hand, the "promise of CBT" should not be overestimated in this important area of therapeutics. Taken as a whole, the hitherto achieved effects are only moderate, and data concerning bipolar disorders are not sufficient. Also, the evidence of efficacy for CBT should not mean that other approaches are now excluded from the search for useful psychotherapies for severe mental disorders. The traditional vulnerability-stress-coping models and also the newer salience theory of psychoses (2) offer a good framework for the development and use of psychological treatment strategies. They show, in fact, that different environmental stressors as well as personal and environmental protective factors may be involved in each individual case. CBT programs can target various but obviously not all of these psychosocial factors.

Furthermore, important psychosocial influences such as trauma or migration interact with genetic-epigenetic and other biological factors (3). Therefore, even enthusiastic psychotherapists should not ignore that treatment and prophylaxis of severe mental disorders primarily deal with the current correction and future prevention of disorder-specific neuronal network pathologies in the human brain. The more we understand these pathologies, the more it will be possible to correct the network alterations by means of targeted neuromodulation. Research is currently testing new psychotropic drugs, neuroprotective substances and various brain stimulation methods to achieve this goal.

The debate on "promise and limitations of CBT" reflects the presently unsatisfactory state of development. To date there are still no really causally effective psychotropic drugs available for the treatment of severe mental disorders, due to the lack of knowledge about etiology. That is why we try to combine substances which only influence the final pathogenetic pathways, and therefore are only partially effective, with complementary psychological interventions. Here, CBT has proven particularly useful, as it has a favorable impact on some of the psychosocial factors which are important for the release of and coping with the clinical symptoms. Nevertheless, the therapeutic problems are far from being solved, and the search for causal treatment approaches must go on.

The directions for future research should include further testing of CBT in the initial high-risk states of psychosis or bipolar disorders (4). In persons who have already suffered from long courses of these diseases, with relapses or chronicity, CBT can only be an adjunct and at best produce the effects described in Thase et al's paper (5). Often the primary therapeutic goal of recovery is not at all achievable and what can be obtained is only coping with symptoms or loss of functions in order to reduce the burden of the disease and improve the quality of life.

On the contrary, in the high-risk states, which can nowadays be characterized very well for psychoses (6) and increasingly better for severe mood disorders (7), we just observe initial changes of experience which, depending on the individual constellation of stressors and protective factors, can progress or not to the actual disease. The prevention of the outbreak of severe mental disorders is what is meant by the concept of indicated prevention (8).

Right from the beginning, CBT was involved in the studies of indicated prevention of schizophrenia and has repeatedly been shown to be effective as the sole therapy without concurrent use of medication (9). It seems to be able to even prevent the transition of early cognitive disorders into attenuated psychotic symptoms and their transition into full schizophrenic symptoms (10). If this approach of indicated prevention is successfully transferred also to severe mood disorders, it promises to be much more useful in the fight against the world's greatest public health problem than the late adjunctive strategy (11).

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DOI 10.1002/wps.20163

CBT for psychotic disorders: beyond meta-analyses and guidelines – it is time to implement!

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The treatment of psychotic disorders has considerably improved since the introduction of antipsychotic medication more than half a century ago, and there is no doubt that this medication can reduce psychotic symptoms and the risk of relapse (1). However, even though pharmacological treatment is significantly better than placebo, there are a number of patients who experience side effects which in some cases can be harmful, and a proportion of people who still experience psychotic symptoms in spite of antipsychotic treatment (2). There are also patients who refuse antipsychotics because of the risk of side effects, the belief that they are able to handle their difficulties without medication, or a fundamental disagreement with the clinician about the nature of their symptoms. In other words: there is room for improvement, and the use of approaches other than medication alone should be explored.

There is clear evidence that cognitive behavior therapy (CBT) can reduce psychotic symptoms in schizophrenia when added to pharmacotherapy (1). Several meta-analyses have supported this conclusion, although many studies did not meet optimal standards for randomized controlled trials with regard to blinded measurement of outcome. The effect size in the most rigorously conducted trials is small (3), and evidence is lacking about the effectiveness of short versus long duration CBT (4). Few trials have directly compared CBT with other talking therapies (5), and it is possible, but not yet proven, that other therapies may also be effective. However, based on current evidence, it has not been established that psychodynamic therapy is better than treatment as usual (1).

On this background, the American Schizophrenia Patient Outcomes Research Team (PORT) recommendations state that persons with schizophrenia who have persistent psychotic symptoms while receiving adequate pharmacotherapy should be offered adjunctive CBT to reduce the severity of symptoms (6), and the National Institute for Clinical Excellence (NICE) guidelines recommend to offer CBT to all people with psychosis or schizophrenia (7).

In a recent paper, Morrison et al (8) presented data indicating that CBT can be effective even among patients who do not want to take antipsychotic medication. Whilst the sample size was small, this result is promising and warrants replication.

Many CBT trials have focused on treatment resistant delusions, where the therapist and the patient will examine the basis and the likelihood of the delusional belief, exploring alternative explanations and identifying behavior that can reduce the stress related to the symptoms. Hallucinations can also be a target for CBT interventions. In a recently published multicenter trial, Birchwood et al (9) reported that CBT focusing on modifying conviction of beliefs linked to the construct of voice power, thereby challenging the omniscience and omnipotence of the voices, can successfully decrease compliance with command hallucinations. This finding is very important from a clinical point of view, as the patients were otherwise treatment resistant, and in many cases posed a significant danger to themselves or others.

Hallucinations and delusions, however, are not the only symptoms in schizophrenia. For many patients, negative symptoms, depression, anxiety and low self-esteem are experienced as much more debilitating. CBT has been shown to be a promising intervention in reducing these phenomena. A more holistic approach to treatment, focusing not only on primary symptoms but also on the functional and psychological consequences of having a severe mental illness, is congruent with the current emphasis on factors that can facilitate recovery.

In order to ensure that guidelines in different countries are actually rolled out, a carefully designed and closely monitored plan for implementation is required, including financial resources for educational material, training and supervision. Politicians and administrators should understand the need for a strong educational fundament. A continuing focus on intervention quality through skilled supervision is necessary to avoid "puppet on a string" therapists, who can only mechanically implement the intervention as taught in training courses without a clear understanding of what is needed in a specific clinical situation (10).

The systematic evaluation of the implementation of CBT interventions in clinical settings can help build on the current evidence base and provide valuable information such as which subgroups may benefit from CBT, the acceptability of the intervention, the durability of treatment effects, and the meaningful outcomes which can be achieved.

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DOI 10.1002/wps.20164

Expand the applicability and acceptability of CBT approaches in mood disorders

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Thase et al (1) succinctly describe the benefits of cognitive behavior therapy (CBT) in both unipolar and bipolar mood disorder.

Concerning the former, it should be noticed that the STAR*D study had an enriched design, open only to patients still depressed after three-month treatment with citalopram (2). Less than a third of the eligible patients agreed to participate. Those who received CBT as an adjunct to citalopram had outcomes similar to those receiving pharmacotherapy alone. A second study showed clear advantages for the CBT group, but the benefitting group constituted less than half of the sample (3). The complexity of the design of the third study reviewed (4) contributes to the ambiguous state of the evidence.

The bipolar depressed patient studies are of particular interest, since some clinically significant risk of illness course worsening is associated with treatment employing the most commonly prescribed antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (5). Some indications of benefit were seen with each of the six CBT studies summarized by Thase et al. The large study in STEP-BD showed benefits sustained for a one-year follow-up period (6). Importantly, outcomes were similar for CBT and two quite different other forms of psychotherapy: family focused therapy with first-degree relatives participating, and interpersonal-social rhythms therapy. Three studies reviewed yielded generally negative results, but one (7) indicated significant adjunctive benefit among patients with fewer lifetime bipolar episodes, whereas patients with more episodes actually underperformed bipolar medications alone.

Thase comments on the importance of determining which patients should not receive CBT. There may also be merit in addressing ways that CBT can be adapted to the complex psychopathology of bipolar disorders. Most bipolar patients will have sleep disorders and anxiety disorders (or, equally relevant as a focus of treatment, anxiety symptomatology) that are not benefitted by primary bipolar drugs. Medications commonly used for anxiety and sleep disturbances, i.e., benzodiazepines and drugs such as zolpidem, often impair memory and judgment. Anxiety is the most consistent predictor of poor treatment response in bipolar studies and is highly associated with suicidality, poor function and greater health services utilization (8). No drug is approved for treatment of anxiety in bipolar disorder. CBT for bipolar disorder could include a focus on such domains as anxiety and sleep/circadian disturbances, and outcome

measures to assess changes in such domains.

Some variants of CBT are presented as adjunctive group psychotherapy (9). These have been reported as superior to unstructured support groups in reducing relapse into syndromal bipolar states. Some evidence indicates that benefits may be greater for manic relapses. Whereas most studies have been technique driven, there are several features that are common. These include attention to medication compliance, identifying early signs of episodes, improving coping skills, involvement of significant others, and provision of information about the features, course and treatment of bipolar disorder.

An underlying assumption of these approaches is that identifying situations that could precipitate relapse coupled with teaching about cognitive and behavioral skills to reduce such risks could benefit long-term wellness. However, these approaches tend to place little emphasis on individual needs, values and issues contributing to poor function. Mindfulness training has in recent years increasingly complemented relapse prevention techniques to better deal with a variety of medical disorders, including depression. Mindfulness aids patients staying in contact with diverse emotional states, both desirable and undesirable, recognizing reasons for associated maladaptive behaviors. A usual component of mindfulness is developing skills in stress recognition and stress reduction. Both emotional and cognitive experiences are utilized to deal more effectively with individual specific issues in achieving and maintaining a state of wellness. Mindfulness as a component of CBT could strengthen self-instituted steps to monitor emotional and thought characteristics, thereby contributing to reduce or limit problematic behaviors or emotional states (10).

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DOI 10.1002/wps.20165

Non-pharmacological and pharmacological treatments act on the same brain

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Treatment strategies for major psychiatric disorders, including affective and anxiety disorders, addictions and schizophrenia, include pharmacological and non-pharmacological interventions. These modalities might appear, at first glance, to have contrasting mechanisms of action, but their mechanisms may actually interact.

Brain structure and function are altered by experience. Defined broadly, experience can include internal states that alter relevant neural pathways, external (including social) stimuli, or exposure to pharmacological agents. Pharmacological and non-pharmacological stimuli can have similar or interacting effects on behavior or brain plasticity. An example is cross-sensitization between rewarding pharmacological (including potentially addictive) stimuli and environmental stressors (1).

Two psychotherapies, or two pharmacological treatments, may have complementary mechanisms of action. However, the fact that one treatment is pharmacological and the other non-pharmacological does not guarantee that they will have complementary mechanisms. Our challenge as clinicians is to determine how to use any potential treatment modalities available in the most efficient manner, especially given extensive evidence that response to single treatments is often suboptimal (2).

Three kinds of stimuli that can influence the course of a psychiatric illness are the following: a) pharmacological treatment could correct imbalances that

contribute to symptoms or relapse; b) external or social stimuli, including the structured stimuli provided by psychotherapies, could address the same, or different, imbalances; c) internally generated stimuli, including those resulting from the illness, and both specific and non-specific adaptations to it, could either ameliorate symptoms or make them worse. For example, episodes or exacerbations of depression, mania, anxiety or psychosis have natural histories in which, in general, they eventually resolve, though too often not before serious or tragic consequences have occurred (3). If mechanisms by which episodes eventually resolve could be identified, treatments could address them.

These three classes of stimuli are likely to interact, and facilitating interactions among them can be an important aspect of successful treatment. A potential example is a pharmacological treatment which reduces susceptibility to anxiety, resulting in enhanced ability to participate in behavioral therapies aimed at broadening the individual's scope of activity.

Thase et al (4) review extensive data from studies comparing combinations of pharmacological treatments with cognitive behavior therapy (CBT). In some ways these studies resemble pharmacological trials in which antidepressant or antimanic monotherapies are combined with placebo or a potential augmenter such as a second-generation antipsychotic. Potential problems in pharmacological and pharmacological plus non-pharmacological combination trials are similar.

The first is choice of treatments. What is the rationale for the specific pharmacotherapy and psychotherapy that were chosen, and the evidence that the specific treatments involved actually have complementary mechanisms? "Psychotherapy" can have neurobiological targets (5), and "pharmacotherapy" can have behavioral targets (6). Most treatment augmentation strategies have not been based on mechanism, though there are notable exceptions, such as studies of augmentation by lithium of response to antidepressant agents, which were based on complementary effects on serotonergic function (7). Different classes of antidepressants can differentially affect brain function (8) and may therefore interact differentially with specific psychotherapies or clinical characteristics.

The second problem is rational selection of patients for treatments, whether based on illness course, symptom pattern, genetics, family history, or other predictors. For example, in one study, a history of more than ten previous episodes was associated with relative lack of response to CBT (9), potentially consistent with an association between treatment non-response and a sensitized course of illness. Such individuals might have synergistic response to CBT combined with a pharmacological treatment that prevents expression of sensitized behavior (1).

The third problem is that pharmacological augmentation studies can be confounded by under-treatment with the medication being augmented, biasing toward a positive effect of augmentation that may not be present if the original treatment were adequately dosed. Examples include studies in mania where lithium or valproate levels were suboptimal and there was no attempt to optimize them before addition of a second-generation antipsychotic (2). The same problem can occur in antidepressant-CBT trials, so choice of medicine and dose, or of type of psychotherapy, should be considered carefully.

The fourth problem is that time courses of responses to treatment may differ, or effects of one treatment may enhance (or interfere with) effects of the other, depending on timing.

Finally, the so-called placebo effect is considered a nemesis of treatment studies, whether pharmacological or not. However, in real life, the placebo effect is an important part of successful treatment, as it is a physiological effect that is integral to the therapeutic alliance (10). Every pharmacological treatment has a non-pharmacological component that cannot be dissociated from it. This alliance can be fostered, or inhibited, by strategies that are nominally pharmacological or non-pharmacological.

While psychotherapy potentially involves more contact and opportunity for a therapeutic alliance to develop, so-called placebo effects are inherent in any treatment and cannot be dissociated from the effect of an "active" treatment (11). Selecting and administering a treatment in a manner that fosters adaptation and resilience is likely to increase its effectiveness as well as that of concomitant treatments.

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DOI 10.1002/wps.20166

How well can post-traumatic stress disorder be predicted from pre-trauma risk factors? An exploratory study in the WHO World Mental Health Surveys

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Post-traumatic stress disorder (PTSD) should be one of the most preventable mental disorders, since many people exposed to traumatic experiences (TEs) could be targeted in first response settings in the immediate aftermath of exposure for preventive intervention. However, these interventions are costly and the proportion of TE-exposed people who develop PTSD is small. To be cost-effective, risk prediction rules are needed to target high-risk people in the immediate aftermath of a TE. Although a number of studies have been carried out to examine prospective predictors of PTSD among people recently exposed to TEs, most were either small or focused on a narrow sample, making it unclear how well PTSD can be predicted in the total population of people exposed to TEs. The current report investigates this issue in a large sample based on the World Health Organization (WHO)'s World Mental Health Surveys. Retrospective reports were obtained on the predictors of PTSD associated with 47,466 TE exposures in representative community surveys carried out in 24 countries. Machine learning methods (random forests, penalized regression, super learner) were used to develop a model predicting PTSD from information about TE type, sociodemographics, and prior histories of cumulative TE exposure and DSM-IV disorders. DSM-IV PTSD prevalence was 4.0% across the 47,466 TE exposures. 95.6% of these PTSD cases were associated with the 10.0% of exposures (i.e., 4,747) classified by machine learning algorithm as having highest predicted PTSD risk. The 47,466 exposures were divided into 20 ventiles (20 groups of equal size) ranked by predicted PTSD risk. PTSD occurred after 56.3% of the TEs in the highest-risk ventile, 20.0% of the TEs in the second highest ventile, and 0.0-1.3% of the TEs in the 18 remaining ventiles. These patterns of differential risk were quite stable across demographic-geographic sub-samples. These results demonstrate that a sensitive risk algorithm can be created using data collected in the immediate aftermath of TE exposure to target people at highest risk of PTSD. However, validation of the algorithm is needed in prospective samples, and additional work is warranted to refine the algorithm both in terms of determining a minimum required predictor set and developing a practical administration and scoring protocol that can be used in routine clinical practice.

Key words: Post-traumatic stress disorder, predictive modeling, machine learning, penalized regression, random forests, ridge regression

(World Psychiatry 2014;13:265–274)

Post-traumatic stress disorder (PTSD) is a commonly occurring and seriously impairing disorder (1). Many people exposed to the traumatic experiences (TEs) that lead to PTSD come to the attention of the criminal justice or health care system shortly after exposure and could be targeted through these systems for early preventive interventions. In recognition of this fact, an increasing amount of research has been carried out to develop and evaluate early preventive interventions for PTSD.

While the interventions developed for delivery in the first few hours after TE exposure have so far proven ineffective (2), cognitive-behavioral (3) and prolonged exposure (4) therapies delivered within a few weeks after TE exposure have been shown to be moderately effective in preventing chronic PTSD. In addition, ongoing research suggests that a wider range of potentially cost-effective preventive interventions might become available in the future (5).

Importantly, though, these preventive interventions for PTSD are labor-intensive, making them infeasible to offer cost-effectively to all people exposed to TEs (1). Prediction rules that successfully target people at highest PTSD risk shortly after TE exposure could improve intervention cost-effectiveness.

Meta-analyses (6-8) and reviews (9-11) of studies that searched for these predictors point to six especially promising predictor classes: type-severity of TE (highest PTSD risk associated with physical or sexual assault) (7,12); socio-demographics (e.g., female gender and young age) (6,8,9); cumulative prior TE exposure (including exposure to childhood family trauma) (6,7,10); prior mental disorders (especially anxiety, mood, and conduct disorders) (10,11); acute emotional and biological responses (6,7,11,13); and proximal social factors occurring in the days and weeks *after* TE exposure (e.g., low social support, heightened life stress) (6,7).

This literature offers no guidance on how to combine information about these predictors into an optimal PTSD risk algorithm. Machine learning methods have been used to develop similar algorithms in other areas of medicine (14,15). However, most studies using information obtained shortly after TE exposure to predict PTSD are based on samples too small (typically N=100-300) to apply these methods. This limitation could be overcome if future prospective studies were either much larger or used much more consistent measures (to allow individual-level data pooling for secondary analysis) than studies carried out up to now.

Prior to that time, a preliminary PTSD risk algorithm could be developed from the first four classes of predictors enumerated above (i.e., socio-demographics, type of focal TE, prior TE exposure, prior psychopathology), based on analysis of existing cross-sectional community epidemiological studies. The latter studies tend to be quite large, which means that machine learning methods could be applied. Although limited by being cross-sectional and relying on retrospective reports to examine associations of putative predictors with subsequent PTSD, these preliminary prediction algorithms could be validated in small prospective studies (that are themselves too small for algorithm development).

The current report presents the results of developing a preliminary PTSD risk algorithm from cross-sectional data in the World Health Organization (WHO)'s World Mental Health (WMH) Surveys (www.hcp.med.harvard.edu/WMH), a series of community epidemiological surveys in 24 countries that included retrospective assessments of PTSD associated with 47,466 lifetime TE exposures. The large and geographically dispersed sample, coupled with the great variety of TEs and predictors assessed, make this database attractive for developing a preliminary PTSD risk algorithm. If the algorithm appears to perform well, it could subsequently be validated in smaller prospective studies and used as a starting point for data collection in future prospective studies.

METHODS

Samples

The WMH surveys were conducted in thirteen countries classified by the World Bank (16) as high income (Australia, Belgium, France, Germany, Israel, Italy, Japan, Spain, The Netherlands, New Zealand, Northern Ireland, Portugal, United States), seven upper-middle income (São Paulo in Brazil, Bulgaria, Lebanon, Mexico, Romania, South Africa, Ukraine), and four lower-middle income (Colombia, Nigeria, Beijing and Shanghai in the People's Republic of China, Peru). Most surveys were based on national household samples, the exceptions being surveys of all urbanized areas in Colombia and Mexico, specific metropolitan areas in Brazil, China and Spain, a series of cities in Japan, and two regions in Nigeria. Response rates were in the range 45.9-97.2% and averaged 70.4%. More detailed sample descriptions are presented elsewhere (17).

Interviews were administered face-to-face in two parts after obtaining informed consent using procedures approved by local institutional review boards. Part I, administered to all respondents (N=126,096), assessed core DSM-IV mental disorders. Part II, administered to all Part I respondents with any lifetime Part I disorder plus a probability subsample of other Part I respondents (N=69,272), assessed additional disorders, including PTSD, and correlates. Part II respondents were weighted by the inverse of their probability of selection from Part I. More details about WMH sample designs and weighting are presented elsewhere (17). The 42,634 Part II respondents who reported lifetime TEs included a sub-sample of 13,610 subjects who were exposed only once to only a single TE and an additional sub-sample of 29,024 subjects who reported multiple TE exposures.

PTSD was assessed for each of the 13,610 exposures in the first sub-sample. The 29,024 respondents with multiple TEs were asked to select a "worst" TE using a two-part question sequence. The first of the two-part sequence asked: "Let me review. You had (two/three/quite a few) different traumatic experiences. After an experience like this, people sometimes have problems like upsetting memories or dreams, feeling emotionally distant or depressed, trouble sleeping or concentrating, and feeling jumpy or easily startled. Did you have any of these reactions after (either/any) of these experiences?".

The 9,791 respondents answering "yes" were then asked the second question in the two-part series: "Of the experiences

you reported, which one caused you the most problems like that?". PTSD was assessed for each exposure reported in response to this question. However, as these "worst" TEs cannot be taken to describe all TEs these respondents experienced, we also assessed PTSD for one exposure selected at random for a probability sub-sample of respondents with multiple exposures (N=4,832). The observational record for each "worst" exposure was assigned a weight of 1, while that for each randomly selected exposure was assigned a weight of 1/tp (t=number of TEs reported by the respondent other than the worst TE; p=probability of case selection), in order to make the total sample of 47,466 exposures assessed representative of all lifetime TE exposures of all respondents.

PTSD diagnosis

Mental disorders were assessed with the Composite International Diagnostic Interview (CIDI, 18), a fully-structured lay-administered interview yielding DSM-IV diagnoses. A clinical reappraisal study carried out in several WMH Surveys (19), assessing the CIDI concordance for DSM-IV PTSD with the Structured Clinical Interview for DSM-IV (SCID) (20) used as the gold standard, found an area under the curve (AUC) of 0.69, a sensitivity of 38.3, and a specificity of 99.1. The resulting likelihood ratio positive (LR+) of 42 is well above the threshold of 10 typically used to consider screening scale diagnoses definitive. Consistent with the high LR+, positive predictive value was 86.1%, suggesting that the vast majority of CIDI cases would be judged to have PTSD in independent clinical evaluations.

Predictors of PTSD

Socio-demographics

Socio-demographics included gender along with age, education, and marital status at focal TE exposure.

Traumatic experiences

WMH Surveys assessed 29 TE types, including 27 specific types from a list, one open-ended question about TEs not included in the list, and a final yes-no question about any other lifetime TE that respondents did not wish to describe concretely (referred to as a "private event"). Respondents were probed separately about number of lifetime occurrences and age at first occurrence of each TE type reported.

Exploratory factor analysis found that the vast majority of TE types loaded on one of five broad factors (Table 1) referred to below as "exposure to organized violence", "participation in organized violence", "interpersonal violence", "sexual-relationship violence", and "other life-threatening TEs". Predictors of PTSD included a separate dummy variable for each focal TE type in addition to 29 dummy variables for prior lifetime exposure to the same types. Temporal clustering among TEs was captured by creating counts of prior lifetime exposure to TEs in each factor and of other TEs in each factor in the same year as exposure to the focal TE.

Prior mental disorders

The CIDI assessed seven lifetime DSM-IV internalizing disorders in addition to PTSD (separation anxiety disorder, specific phobia, social phobia, agoraphobia and/or panic disorder, generalized anxiety disorder, major depressive disorder and/or dysthymia, bipolar disorder I-II) and six lifetime externalizing disorders (attention-deficit/hyperactivity disorder (ADHD), intermittent explosive disorder, oppositional-defiant disorder (ODD), conduct disorder (CD), alcohol abuse with or without dependence, drug abuse with or without dependence).

Age of onset of each disorder was assessed using special probing techniques shown experimentally to improve recall accuracy (21). DSM-IV organic exclusion rules and diagnostic hierarchy rules were used other than for ODD (defined with or without CD) and substance abuse (defined with or without dependence). As detailed elsewhere (19), generally good concordance was found between diagnoses based on the CIDI and blinded clinical diagnoses based on the SCID (20).

Analysis methods

Conventional multiple regression (with all predictors in the model) (22) and four machine learning algorithms were used to predict PTSD. The machine learning algorithms included random forests (23) and three elastic net penalized logistic regressions (24) designed to address two problems in conventional multiple regression: that coefficients are unstable when high correlations exist among predictors, which is the case for the predictors considered here, leading to low replication of predictions in independent samples (25); and that conventional regression assumes additivity, whereas the predictors considered here might have non-additive effects (7,8,10).

Random forests is an ensemble machine learning method that generates many regression trees to detect interactions, each based on a separate bootstrapped pseudo-sample to protect against over-fitting, and assigns individual-level predicted probabilities of outcomes based on modal values across replicates (23). The algorithm was implemented in the R-package randomForest (26). The R-package r-part (27) was also used to examine the distribution of higher-order interactions underlying the data.

Elastic net penalized regression is an approach that trades off bias to decrease standard errors of estimates, reducing instability caused by high correlations among predictors using a mixing parameter penalty (MPP) that varies in the range 0-1. The three penalties we used included: the lasso penalty (MPP=1.0), which favors sparse models that force coefficients for all but one predictor in each strongly

Table 1 Distribution and conditional risk of DSM-IV/CIDI PTSD associated with exposure to the 29 types of traumatic experience (TE) assessed in the WMH Surveys (N=47,566)

	Proportion of all TE exposures % (SE)	Conditional risk of PTSD % (SE)	Proportion of all PTSD % (SE)
Exposed to organized violence			
Civilian in war zone	1.4 (0.1)	1.3 (0.5)	0.5 (0.2)
Civilian in region of terror	1.0 (0.1)	1.6 (0.6)	0.4 (0.1)
Relief worker in war zone	0.3 (0.1)	0.8 (0.7)	0.1 (0.1)
Refugee	0.7 (0.1)	4.5 (2.0)	0.8 (0.4)
Kidnapped	0.4 (0.1)	11.0 (3.0)	1.0 (0.3)
Any	3.9 (0.2)	2.9 (0.5)	2.8 (0.5)
Participated in organized violence			
Combat experience	1.0 (0.1)	3.6 (0.8)	0.9 (0.2)
Witnessed death/serious injury or discovered dead body	16.2 (0.5)	1.3 (0.3)	5.3 (1.0)
Saw atrocities	2.7 (0.3)	5.4 (4.1)	3.7 (2.8)
Accidentally caused death/serious injury	0.7 (0.1)	2.8 (1.0)	0.5 (0.2)
Purposefully caused death/serious injury	0.7 (0.1)	4.0 (3.1)	0.7 (0.5)
Any	21.3 (0.6)	2.1 (0.6)	11.2 (3.1)
Interpersonal violence			
Witnessed physical fights at home as a child	2.4 (0.1)	3.9 (0.7)	2.3 (0.4)
Childhood physical abuse	2.7 (0.1)	5.0 (1.0)	3.4 (0.7)
Beaten by someone else (not spouse/partner)	3.3 (0.2)	2.5 (0.6)	2.1 (0.5)
Mugged or threatened with weapon	8.2 (0.3)	1.8 (0.4)	3.8 (0.8)
Any	16.6 (0.4)	2.8 (0.3)	11.5 (1.3)
Sexual-relationship violence			
Beaten by spouse/partner	1.4 (0.1)	11.7 (1.3)	4.1 (0.5)
Raped	1.8 (0.1)	19.0 (2.2)	8.4 (1.0)
Sexually assaulted	3.2 (0.2)	10.5 (1.5)	8.4 (1.2)
Stalked	2.9 (0.2)	7.6 (2.0)	5.4 (1.4)
Other event	1.4 (0.1)	9.1 (1.0)	3.1 (0.4)
"Private event" (see text)	1.5 (0.1)	9.2 (1.1)	3.5 (0.4)
Any	12.1 (0.3)	10.9 (0.8)	32.9 (2.1)
Other life-threatening TEs			
Life-threatening illness	5.1 (0.2)	2.0 (0.3)	2.5 (0.4)
Life-threatening motor vehicle accident	6.2 (0.2)	2.6 (0.4)	4.1 (0.7)
Other life-threatening accident	3.0 (0.2)	4.9 (2.3)	3.7 (1.8)
Natural disaster	3.9 (0.4)	0.3 (0.1)	0.3 (0.1)
Toxic chemical exposure	3.5 (0.3)	0.1 (0.0)	0.1 (0.0)
Other man-made disaster	1.9 (0.2)	2.9 (1.3)	1.4 (0.7)
Any	23.7 (0.6)	2.0 (0.4)	12.0 (2.1)
Network traumatic experiences			
Unexpected death of loved one	16.8 (0.4)	5.4 (0.5)	22.6 (1.9)
Life-threatening illness of child	3.3 (0.1)	4.8 (0.6)	4.0 (0.5)
Other traumatic experience of loved one	2.4 (0.2)	5.1 (1.3)	3.1 (0.8)
Any	22.5 (0.4)	5.3 (0.4)	29.7 (2.0)
Total	100.0	4.0 (0.2)	100.0

CIDI – Composite International Diagnostic Interview, PTSD – post-traumatic stress disorder, WMH – World Mental Health

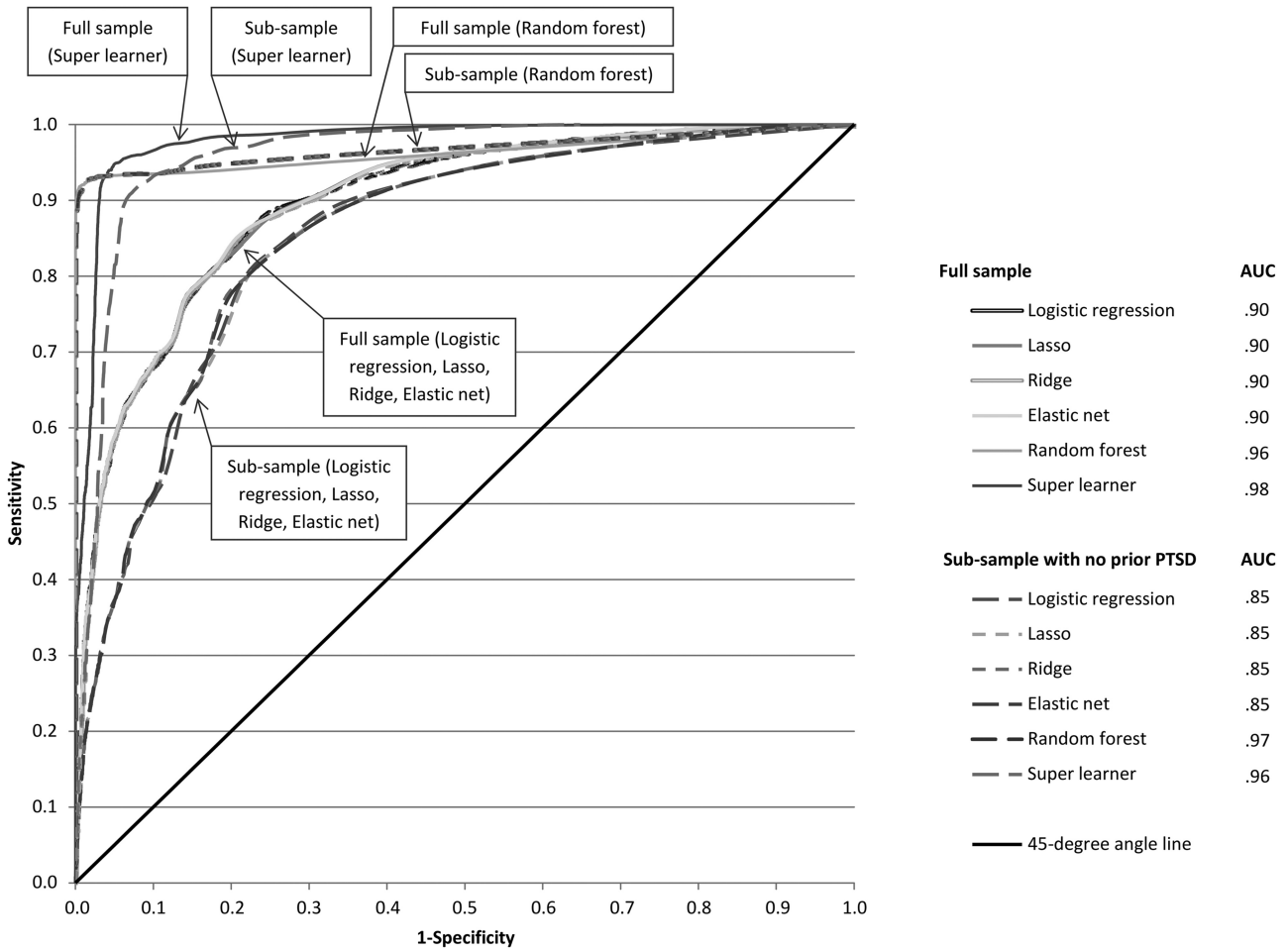

Figure 1 Receiver operating characteristic (ROC) curves for predicted probability of DSM-IV/CIDI PTSD after TE exposure based on the different algorithms in the total sample (N=47,466) and the sub-sample of exposures occurring to respondents with no history of prior PTSD (N=45,556). CIDI – Composite International Diagnostic Interview, TE – traumatic experience, PTSD – post-traumatic stress disorder, AUC – area under the curve

correlated set to zero; the ridge penalty (MPP=0), which uses proportional coefficient shrinkage to retain all predictors; and an intermediate elastic net (MPP=0.5), which combines both approaches. Internal cross-validation was used to select the coefficient in front of the penalty. The algorithms were implemented in the R-package glmnet (24).

Finally, we used an ensembling method known as super learner (28,29) to generate an optimally weighted composite prediction algorithm averaged across the five individual algorithms using internal cross-validation implemented in the R-package Super Learner (30).

It is important to note that the internal cross-validation used in the penalized regressions improves on a more conventional approach, that fits a model in a discovery sample and then tests the model fit in a hold-out sample, in two ways. First, the internal cross-validation used the 10-fold cross-validation technique, which divides the sample into 10 equal-sized sub-samples and estimates a model for each of a large number of fixed coefficients in front of the penalty 10 times, in each of which one of the sub-samples is held out and then the coefficients are applied to the hold-out sample. Model fit was then estimated across the 10 hold-out subsamples to evaluate model fit for the fixed value of the coefficient in front of the penalty. The value of that coefficient was then selected to maximize cross-validated model fit. Second, MPP itself was varied, which leads to variation in the number of predictors in the model. Super learner applied a separate 10-fold cross-validation to this entire set of procedures to assign differential weights to the models with different MPP values as well as to the other algorithms.

Individual-level predicted PTSD probabilities based on the separate algorithms and super learner were created, receiver operating characteristic (ROC) curves generated, and AUC calculated to evaluate prediction accuracy. Super learner predicted probabilities were then discretized into ventiles (20 groups of equal size ordered by percentiles) and cross-classified with observed PTSD. As prior PTSD was a dominant predictor in all algorithms, analysis was replicated for the 45,556 TE exposures that occurred to respondents without a history of prior PTSD. All analyses were based on

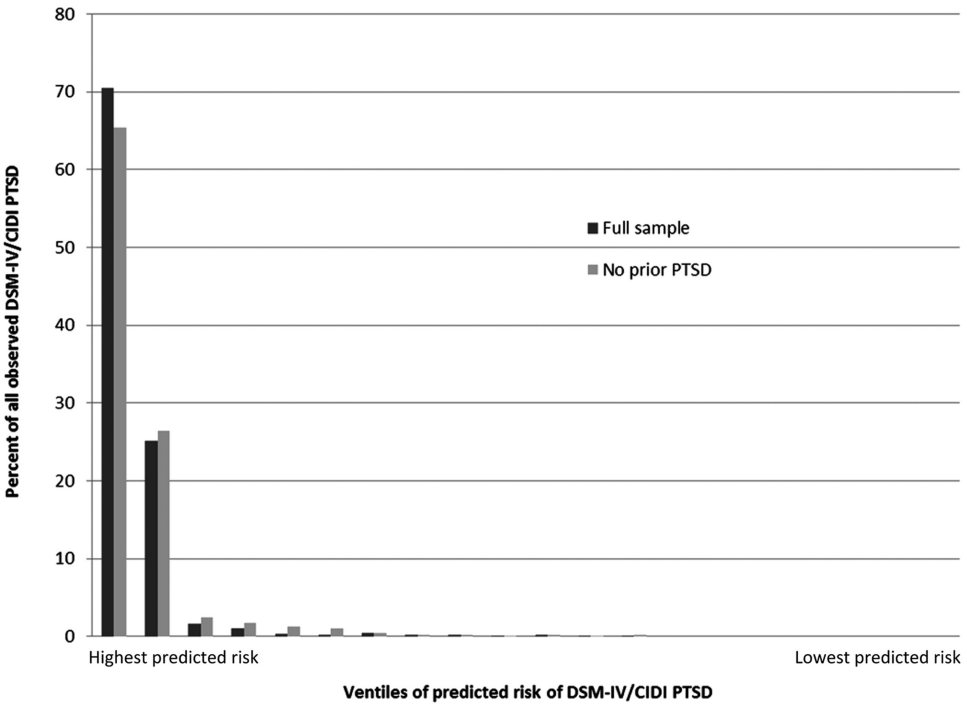

Figure 2 Concentration of risk for DSM-IV/CIDI PTSD. CIDI – Composite International Diagnostic Interview, PTSD – post-traumatic stress disorder

weighted data to adjust for individual differences in probabilities of TE selection.

RESULTS

Distribution and associations of TEs with PTSD

Weighted DSM-IV/CIDI PTSD prevalence was 4.0% in the total sample, and ranged across TEs between 0.1-0.3% (natural and man-made disasters) and 19.0% (rape) (χ^2=639.4, df=28, p<0.001) (Table 1).

The three TEs accounting for the highest proportions of PTSD cases included unexpected death of a loved one, rape, and other sexual assault. Unexpected death of a loved one was the most commonly reported TE (accounting for 16.8% of all TE exposures) and accounted for a somewhat higher proportion of PTSD (22.6%) than of all TE exposures, due to a conditional risk of PTSD slightly higher than average (5.4%). The other two TEs with highest proportions of PTSD cases (8.4% each) were rape and sexual assault. Rape and sexual assault were both much less common than unexpected death of a loved one (rape accounting for 1.8% of all TE exposures and sexual assault for 3.2%), but had much higher conditional PTSD risks (19.0 and 10.5%, respectively).

These high conditional PTSD risks associated with rape and sexual assault were part of a broader pattern of highest PTSD risk being associated with TEs involving interpersonal violence (kidnapping, beaten by spouse/partner, rape, sexual assault), which together accounted for 6.8% of TE exposures and 21.9% of PTSD.

Concentration of risk

ROC curves show that super learner substantially outperformed the individual algorithms other than random forests (AUC=0.96 vs. 0.90 in the total sample; 0.97 vs. 0.85 in the sub-sample with no prior PTSD) (Figure 1).

Inspection of observed PTSD distributions across ventiles of predicted risk based on super learner shows that 95.6% of observed PTSD occurred after the 10% of exposures having highest predicted risk (Figure 2). Conditional PTSD risk was 56.3% in the highest ventile, 20.0% in the second highest ventile, and 0.0-1.3% in the remaining 18 ventiles.

In the sub-sample with no history of prior PTSD, 91.9% of observed PTSD occurred after the 10% of exposures having highest predicted risk. Conditional PTSD risk was 32.2% for the highest ventile, 13.0% for the second highest ventile, and 0.0-1.2% in the remaining 18 ventiles.

Stability of results

Results were found to be stable across sub-samples defined by individual-level characteristics (sex, age, income) and country-level characteristics (economic development, recent history of war or sectarian violence) (Table 2). Between

Table 2 Concentration of observed DSM-IV/CIDI PTSD in the 10% of exposures having highest predicted risk based on the super learner algorithm across sub-samples

	Proportion of all PTSD associated with the 10% of exposures having highest predicted risk		Conditional observed PTSD risk in the 10% of exposures having highest predicted risk vs. other exposures			
			Total sample		Respondents with no prior PTSD	
	Total sample % (SE)	Respondents with no prior PTSD % (SE)	Top 10% % (SE)	Other 90% % (SE)	Top 10% % (SE)	Other 90% % (SE)
Gender						
Male	97.6 (0.6)	96.4 (1.1)	43.4 (3.8)	0.06 (0.01)	27.7 (4.2)	0.05 (0.01)
Female	94.3 (1.0)	92.6 (1.4)	35.9 (1.4)	0.40 (0.07)	21.4 (1.1)	0.34 (0.07)
Age at TE exposure						
Less than 25	95.2 (0.9)	93.3 (1.4)	41.5 (2.4)	0.22 (0.04)	23.0 (2.3)	0.18 (0.03)
25 or older	95.8 (1.2)	94.6 (1.8)	33.9 (2.0)	0.18 (0.05)	23.3 (1.6)	0.16 (0.06)
Education*						
Low/low-average	94.7 (0.8)	92.6 (1.2)	37.5 (1.8)	0.24 (0.04)	21.0 (1.4)	0.20 (0.03)
High-average/high	96.9 (1.4)	96.1 (2.1)	39.5 (3.1)	0.13 (0.06)	28.2 (2.9)	0.11 (0.06)
Country World Bank income level						
High	95.5 (0.6)	94.3 (0.8)	34.3 (1.5)	0.26 (0.03)	20.5 (1.2)	0.20 (0.03)
All others	95.3 (2.0)	92.6 (3.2)	52.6 (3.6)	0.14 (0.06)	33.2 (4.2)	0.13 (0.06)
Country involved in war or sectarian violence**						
Yes	95.9 (1.7)	94.4 (2.5)	44.4 (5.2)	0.13 (0.05)	28.8 (5.2)	0.13 (0.05)
No	95.3 (0.8)	93.6 (1.2)	36.6 (1.3)	0.23 (0.04)	21.6 (1.0)	0.19 (0.04)

PTSD – post-traumatic stress disorder, TE – traumatic experience
*Educational level relative to others in the same country; **countries classified "yes" include Colombia, Israel, Lebanon, Nigeria, Northern Ireland, and South Africa

94.3% and 97.6% of observed PTSD in each sub-sample was associated with the 10% of TEs having highest predicted risk (92.6-96.4% in the sub-sample with no prior PTSD). PTSD prevalence in these high-risk sub-samples was 33.9-52.6% (20.5-33.2% in the sub-sample with no prior PTSD).

Components of risk

Although it is hazardous to interpret individual machine learning model coefficients, since the algorithms maximize overall prediction accuracy at the expense of individual coefficient accuracy, an understanding of important predictors is nonetheless useful. We used a two-part approach to achieve this understanding. We first examined multivariate predictor profiles in 100 bootstrapped r-part trees to determine which interactions were important. These profiles all involved history of prior PTSD interacting either with history of prior unexpected death of a loved one and/or with history of prior sexual trauma. We then included dummy variables for those multivariate profiles along with variables for the main effects of individual predictors in lasso regressions.

Socio-demographic differences in PTSD risk were restricted to elevated odds ratios among women (1.5-1.6) and the previously married (1.5). Nine TE types also had elevated odds ratios, all but one of which (the exception being exposure to a life-threatening accident, with odds ratios of 1.4-1.8) involved interpersonal violence: rape (3.2-3.5), kidnap (1.8-3.4), childhood physical abuse (1.5-1.8), witnessing atrocities (1.4), and four other (than rape) TE types in the relationship-sexual violence factor (1.5-1.8). Three TE types had meaningfully reduced odds ratios: witnessing death/injury, toxic chemical spill, and natural disasters (0.4-0.7) (Table 3).

Five summary measures of collateral TEs occurring in the same year as the focal TE had meaningful odds ratios. Four of these five (the exception being unexpected death of a loved one) involved violence: two or more TEs in the organized violence factor, three or more TEs in the interpersonal violence factor, and any as well as two or more TEs in

Table 3 Lasso penalized logistic regression coefficients (odds ratios) to predict onset of DSM-IV/CIDI PTSD after exposure to a traumatic experience (TE)

	Total sample OR	Sub-sample without prior PTSD OR	Total sample with interaction OR
Focal TE			
Organized violence			
Witnessed atrocities	1.4	1.4	1.4
Witnessed death/injury or discovered dead bodies	0.6	0.7	0.6
Kidnapped	3.0	1.8	3.4
Interpersonal violence			
Childhood physical abuse	1.5		
Sexual-relationship violence			
Beaten by spouse-partner	1.8	1.5	1.7
Raped	3.2	3.5	3.5
Sexually assaulted			1.5
"Private TE" (see text)	1.8	1.5	1.8
Some other TE	1.6		1.5
Other			
Toxic chemical exposure	0.5	0.6	0.5
Natural disaster	0.4		0.5
Other life-threatening accident	1.8	1.4	1.6
Collateral TEs			
Multiple (2+) participants in organized violence	2.5	3.8	2.7
High (3+) exposure to interpersonal violence	6.8	11.5	9.3
Any exposure to sexual-relationship violence	1.6	1.7	1.6
Multiple (2+) exposures to sexual-relationship violence	4.0	3.2	3.5
Unexpected death of loved one	2.1	2.1	2.2
Socio-demographics			
Female		1.6	1.5
Previously married	1.5		1.5
Lifetime prior TEs			
Witnessed atrocities	1.6	1.8	1.6
Raped		2.3	1.6
Sexually assaulted			1.4
Unexpected death of loved one			1.6
Lifetime prior DSM-IV/CIDI disorders			
Separation anxiety disorder	2.0	1.7	1.9
Specific phobia			1.5
Attention-deficit/hyperactivity disorder	1.6		1.7
Generalized anxiety disorder	2.2	2.5	2.2
PTSD	27.2		
Interactions of lifetime prior PTSD with lifetime prior			
Sexual violence and unexpected death of loved one			5.4
Sexual violence but no unexpected death of loved one			12.9
Unexpected death of loved one but no sexual violence			5.7
Neither sexual violence nor unexpected death of loved one			134.7

CIDI – Composite International Diagnostic Interview, PTSD – post-traumatic stress disorder, OR – odds ratio

the relationship-sexual violence factor. The collateral TEs involving single exposures (sexual or death) had odds ratios of 1.6-2.2, while those involving two-three or more exposures had odds ratios of 2.5-11.5. Four of the 29 prior lifetime TE types had meaningful odds ratios, all of them elevated: witnessing atrocities (1.6-1.8), being raped (1.6-2.3) or sexually assaulted (1.4), and experiencing the unexpected death of a loved one (1.6) (Table 3).

Five of the 14 prior lifetime DSM-IV/CIDI disorders had meaningful odds ratios: ADHD (1.6-1.7), separation anxiety disorder (1.7-2.0), specific phobia (1.5), generalized anxiety disorder (2.2-2.5), and PTSD (27.2) (Table 3). The high odds ratio for prior PTSD was due to the 3.5% of exposures occurring to respondents with prior PTSD accounting for 40.5% of all episodes of PTSD. Disaggregation into underlying multivariate profiles showed that this strong effect of prior PTSD was limited to people marked as vulnerable by virtue of having past PTSD associated with TEs generally not associated with high PTSD risk.

DISCUSSION

Although caution is needed in interpreting these results, since the WMH Survey data were based on retrospective reports and fully structured lay-administered diagnostic interviews, it is nonetheless striking that we were able to produce a prediction algorithm in which the vast majority of PTSD cases were associated with the 10% of TE exposures having highest predicted risk. By far the most powerful predictor in the algorithm was history of prior PTSD, but a number of other prior lifetime mental disorders were also significant predictors, along with a number of measures of prior lifetime trauma exposure as well as socio-demographic characteristics of respondents and information about characteristics of the focal TE.

Limitations introduced by the retrospective nature of the data could have led to upward bias in odds ratios if respondents defined as having a history of PTSD were more likely than others to recall prior lifetime TE exposures and/or mental disorders. Importantly, evidence has been presented in the literature that this type of bias does, in fact, exist in retrospective reports among people with PTSD (31-33). In addition, the concentration-of-risk estimates could have been upwardly biased compared to those that would be found among people who sought help in the immediate aftermath of TE exposure in criminal justice or health care settings, to the extent that this help-seeking predicted subsequent PTSD.

Despite these limitations, the WMH Survey results are important in suggesting that a PTSD risk algorithm based on machine learning methods might help improve targeting and subsequent cost-effectiveness of preventive interventions for PTSD by pinpointing the small proportion of TE-exposed people having high PTSD risk that account for most subsequent PTSD. Our study is much larger than all other previous studies attempting to predict onset of PTSD from information about trauma types and pre-trauma predictors. We showed that a composite risk score can be constructed from such data that classifies the vast majority of people who go on to develop PTSD into a high-risk segment of the population.

External validation of the risk algorithms in prospective samples is, however, needed. A number of such prospective studies exist. All these studies are much smaller than the WMH Survey database and not all assessed the full range of predictors considered in our analysis. Nonetheless, the strong results found here suggest that it would be valuable to carry out replications in these prospective studies. We are currently involved in several collaborative replication analyses of this sort and are eager to work with others to evaluate the extent to which our algorithm fits in independent prospective samples. In addition, we are interested in collaborating with other groups to apply the methods used here to determine the predictive accuracy of algorithms based on data involving an expanded set of predictors, including biomarkers. If the results of this ongoing work are encouraging, subsequent prospective studies should be designed so that they include the full range of predictors found to be important. This would advance the agenda of creating broadly useful PTSD risk algorithms (and subsequent algorithms to predict other psychopathological responses to TE exposure) to target preventive interventions across a wide range of settings.

It is important to note that different predictors will almost certainly be found to be important in different populations (e.g., military personnel, first responders in disaster situations, civilians in less developed countries), in association with different TEs (e.g., sectarian violence in war zones or regions of terror, large-scale natural disasters) and in different screening settings (e.g., temporary emergency clinics established at the site of natural or man-made disasters, medical clinics in war zones, trauma units, emergency departments) (6,7,11,13). This means that an expansion of the current line of work will ultimately lead either to the development of a family of risk prediction algorithms or to a consolidated master algorithm that allows for complex interactions across populations, TEs, and screening settings.

It will also be important, in developing such algorithms, to be sensitive to variation in the costs of collecting different types of data (e.g., self-reports versus biomarkers), even data ostensibly assessing the same underlying constructs (e.g., self-reports of impulsivity versus neurocognitive tests of impulsivity), as well as the burdens associated with administering detailed risk factors assessments (both in terms of time burden and the psychological burden of asking people detailed questions of a sensitive nature in the immediate aftermath of TE exposure). Thoughtful analysis will be needed of the cost-benefit trade-offs associated with including-excluding expensive and burdensome elements of the assessments depending on strength of predictions.

Acknowledgements

The research reported here is supported by U.S. Public Health Service grant 1 R01MH101227-01A1 and is carried out in conjunction with the WHO's WMH Survey initiative, which is supported by the National Institute of Mental Health (R01 MH070884 and R01 MH093612-01), the John D. and Catherine T. MacArthur Foundation, the Pfizer Foundation, the U.S. Public Health Service (R13-MH066849, R01-MH069864, and R01 DA016558), the Fogarty International Center (FIRCA R03-TW006481), the Pan American Health Organization, Eli Lilly and Company, Ortho-McNeil Pharmaceutical, GlaxoSmithKline, and Bristol-Myers Squibb. The authors thank the staff of the WMH Data Collection and Data Analysis Coordination Centres for assistance with instrumentation, fieldwork, and consultation on data analysis. None of the funders had any role in the design, analysis, interpretation of results, or preparation of this paper. A complete list of all within-country and cross-national WMH Survey publications can be found at http://www.hcp.med.harvard.edu/WMH/. The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of the sponsoring organizations, agencies, or governments.

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DOI 10.1002/wps.20150

The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia

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In people suffering from schizophrenia, major areas of everyday life are impaired, including independent living, productive activities and social relationships. Enhanced understanding of factors that hinder real-life functioning is vital for treatments to translate into more positive outcomes. The goal of the present study was to identify predictors of real-life functioning in people with schizophrenia, and to assess their relative contribution. Based on previous literature and clinical experience, several factors were selected and grouped into three categories: illness-related variables, personal resources and context-related factors. Some of these variables were never investigated before in relationship with real-life functioning. In 921 patients with schizophrenia living in the community, we found that variables relevant to the disease, personal resources and social context explain 53.8% of real-life functioning variance in a structural equation model. Neurocognition exhibited the strongest, though indirect, association with real-life functioning. Positive symptoms and disorganization, as well as avolition, proved to have significant direct and indirect effects, while depression had no significant association and poor emotional expression was only indirectly and weakly related to real-life functioning. Availability of a disability pension and access to social and family incentives also showed a significant direct association with functioning. Social cognition, functional capacity, resilience, internalized stigma and engagement with mental health services served as mediators. The observed complex associations among investigated predictors, mediators and real-life functioning strongly suggest that integrated and personalized programs should be provided as standard treatment to people with schizophrenia.

Key words: Schizophrenia, real-life functioning, neurocognition, positive symptoms, disorganization, avolition, personal resources, resilience, internalized stigma, engagement with mental health services

(World Psychiatry 2014;13:275-287)

Despite significant advances in pharmacological and psychological treatments, schizophrenia still ranks among the first ten leading causes of disability worldwide. It has a direct negative influence on the real life of about 26 millions of people and an indirect negative impact on more than twice this number when considering patients' relatives and caregivers (1). Major areas of everyday life are impaired, including independent living, productive activities and social relationships (2).

The lessening of symptoms and the reduction of relapse rate contributes to improve real-life functioning, but is not sufficient to attain functional recovery (3-6). Enhanced understanding of factors that hinder functioning in schizophrenia is vital for treatments to translate into more positive outcomes (7). Studies carried out so far have led to partial and sometimes discrepant findings. Furthermore, they usually focused on neurocognitive deficits, negative symptoms and depression, and often failed to simultaneously consider several relevant variables (8-10).

For neurocognitive impairment, small to large correlations with global indices of functioning have been reported,

depending on the investigated domains, the use of a composite score (higher correlations for the composite score than for individual cognitive domains) and the rater of patient functioning (higher correlations for clinician rating than for patient self-report) (11,12). Recent studies have shown that the impact of neurocognitive impairment may be mediated by functional capacity, i.e., the ability to perform tasks relevant to everyday life in a structured environment, guided by an examiner. In some studies, the impact of cognitive impairment on real-life functioning was negligible when functional capacity was included in the model (13,14). Discrepant results have also been reported, i.e., no correlation between neurocognitive indices or functional capacity and self-reported real-life functioning (15), or a significant influence of neurocognitive dysfunction on everyday-life functioning in the presence of no influence of functional capacity (16).

Social cognition is currently considered a domain partly independent of neurocognitive functions and encompassing a large array of mental functions, from social perception to affect recognition, to theory of mind (17,18). Relationships between deficits in social cognition and impaired social and occupational functioning have been reported (17,19,20). According to some studies, social cognition mediates the effect of neurocognitive impairment on real-life functioning (21,22).

Negative symptoms have also been associated with patients' functional outcome (9,23,24). Both direct and indirect relationships between this psychopathological domain and real-life functioning have been reported (7,13). Evidence of the role of negative symptoms as mediators of the impact of other variables (i.e., neurocognition or functional capacity) on real-life functioning has also been provided (9,25). However, several limitations of previous studies might prevent solid conclusions and generalizability. In fact, negative symptoms have generally been regarded as a unitary construct, while the most recent literature suggests that these symptoms are heterogeneous and include at least two factors, "avolition" and "poor emotional expression", that might be underpinned by different pathophysiological substrates (26,27) and show different relationships to functional outcome (23). Moreover, largely used scales for the assessment of negative symptoms have been criticized for the inclusion of items assessing neurocognition and the focus on behavioral aspects, as opposed to internal experience, which may lead to artefactual associations with functional outcome measures (28,29).

An impact of depressive symptoms on real-life functioning in schizophrenia has also been reported (30-32). However, an association has generally been found only when studies examined subjective indicators of real-life functioning (13,33), suggesting that depression affects person's self-evaluation of functioning but not "real" functioning. The symptoms of depression may also affect functioning by interfering with subject's motivation and ability to properly organize him/herself in daily living activities. In this respect, the simultaneous evaluation of negative and depressive symptoms is important to clarify the relative contribution of these two psychopathological domains to real-life functioning.

Besides the variables summarized above, some studies have reported that patients with comparable severity of psychopathology may differ in their real-life functioning as a result of differences in personal resources (34-36). Resilience is a construct encompassing several aspects of personal resources. It is variously defined as a personal trait protective against mental disorders and a dynamic process of adaptation to challenging life conditions (37-40). In patients with schizophrenia, a significant correlation between resilience and psychosocial functioning has been reported (41); furthermore, lower baseline resilience was found among ultra-high risk subjects who converted to frank psychosis than among those who did not (42). Resilience is also related to patterns of mental health service engagement of patients with schizophrenia, which can affect real-life functioning (43).

Although it is obvious that real-life functioning is also influenced by the societal context, which includes disability compensation, job or housing opportunities, residential support, and various elements of attitudes and stigma (2), the identification of the most appropriate indices to capture the complexity of these variables is not an easy task. The evaluation of subjects' functioning with respect to employment or housing, for example, must take into account the offer of employment or housing in the place where the patient lives and the availability of social support, such as a disability pension. According to a recent study, differences in residential outcomes are likely based on differences in social services systems (44). Similarly, in a two-year follow-up of people with schizophrenia after their first episode, only those who were receiving disability compensation or were supported by their families were living independently (45). Indeed, it appears likely that interventions which modify the level of social support have an impact on real-life functioning in people with schizophrenia.

A higher level of internalized stigma – the process whereby people with severe mental disorders anticipate social rejection and consider themselves as devalued members of society (46-48) – has been found in association with lower levels of hope, empowerment, self-esteem, self-efficacy, quality of life, social support and adherence to treatment (49), suggesting an impact of this variable on real-life functioning, and the need to consider it in relevant studies.

From the summarized evidence, it is clear that real-life functioning of people with schizophrenia depends on a number of variables, some related to the disease, others to personal resources, and some more to the context in which the person lives. In the light of this complexity, it is crucial to consider all these aspects in order to explore their relative contribution.

In this paper we report on a large Italian multicenter study aimed to identify factors affecting real-life functioning of patients with schizophrenia and to assess their relative contribution. Factors to be included were chosen in the light of the literature review briefly summarized and of clinical experience, and were grouped into three categories: illness-related variables, personal resources and context-related variables. We predicted a significant association between the impairment of real-life functioning and the severity of

negative symptoms and cognitive deficits, such as the more severe the negative symptoms and cognitive deficits, the more impaired the everyday functioning. As to negative symptoms, we expected that avolition would show a stronger association with real-life functioning than poor emotional expression. An association between neurocognition and real-life functioning was also expected, partly or entirely mediated by functional capacity and social cognition. We also hypothesized that the variables included among personal resources mediate the impact of symptoms and cognitive impairment on real-life functioning. Due to the paucity of literature data, it was more difficult to predict which context-related variables would show a direct or indirect association with real-life functioning. Nevertheless, we anticipated that a large social network and having access to social and family incentives would have a favorable impact on functioning, and that internalized stigma would mediate the influence of symptoms and cognitive deficits on functioning.

Several limitations of previous studies were addressed in the present investigation. The Brief Negative Symptom Scale (BNSS, 28) was used to assess negative symptoms; this is a recently developed instrument designed to overcome the above-mentioned limitations of other largely used scales for the assessment of negative symptoms. Depressive and extrapyramidal symptoms were evaluated to ascertain their possible influence on negative symptoms and real-life functioning. The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) was chosen for cognitive assessment, as it is regarded as the "state of the art" neuropsychological battery for research purposes in schizophrenia (50,51). A full assessment of different aspects of social cognition was carried out, including emotional intelligence, emotion recognition and theory of mind. Personal resources and context related factors were included in the study.

In the light of difficulties in defining and measuring real-life functioning (2), the Specific Levels of Functioning Scale (SLOF) was selected to measure social, vocational, and everyday living outcomes (52). This instrument was endorsed by the panel of experts involved in the Validation of Everyday Real-World Outcomes (VALERO) initiative as a suitable measure of real-life functioning (12,53).

Due to the high number of included variables, a large multicenter study was designed to be carried out in 26 university psychiatric clinics and/or mental health departments, recruiting up to 1000 subjects with schizophrenia.

METHODS

Participants

Study participants were recruited from patients living in the community and consecutively seen at the outpatient units of 26 Italian university psychiatric clinics and/or mental health departments. Inclusion criteria were a diagnosis of schizophrenia according to DSM-IV, confirmed with the Structured Clinical Interview for DSM-IV - Patient version (SCID-I-P), and an age between 18 and 66 years. Exclusion criteria were: a history of head trauma with loss of consciousness; a history of moderate to severe mental retardation or of neurological diseases; a history of alcohol and/or substance abuse in the last six months; current pregnancy or lactation; inability to provide an informed consent; treatment modifications and/or hospitalization due to symptom exacerbation in the last three months.

All patients signed a written informed consent to participate after receiving a comprehensive explanation of the study procedures and goals.

Procedures

Approval of the study protocol was obtained from the Local Ethics Committees of the participating centers. Recruitment took place from March 2012 to September 2013.

Enrolled patients completed the assessments in three days with the following schedule: collection of socio-demographic information, psychopathological evaluation and neurological assessment on day 1, in the morning; assessment of neurocognitive functions, social cognition and functional capacity on day 2, in the morning; assessment of personal resources and perceived stigma either on day 3 (morning or afternoon) or in the afternoon of day 1 or 2, according to the patient's preference. For real-life functioning assessment, patient's key caregiver was invited to join one of the scheduled sessions.

Assessment tools

Evaluation of illness-related factors

A clinical form was filled in with data on age of disease onset, course of the disease and treatments, using all available sources of information (patient, family, medical records and mental health workers).

The Positive and Negative Syndrome Scale (PANSS, 54) was used to rate symptom severity. Scores for the dimensions "disorganization" and "positive symptoms" were calculated based on the consensus 5-factor solution proposed by Wallwork et al (55).

Negative symptoms were assessed using the BNSS, which includes 13 items, rated from 0 (normal) to 6 (most impaired), and five negative symptoms domains: anhedonia, asociality, avolition, blunted affect and alogia. The Italian version of the scale was validated as part of the Italian Network for Research on Psychoses activities. In line with previous research (28,56), domains evaluated by the scale loaded on two factors: "avolition", consisting of anhedonia, asociality and avolition, and "poor emotional expression", including blunted affect and alogia.

Depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia (CDSS, 57), a rating

scale designed to assess the level of depression in people with schizophrenia.

Extrapyramidal symptoms were assessed by means of the St. Hans Rating Scale (SHRS, 58), a multidimensional rating scale consisting of four subscales: hyperkinesias, parkinsonism, akathisia and dystonia. Each subscale includes one or more items, with a score ranging from 0 (absent) to 6 (severe).

Neurocognitive functions were rated using the MCCB. This battery includes tests for the assessment of seven distinct cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, social cognition, and reasoning and problem solving.

The assessment of social cognition, partly included in the MCCB Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) managing emotion section, was integrated by the Facial Emotion Identification Test (FEIT, 59) and The Awareness of Social Inference Test (TASIT, 60), which is a theory of mind test.

Assessment of personal resources

Resilience was evaluated by the Resilience Scale for Adults (RSA, 61), a self-administered scale including 33 items that examine intra- and inter-personal protective factors thought to facilitate adaptation when facing psychosocial adversity. Items are organized in six factors: perception of self, perception of the future, structured style, social competence, family cohesion, and social resources. To avoid overlap with other measures, the "structured style" and "social resources" factors were not included in the analysis.

The Service Engagement Scale (SES, 62), an instrument including 14 items, rated on a 4-point Likert scale (with higher scores reflecting greater levels of difficulty engaging with services), was used to explore patients' relationship with mental health services. Items are grouped into four subscales: availability, cooperation, help seeking, and adherence to treatment. In the present paper, we used the total score provided by the instrument.

Evaluation of context-related factors

A socio-demographic questionnaire was developed *ad hoc* to collect data on gender, age, marital status, schooling, housing, eating habits, substance use, socio-economic status, availability of a disability pension, and access to family and social incentives.

The socio-economic status was determined from the education level and the type of work of each parent. The education level was measured on a 7-level scale (1=elementary school, 7=post-degree/specialization courses) and the type of work was ranked on 9 levels (1=laborer, 9=high level managerial position). The Hollingshead index was calculated as the average of the indices of the two parents (63).

The Social Network Questionnaire (SNQ, 64) was used to assess structural and qualitative aspects of participants' social network. This is a self-administered questionnaire including 15 items rated on a 4-point scale (from 1 "never" to 4 "always"), organized into four factors: quality and frequency of social contacts, practical social support, emotional support, and quality of an intimate relationship.

The Internalized Stigma of Mental Illness (ISMI, 65) was used to evaluate the experience of stigma and internalized self-rejection. It includes 29 items and 5 subscales for self-assessment of subjective experience of stigma. Each item is rated on a 4-level Likert scale, where higher scores indicate greater levels of internalized stigma.

Assessment of functional capacity and real-life functioning

Functional capacity was evaluated using the short version of the University of California San Diego (UCSD) Performance-based Skills Assessment Brief (UPSA-B, 66), a performance-based instrument that assesses "financial skills" (e.g., counting money and paying bills) and "communication skills" (e.g., to dial a telephone number for emergency or reschedule an appointment by telephone). The total score, ranging from 0 to 100, was used in statistical analyses.

Real-life functioning was assessed by the Specific Level of Functioning Scale (SLOF), a hybrid instrument that explores many aspects of functioning and is based on the key caregiver's judgment on behavior and functioning of patients. It consists of 43 items and includes the following domains: physical efficiency, skills in self-care, interpersonal relationships, social acceptability, community activities (e.g., shopping, using public transportation), and working abilities. Higher scores correspond to better functioning. In our study, the key relative was interviewed, as usually this is the individual most frequently and closely in contact with the patient in the Italian context. The Italian version of the scale has recently been validated (67).

Training of researchers

For each category of variables (illness-related factors, personal resources and context-related factors), at least one researcher per site was trained. In order to avoid halo effects, the same researcher could not be trained for more than one category.

The inter-rater reliability was formally evaluated by Cohen's kappa for categorical variables, and intraclass correlation coefficient (ICC) or percentage agreement for continuous variables. An excellent inter-rater agreement was found for the SCID-I-P (Cohen's kappa=0.98). Good to excellent agreement among raters was observed for SLOF (ICC=0.55-0.99, percentage agreement=70.1-100%); BNSS (ICC=0.81-0.98); PANSS (ICC=0.61-0.96, percentage agreement=67.7-93.5%); CDSS (ICC=0.63-0.90) and MCCB (ICC=0.87).

Statistical analysis

The demographic and clinical characteristics of study participants and the scale scores were summarized as mean ±SD, median and interquartile range, and percentages where appropriate.

Structural equation models (SEM) were used to test the relationships of variables inherent to illness, personal resources and context with real-life functioning. These models can be interpreted as a set of simultaneous multiple regression models, in which variables can serve as predictors or outcomes. As a preliminary step, we examined the pairwise correlation and covariance matrix for the study variables. Given the large number of cases, correlations were interpreted taking into account the absolute value of the correlation coefficient and not its significance. We chose to consider correlation coefficients between predictors and SLOF scales $\geq$0.20 as trustworthy.

Since two variables may be connected in a SEM through several pathways, direct effects, indirect effects and total effects were estimated. A direct effect is a relationship between two variables not mediated by any other variable in the model. An indirect effect of one variable on another is a relationship mediated by one or more variables along a specific pathway and is calculated as the product of all the involved direct effects. The total effect is the sum of the direct and all indirect effects.

The model parameters, which provide information about the relationships among the variables, can be interpreted as standardized regression weights, as in linear regression models. Squared multiple correlations (R^2) were obtained for each endogenous variable to estimate the amount of variance explained by its predictors. Lastly, the standardized coefficients for indirect effects were examined to evaluate mediation effects. Significant effects suggest mediation is present, and full mediation is indicated by the direct path no longer being significant.

An advantage of SEM is the use of latent variables. This implies using more than one variable to map onto a theoretical construct, thus allowing reduction of the measurement error and a more accurate estimation of the true value of the construct than it would be possible using a single variable.

In the present study, neurocognition, social cognition, resilience and real-life functioning (SLOF) were defined as latent variables. Neurocognition included the MCCB domains "processing speed", "attention", "working memory", "verbal memory", "visual memory" and "problem solving"; social cognition corresponded to FEIT, TASIT and MSCEIT scores; resilience combined "perception of self", "perception of the future", "social competence" and "family cohesion", and SLOF reflected the five domains of the scale, i.e., "skills in self-care", "interpersonal relationships", "social acceptability", "community activities" and "working abilities".

For the purpose of the SEM, neurocognition, social cognition and functional capacity variables were standardized with respect to Italian normative data. All the other variables were transformed into z-scores. Disability pension was coded as a dichotomous variable (yes/no). Other incentives, including financial and/or practical support from the family, as well as registration in an unemployment list, were used as a count variable, ranging from 0 to 3.

To define our initial SEM model, we hypothesized relationships between variables consistent with published research. Specifically, we hypothesized that psychopathology (including positive symptoms, disorganization, negative symptoms and depression), neurocognition, extrapyramidal symptoms, incentives, and socio-economic status would predict functioning both directly and indirectly, through the mediation of social cognition and functional capacity. Moreover, we assumed first that SES, resilience, and ISMI would be further mediators of the relationship of predictors with functioning and tested this hypothesis in the model.

The final model was obtained by removing non-significant effects and correlations among predictors lower than 0.20 and testing alternative hypotheses on the relationships among mediators.

Model fit was evaluated using the comparative fit index (CFI, 68), Tucker-Lewis index (TLI, 69) and the root mean square error of approximation (RMSEA, 70). TLI and CFI values $>$0.90 reflect acceptable fit and values $>$0.95 imply very good fit (71). RMSEA values $<$0.05 indicate close model fit; values up to 0.08 suggest a reasonable error of approximation in the population, and values $>$0.10 indicate poor fit (72). The fit indices were assessed collectively, such that a single index that fell just outside the acceptable range was not necessarily considered to reflect poor model fit, provided that the other statistics indicated good model fit. Power analysis was carried out using MacCallum et al's (73) criterion to test the hypothesis of RMSEA's not-close fit. The best-fitting models were compared using the Akaike Information Criterion (AIC, 74). This index has no predefined cut-offs and can only be interpreted when comparing two different models. A lower AIC indicates better model fit.

Analyses were carried out using Stata, version 13.1, and Mplus, version 7.1.

RESULTS

Out of 1691 screened patients, 1180 were eligible; of these, 202 refused to participate, 57 dropped out before completing the procedures and 921 were included in the analyses (641 males, 280 females). Data on demographic and illness-related variables are provided in Tables 1 and 2. Almost all patients were treated with antipsychotics, mostly second-generation drugs, and about one quarter received an integrated treatment, i.e., psychosocial interventions in addition to pharmacotherapy (including cognitive rehabilitation, psychoeducation, social skills training, self-help groups or sheltered employment).

Data on personal resources, context-related factors and functional capacity, and SLOF scale scores are provided in

Table 1 Characteristics of the study sample (N=921)

Gender (% males)	69.6
Age (years, mean±SD)	40.2±10.7
Married (% yes)	7.8
Working (% yes)	29.2
Education (years, mean±SD)	11.6±3.4
Age at first psychotic episode (years, mean±SD)	24.0±7.2
Antipsychotic treatment (%)	
First generation	14.2
Second generation	48.5
Both	14.1
None	3.2
Integrated treatment (% yes)	26.8
Suicide attempts (% yes)	17.1

Table 3. Overall, study participants showed a modest degree of functional impairment. SLOF domains showing a moderate degree of impairment included interpersonal relationships, community activities and working abilities.

Inspection of the bivariate correlation matrix revealed that the socio-economic status (Hollingshead index), the social network and extrapyramidal symptoms were unrelated to all mediators and SLOF; therefore, these variables were not used in further analyses.

In our first SEM model (Figure 1), PANSS positive, PANSS disorganization, BNSS avolition, BNSS poor emotional expression, depression, neurocognition, and incentives were used as independent predictors; social cognition, functional capacity, internalized stigma, resilience and service engagement were used as mediators, and SLOF was the dependent variable.

PANSS positive and PANSS disorganization, as well as BNSS avolition, proved to have significant direct and indirect effects; depression had no significant effect on SLOF, and BNSS poor emotional expression was only indirectly and weakly related with SLOF (Table 4, Figure 1). Neurocognition had only indirect effects on SLOF. Incentives proved to be a significant predictor, and social cognition, functional capacity, resilience, internalized stigma and service engagement served as mediators, as hypothesized.

CFI and TLI indices for this model were 0.925 and 0.916, respectively, and the RMSEA index was 0.047, denoting a good fit to the data. The included variables explained 53.5% of SLOF variance.

After trimming non-significant paths (from neurocognition, CDSS, BNSS poor emotional expression to SLOF, and from social cognition to internalized stigma), a final model was obtained with five predictors and five mediators (Figure 2). This model accounted for 53.8% of variance of the SLOF, was more parsimonious and proved to have a better fit compared with the initial model (CFI=0.940, TLI=0.932, RMSEA=0.044). Comparison of the AIC indices for the initial and the final model (84686.906 and 80400.015, respectively) further supported the choice of the latter to represent the relationships among variables without loss of information.

In this final model, PANSS positive, PANSS disorganization and BNSS avolition showed a negative direct effect on SLOF (Table 4), indicating that higher levels of psychopathology are associated with poorer functioning. Several indirect effects on SLOF were also observed: PANSS positive through service engagement, PANSS disorganization through functional capacity, and BNSS avolition through service engagement and resilience. BNSS avolition had also an effect on internalized stigma that, in its turn, was indirectly associated with SLOF through resilience. Neurocognition showed indirect effects on SLOF through four different mediators: service engagement, functional capacity, internalized stigma (through resilience) and social cognition, and when compared with other predictors of the same mediator, it always showed the strongest effect (Figure 2).

Table 4 provides a summary of direct, indirect and total effects on SLOF of variables included in the final model. Neurocognition showed the strongest total effect, followed

Table 2 Data on illness-related variables

	Mean±SD	Min/Max
PANSS positive	9.8±4.7	4/28
PANSS disorganization	8.6±3.8	3/21
BNSS poor emotional expressivity	12.8±8.0	0/33
BNSS avolition	20.7±9.6	0/45
CDSS (total score)	4.0±4.0	0/21
TMT (total time)	66.3±46.2	15/300
BACS SC (correct responses)	31.5±13.2	0/96
Fluency (number animal names)	16.5±5.7	0/47
CPT-IP (D Prime average)	1.7±0.8	−0.39/4.03
WMS-III SS (correct sequences)	12.3±4.1	1/26
LNS (correct responses)	10.4±4.2	0/21
HVLT-R (correct recalls)	19.0±5.6	0/35
BVMT-R (total score)	16.3±8.8	0/36
NAB mazes (total score)	9.7±6.4	0/26
TASIT Sect. 1 (correct items)	19.7±5.4	0/28
TASIT Sect. 2 (correct items)	36.9±11.7	0/60
TASIT Sect. 3 (correct items)	37.4±12.2	0/64
FEIT (correct responses)	36.8±8.5	7/53
MSCEIT (SS-B4)	78.5±9.0	54.6/109.2

PANSS – Positive and Negative Syndrome Scale, BNSS – Brief Negative Symptom Scale, CDSS – Calgary Depression Scale for Schizophrenia, TMT – Trail Making Test - Part A, BACS SC – Brief Assessment of Cognition in Schizophrenia Symbol Coding, Fluency – Category Fluency, Animal Naming, CPT-IP – Continuous Performance Test, Identical Pairs, WMS-III SS – Wechsler Memory Scale Spatial Span, LNS – Letter-Number Span, HVLT-R – Hopkins Verbal Learning Test - Revised, BVMT-R – Brief Visuospatial Memory Test - Revised, NAB – Neuropsychological Assessment Battery, TASIT – The Awareness of Social Inference Test, FEIT – Facial Emotion Identification Test, MSCEIT – Mayer-Salovey-Caruso Emotional Intelligence Test, SS-B4 – standard score for the managing emotions branch

Table 3 Data on personal resources, context-related variables and functioning

Personal resources	
SES (total score, mean±SD, min/max)	12.9±7.7, 0/42
Resilience Scale for Adults (mean±SD, min/max)	
Perception of self	18.1±5.5, 0/30
Perception of future	10.8±4.3, 0/20
Social competence	18.9±5.3, 6/30
Family cohesion	20.3±5.7, 3/30
Context-related factors	
ISMI (total score, without stigma resistance, mean±SD, min/max)	2.1±0.5, 1.00/3.92
Number of incentives (%)*	
None	12.7
One	29.2
Two	32.9
Three	18.2
Four	7.0
Functional capacity and real-life functioning	
UPSA-B (total score, mean±SD, min/max)	67.5±22.3, 0/100
SLOF (mean±SD, min/max)	
Physical functioning	24.2±1.3, 15/25
Skills in self-care	31.7±4.0, 10/35
Interpersonal relationships	22.3±6.1, 7/35
Social acceptability	32.5±3.3, 14/35
Community activities	45.9±8.6, 11/55
Working abilities	20.0±6.2, 6/30

SES – Services Engagement Scale, ISMI – Internalized Stigma of Mental Illness, UPSA-B – UCSD Performance-Based Skills Assessment, SLOF – Specific Levels of Functioning
*Including financial support from the family, practical support from the family, registered in an unemployment list, disability pension

by disorganization, avolition, functional capacity, service engagement, social cognition, positive symptoms, incentives, resilience and internalized stigma.

DISCUSSION

To our knowledge, this is the largest study carried out so far on factors associated with real-life functioning in people with schizophrenia, in terms of both sample size and number of investigated domains. According to our findings, variables relevant to the disease, personal resources and social context explain 53.8% of real-life functioning variance in patients with schizophrenia living in the community and treated with antipsychotics, mainly second-generation drugs.

Neurocognition exhibited the strongest association with real-life functioning. This result corroborates previous findings of moderate to large correlations of neurocognition with everyday functioning measures (75-77). Our use of neurocognition as a latent variable, to reduce its measurement error, further supports the robustness of the finding. In line with previous research (77,78), neurocognition proved to be a distal variable with respect to real-life functioning, since its relationship with SLOF was mediated by functional capacity, social cognition, service engagement and internalized stigma.

Associations between functional capacity and neurocognition have previously been reported in cross-sectional studies (79-81). In our model neurocognition was the strongest predictor of functional capacity, which reflects its important contribution to the latter construct. Actually, both measures assess the individuals' capability of performing tasks and/or behaviors in a standardized setting, but tests of functional capacity do so in more "ecological" way, i.e., simulating everyday life tasks, though not carried out in the community (15,82). The role of functional capacity as mediator of the impact of neurocognition on real-life functioning reported in our study has also been previously observed (13,14).

The correlation between social cognition and real-life functioning ranged from small to large in previous studies, mainly depending on the examined aspect of social cognition, with largest effects observed for theory of mind tasks (17,20). Our findings confirm that social cognition accounts for a unique proportion of functioning variance, independent of neurocognition (83-87), support its independence from negative symptoms (18,22), and do not support its role as mediator of the impact of negative symptoms on real-life functioning (7).

To our knowledge, the role of service engagement and internalized stigma as mediators between neurocognition and real-life functioning has not been investigated in previous studies. In our model, service engagement was directly associated with SLOF, while internalized stigma showed, in its turn, an indirect association with SLOF, mediated by resilience. Service engagement, as assessed in the present study, reflects subject's degree of collaboration with mental health services (e.g., active participation in defining treatment plans, ability to seek service help if needed and to show up on time for the appointments) and adherence to prescribed treatments. According to our results, impaired cognitive functioning interferes with subject's collaboration to treatment and therefore it is an obstacle to successful outcome.

Internalized stigma, according to a recent meta-analysis including 127 studies, is directly associated with severity of psychiatric symptoms and inversely related to levels of hope, empowerment, self-efficacy, quality of life and adherence to treatment (49). Our data confirm the previously reported association between internalized stigma and negative symptoms (88), and extend this finding to neurocognition. An association between social cognition and internalized stigma has been reported by other authors (89), but has not been observed in our model. A possible interpretation of this discrepancy could be that the relationship between social cognition and internalized stigma is spurious; in other words, it

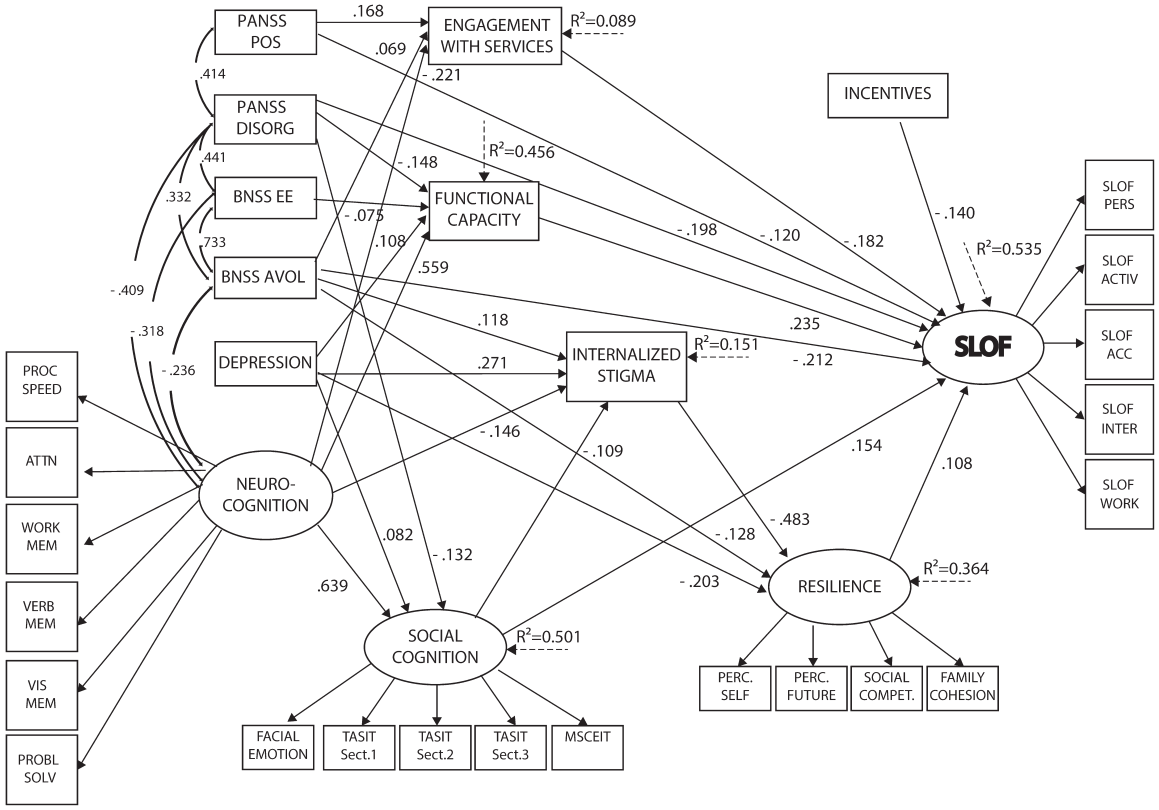

Figure 1 Initial structural equation model. Neurocognition, social cognition, resilience and SLOF are latent variables (with arrows pointing to their respective indicators). PANSS POS, PANSS DISORG, BNSS avolition, BNSS-EE, depression, neurocognition and incentives are independent predictors. Social cognition, functional capacity, internalized stigma, resilience and service engagement are mediators, and SLOF is the dependent variable. PANSS – Positive and Negative Syndrome Scale, POS – positive, DISORG – disorganization, BNSS – Brief Negative Symptom Scale, EE – poor emotional expression, AVOL – avolition, PROC SPEED – processing speed, ATTN – attention, WORK MEM – working memory, VERB MEM – verbal memory, VIS MEM – visuospatial memory, PROBL SOLV – problem solving, TASIT – The Awareness of Social Inference Test, MSCEIT – Mayer-Salovey-Caruso Emotional Intelligence Test, PERC. SELF – perception of self, PERC. FUTURE – perception of the future, SOCIAL COMPET. – social competence, SLOF – Specific Level of Functioning, PERS – skills in self-care, ACTIV – community activities, ACC – social acceptability, INTER – interpersonal relationships, WORK – working abilities

is possible that neurocognitive impairment underlies both these variables and therefore accounts for their relationship.

The illness-related variables disorganization, positive symptoms and avolition were both directly and indirectly related to functioning. The key role of disorganization observed in our study deserves comments. The PANSS items "conceptual disorganization", "difficulties in abstract thinking" and "poor attention" are generally considered

Table 4 Direct, indirect and total effects on SLOF in the final model

	Direct	p	Total indirect	p	Total	p
Functional capacity	0.245	<0.001	-	-	0.245	<0.001
Social cognition	0.169	<0.001	-	-	0.169	<0.001
Internalized stigma	-	-	−0.061	0.001	−0.061	<0.001
Resilience	0.116	0.001	-	-	0.116	<0.001
Neurocognition	-	-	0.302	<0.001	0.302	<0.001
PANSS positive	−0.117	0.001	−0.031	<0.001	−0.148	<0.001
PANSS disorganization	−0.201	<0.001	−0.063	<0.001	−0.264	<0.001
BNSS avolition	−0.210	<0.001	−0.046	0.001	−0.255	<0.001
Incentives	−0.142	<0.001	-	-	−0.142	<0.001
Service engagement	−0.184	<0.001	-	-	−0.184	<0.001

SLOF – Specific Levels of Functioning, PANSS – Positive and Negative Syndrome Scale, BNSS – Brief Negative Symptom Scale

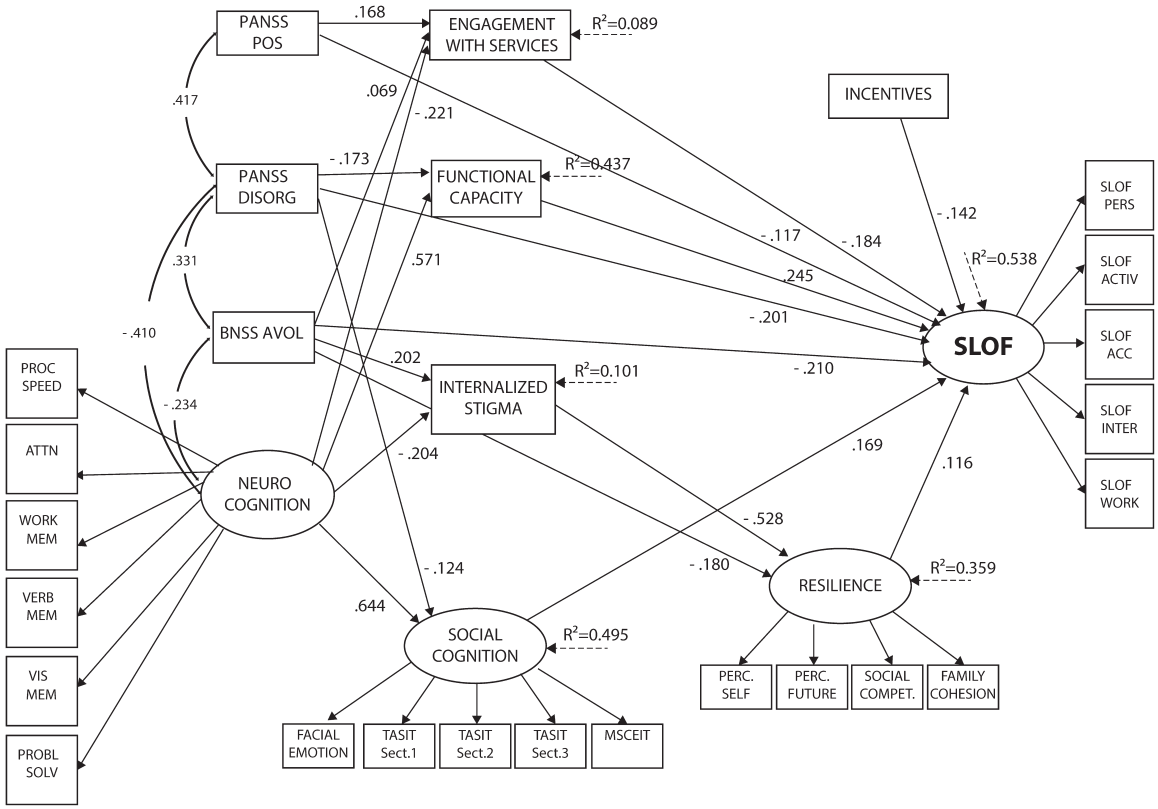

Figure 2 Final structural equation model after trimming of non-significant paths. Neurocognition, social cognition, resilience and SLOF are latent variables (with arrows pointing to their respective indicators). PANSS POS, PANSS DISORG, BNSS avolition, neurocognition and incentives are independent predictors. Social cognition, functional capacity, internalized stigma, resilience and service engagement are mediators, and SLOF is the dependent variable. PANSS – Positive and Negative Syndrome Scale, POS – positive, DISORG – disorganization, BNSS – Brief Negative Symptom Scale, EE – poor emotional expression, AVOL – avolition, PROC SPEED – processing speed, ATTN – attention, WORK MEM – working memory, VERB MEM – verbal memory, VIS MEM – visuospatial memory, PROBL SOLV – problem solving, TASIT – The Awareness of Social Inference Test, MSCEIT – Mayer-Salovey-Caruso Emotional Intelligence Test, PERC. SELF – perception of self, PERC. FUTURE – perception of the future, SOCIAL COMPET. – social competence, SLOF – Specific Level of Functioning, PERS – skills in self-care, ACTIV – community activities, ACC – social acceptability, INTER – interpersonal relationships, WORK – working abilities

core aspects of the disorganization factor (90-92); in the present study, the structure of the PANSS disorganization dimension was defined according to the consensus 5-factor solution proposed by Wallwork et al (55), in which the three above-mentioned items load on the disorganization factor. The overlap of the items "difficulties in abstract thinking" and "poor attention" with neurocognitive impairment cannot be underestimated. As a matter of fact, in our data, neurocognition and disorganization showed a significant inverse correlation and a similar pattern of association with SLOF, through functional capacity and social cognition.

Avolition had both a direct and an indirect relationship with SLOF. In the indirect path, it has service engagement, resilience and internalized stigma (in its turn associated with SLOF through resilience) as mediators. In the initial model, both BNSS factors had been included, but BNSS poor emotional expression only showed an indirect and weak relation with SLOF, and its exclusion from the final model did not worsen the fit or reduce the explanatory power of the model.

A significant relationship between avolition and poor social outcome has been reported in previous studies (93-95). In a recent investigation on long-term stability and outcome of negative symptoms, Galderisi et al (23) found that avolition has a higher predictive value of functional outcome than poor emotional expression at 5-year follow-up. The scarce relevance of poor emotional expression to real-life functioning is in line with Foussias et al's findings (96).

The strong impact of avolition on real-life functioning might be due to the partial overlap between these two measures. However, the degree of overlap was most probably limited in our study, since avolition, as measured by the BNSS, provides an assessment of both behavioral (e.g., deficit in initiating and persisting in different activities) and inner experience aspects (e.g., lack of interest and motivation in different activities, impaired anticipation of rewarding outcome), while the real-life assessment provided by a caregiver mainly focuses on subject's performance and behavior in several types of everyday activities. Efforts aimed to improve our

understanding of the pathophysiology of avolition represent a priority of research in schizophrenia, and the implementation of treatments targeting motivation is likely to be an important tool to enable people with schizophrenia to achieve a meaningful life.

At odds with previous literature (8,13,14,53,97,98), no impact of depression on real-life functioning was observed in our study. The discrepancy with previous studies might be due to the use of different instruments for the assessment of depression (mostly the Beck Depression Inventory, a self-report measure, in prior investigations) and the low degree of severity of depression in our sample (mean score=4, with a cutoff of 6/7 for depression in the CDSS).

Extrapyramidal symptoms, family socio-economic status and social network were not included in the SEM, as they showed no or weak associations with SLOF and mediating variables. As to extrapyramidal symptoms, we cannot exclude that the prevalence of treatment with second-generation antipsychotics yielded a floor effect, making their impact on SLOF negligible, while for both social network and socio-economic status we cannot rule out the possibility of redundancy with other variables, or poor performance of the used instruments.

Access to family and social incentives had a negative association with SLOF, i.e., a higher number of incentives was associated with a poorer real-life functioning. Due to the cross-sectional study design, this association may be interpreted either way, i.e., access to incentives may be due to functional impairment or incentives may have a negative impact on real-life functioning. In fact, many patients would not renounce to the disability pension or the support received by the family for a job, as the latter is generally regarded as less stable and more effortful. Directly relevant to this point is the finding by Rosenheck et al (99) that disability compensation status, which is often linked to the individual's health insurance coverage, had the largest negative impact on vocational outcomes of all the measured predictors.

In conclusion, we found that some illness-related variables (neurocognition, disorganization, avolition and positive symptoms) and incentives predict real-life functioning either directly or through the mediation of resilience, stigma, social cognition, functional capacity and engagement with mental health services. The final SEM model explained about 54% of the SLOF variance, a higher percentage compared with those reported in similar studies that used neurocognition, social cognition, social competence and negative symptoms to predict real-life functioning (7-25%) (7,22,83,87).

The strengths of this study include the large sample size and the use of state-of-the-art instruments to assess neurocognitive, psychopathological, social cognition, and personal resources domains. Some possible limitations include the restricted variability range of patients' clinical characteristics and functioning in the real life (most of the patients showed a mild/moderate degree of symptoms severity and functional impairment); the use of SLOF as a latent variable, which might have advantages, but might also prevent the identification of predictors of specific domains, and the cross-sectional design, which does not allow to test causal relationships.

Our findings can have important treatment and research implications. The impact of neurocognition and social cognition on real-life functioning suggests that training addressing neurocognitive and social cognition impairment should be part of integrated treatment packages for schizophrenia. A greater emphasis on social cognition than on neurocognition has been suggested, given the greater proximity and higher direct explanatory power of the former, with respect to the latter domain (100). However, there is no evidence that social cognitive training alone counteracts neurocognitive impairment, whose impact on other domains, i.e., functional capacity and service engagement, would probably persist, in spite of possible improvement in social cognition.

The complexity of the pathway from neurocognition to real-life functioning through internalized stigma suggests that, in order to enhance the impact of interventions targeting neurocognitive impairment on functioning in the real life, we also need to promote reduction of internalized stigma related to mental illness and minimize its negative effects. Data have been provided that anti-stigma interventions are effective at reducing internalized stigma (101-103), but the impact of such positive outcome on other dimensions of the disorder and on patients' functioning does need further investigation.

Our finding that avolition is an independent domain with respect to both neurocognition and social cognition suggests that the search for treatments with an impact on this domain should be a priority of mental health research strategies.

The contribution of resilience to real-life functioning highlights the importance of personalization when designing treatment plans and defining life goals together with our patients. Prejudicial optimistic or, more frequently, pessimistic attitudes should always be modulated by the awareness that individuals do vary a lot in terms of personal resources, and such a variability does not allow undue generalization.

Improved understanding of factors that hinder real-life functioning is vital for treatments to translate into more positive outcomes. Findings from the present study provide a valuable contribution in this direction; in particular, the observed complex associations among investigated predictors, mediators and real-life functioning strongly suggest that integrated and personalized programs should be provided as standard treatment to people with schizophrenia.

Appendix

Members of the Italian Network for Research on Psychoses include: Marcello Chieffi, Stefania De Simone, Francesco De Riso, Rosa Giugliano, Giuseppe Piegari, Annarita Vignapiano (University of Naples SUN, Naples); Grazia Caforio, Marina Mancini, Lucia Colagiorgio (University of Bari); Stefano Porcelli, Raffaele Salfi, Oriana Bianchini (University of

Bologna); Alessandro Galluzzo, Stefano Barlati (University of Brescia); Bernardo Carpiniello, Francesca Fatteri, Silvia Lostia di Santa Sofia (University of Cagliari); Dario Cannavò, Giuseppe Minutolo, Maria Signorelli (University of Catania); Giovanni Martinotti, Giuseppe Di Iorio, Tiziano Acciavatti (University of Chieti); Stefano Pallanti, Carlo Faravelli (University of Florence); Mario Altamura, Eleonora Stella, Daniele Marasco (University of Foggia); Pietro Calcagno, Matteo Respino, Valentina Marozzi (University of Genoa); Ilaria Riccardi, Alberto Collazzoni, Paolo Stratta, Laura Giusti, Donatella Ussorio, Ida Delauretis (University of L'Aquila); Marta Serati, Alice Caldiroli, Carlotta Palazzo (University of Milan); Felice Iasevoli (University of Naples Federico II); Carla Gramaglia, Sabrina Gili, Eleonora Gattoni (University of Eastern Piedmont, Novara); Elena Tenconi, Valeria Giannunzio, Francesco Monaco (University of Padua); Chiara De Panfilis, Annalisa Camerlengo, Paolo Ossola (University of Parma); Paola Landi, Grazia Rutigliano, Irene Pergentini, Mauro Mauri (University of Pisa); Fabio Di Fabio, Chiara Torti, Antonino Buzzanca, Anna Comparelli, Antonella De Carolis, Valentina Corigliano (Sapienza University of Rome); Giorgio Di Lorenzo, Cinzia Niolu, Alfonso Troisi (Tor Vergata University of Rome); Giulio Corrivetti, Gaetano Pinto, Ferdinando Diasco (Department of Mental Health, Salerno); Arianna Goracci, Simone Bolognesi, Elisa Borghini (University of Siena); Cristiana Montemagni, Tiziana Frieri, Nadia Birindelli (University of Turin).

Acknowledgements

The study was funded by the Italian Ministry of Education, the Italian Society of Psychopathology (SOPSI), the Italian Society of Biological Psychiatry (SIPB), Roche, Lilly, AstraZeneca, Lundbeck and Bristol-Myers Squibb.

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DOI 10.1002/wps.20167

Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis

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Internet-delivered cognitive behavior therapy (ICBT) has been tested in many research trials, but to a lesser extent directly compared to face-to-face delivered cognitive behavior therapy (CBT). We conducted a systematic review and meta-analysis of trials in which guided ICBT was directly compared to face-to-face CBT. Studies on psychiatric and somatic conditions were included. Systematic searches resulted in 13 studies (total N=1053) that met all criteria and were included in the review. There were three studies on social anxiety disorder, three on panic disorder, two on depressive symptoms, two on body dissatisfaction, one on tinnitus, one on male sexual dysfunction, and one on spider phobia. Face-to-face CBT was either in the individual format (n=6) or in the group format (n=7). We also assessed quality and risk of bias. Results showed a pooled effect size (Hedges' g) at post-treatment of −0.01 (95% CI: −0.13 to 0.12), indicating that guided ICBT and face-to-face treatment produce equivalent overall effects. Study quality did not affect outcomes. While the overall results indicate equivalence, there are still few studies for each psychiatric and somatic condition and many conditions for which guided ICBT has not been compared to face-to-face treatment. Thus, more research is needed to establish equivalence of the two treatment formats.

Key words: Guided Internet-delivered cognitive behavior therapy, face-to-face therapy, anxiety and mood disorders, somatic disorders, meta-analysis

(World Psychiatry 2014;13:288–295)

Internet-delivered psychological treatments have a relatively short history, with the first trials being conducted in late 1990s (1). A large number of programs have been developed, and trials have been conducted for a range of psychiatric and somatic conditions, mostly using Internet-delivered cognitive behavior therapy (ICBT) (2).

Many ICBT programs involve therapist guidance over encrypted e-mail, which to date, with a few exceptions (3), tend to generate larger effects than unguided programs (4). Many interventions are text-based and can be described as online bibliotherapy, even if streamed video clips, audio files and interactive elements are involved. These programs are typically comprised of 6-15 modules, which are text chapters corresponding to sessions in face-to-face therapy, and require little therapist involvement more than guidance and feedback on homework assignments (approximately 10-15 min per client and week). Other programs, such as Interapy (5), require more therapist input, as more text is exchanged between the therapist and the client. Finally, there are real time chat-based Internet treatments in which no therapist time is saved (6).

In terms of content, programs vary as well, but many tend to mirror face-to-face treatments in terms of content and length. Thus, for example, a program for depression can be 10 weeks long, with weekly modules mirroring sessions in manualized cognitive behavior therapy (CBT) (4), and the content may include psychoeducation, behavioral activation, cognitive restructuring, relapse prevention and homework assignments (7).

While most studies have been on ICBT (8), there are also studies on other psychotherapeutic orientations, such as psychodynamic psychotherapy (9), and physical exercise (10). Different forms of ICBT have also been used, such as attention bias modification (11), problem solving therapy (12), and acceptance and commitment therapy (13). In addition to short-term effects indicating equivalence compared to therapist administered therapy (14-16), there are also a few long-term follow-up studies showing lasting effects over as much as 5 years post-treatment (17).

In spite of promising results in the controlled trials, an outstanding question is how well-guided ICBT compares against standard manualized face-to-face treatments. This was partly investigated in a meta-analysis by Cuijpers et al (18), who studied the effects of guided self-help on depression and anxiety vs. face-to-face psychotherapies. They included 21 studies with 810 participants and found no differences between the formats (Cohen's d=0.02). However, that meta-analysis mixed bibliotherapy and Internet interventions and focused on anxiety and depression only. Furthermore, new studies have emerged since that publication. Thus, there is a need for a systematic review and meta-analysis focusing on guided ICBT.

The aim of this study was to investigate the efficacy of guided ICBT compared to face-to-face CBT for psychiatric and somatic disorders. We conducted a systematic review and meta-analysis of studies directly comparing the two treatment formats in randomized trials. We hypothesized that guided ICBT and face-to-face CBT would produce equivalent treatment effects.

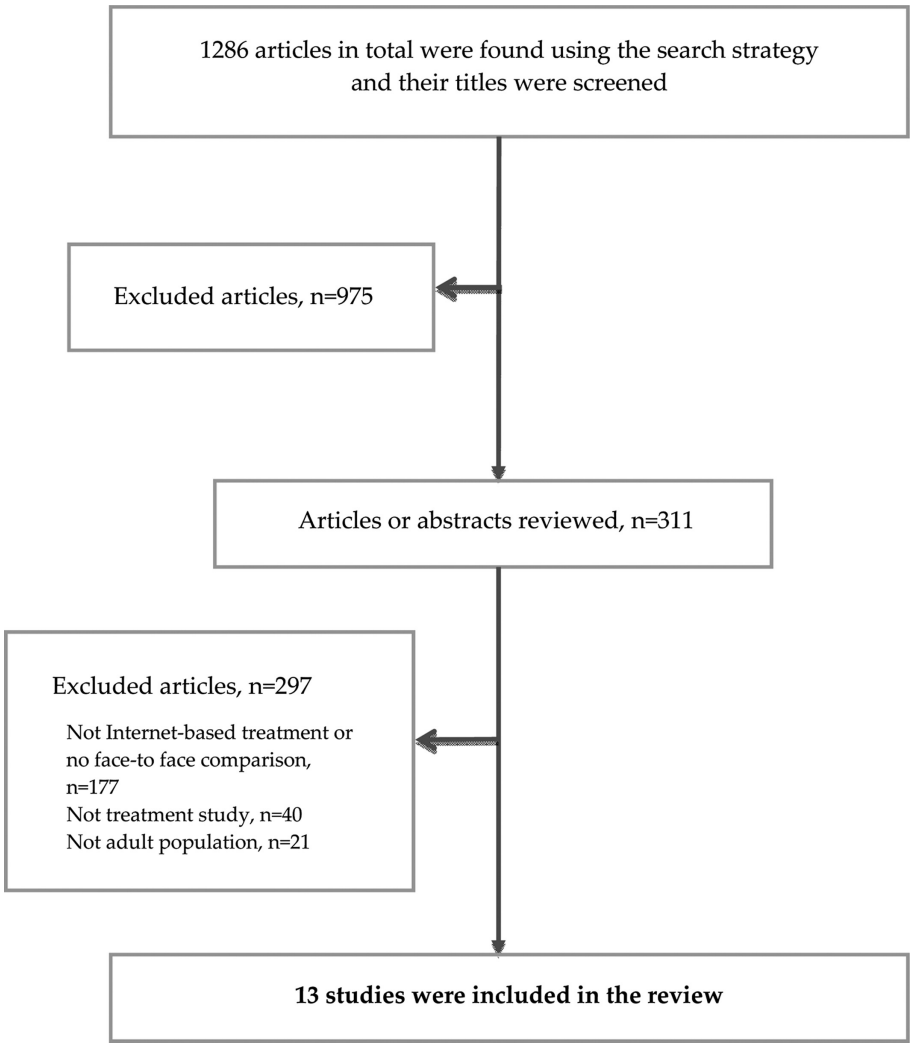

Figure 1 Study inclusion process

METHODS

This was a systematic review and meta-analysis of original articles investigating the effect of guided ICBT compared to face-to-face treatments. To be included in the review, the original studies had to: a) compare therapist-guided ICBT to face-to-face treatment using a randomized controlled design; b) use interventions that were aimed at treatment of psychiatric or somatic disorders (not, for example, prevention or merely psychoeducation); c) compare treatments that were similar in content in both treatment conditions; d) investigate a form of ICBT where the Internet treatment was the main component and not a secondary complement to other therapies; e) investigate a form of full length face-to-face treatment; f) report outcome data from an adult patient sample; g) report outcomes in terms of assessment of symptoms of the target problem; and h) be written in English. We included only studies in which there was some therapist contact during the trial (7).

We calculated effect sizes based on the primary outcome measure at post-treatment in each study. If no primary outcome measure was specified in the original study, a validated measure assessing target symptoms of the clinical problem was used, following the procedures by Thomson and Page (19).

To identify studies, systematic searches in PubMed (Medline database) were conducted using various search terms related to psychiatric and somatic disorders, such as "depression", "panic disorder", "social phobia", "social anxiety disorder", "generalized anxiety disorder", "obsessive-compulsive disorder", "post-traumatic stress disorder", "specific phobia", "hypochondriasis", "bulimia", "tinnitus", "erectile dysfunction", "chronic pain", or "fatigue". These search terms relating to the clinical problem were combined with "Internet" or "computer", or "computerized", and the search filter "randomized controlled trial" was used.

In addition to the above, reference lists in the included studies were checked for potential additional studies. We

Table 1 Characteristics of the included studies

Study	Disorder	N INT	N FTF	Outcome evaluation	Mean (SD) INT pre	Mean (SD) INT post	Mean (SD) FTF pre	Mean (SD) FTF post	Quality*	Dropout rate	ITT	Sample
Hedman et al (25)	Social anxiety disorder	62	64	LSAS	68.4 (21.0)	39.4 (19.9)	71.9 (22.9)	48.5 (25.0)	Low risk of bias on all criteria	12%	Yes	Mixed
Andrews et al (23)	Social anxiety disorder	23	14	SIAS	54.5 (12.4)	44.0 (15.9)	57.8 (43.9)	43.9 (18.7)	Unclear/high risk on at least one criterion	32%	Yes	Clinical
Botella et al (24)	Social anxiety disorder	62	36	FPSQ	53.3 (14.3)	39.7 (15.5)	50.5 (11.9)	39.3 (13.0)	Unclear/high risk on at least one criterion	55%	Yes	Mixed
Carlbring et al (27)	Panic disorder	25	24	BSQ	48.7 (11.7)	31.8 (11.6)	52.6 (10.8)	31.3 (9.1)	Low risk of bias on all criteria	12%	Yes	Self-referred
Bergström et al (26)	Panic disorder	53	60	PDSS	14.1 (4.3)	6.3 (4.7)	14.2 (4.0)	6.3 (5.6)	Low risk of bias on all criteria	18%	Yes	Mixed
Kiropoulous et al (28)	Panic disorder	46	40	PDSS	14.9 (4.4)	9.9 (5.9)	14.8 (4.0)	9.2 (5.7)	Low risk of bias on all criteria	0%	Yes	Self-referred
Spek et al (29)	Depressive symptoms in elderly	102	99	BDI	19.2 (7.2)	12.0 (8.1)	17.9 (10.0)	11.4 (9.4)	Low risk of bias on all criteria	39%	Yes	Self-referred
Wagner et al (30)	Depressive symptoms	32	30	BDI	23.0 (6.1)	12.4 (10.0)	23.4 (7.6)	12.3 (8.8)	Unclear/high risk on at least one criterion	15%	Yes	Self-referred
Gollings & Paxton (31)	Body dissatisfaction	21	19	BSQ	129.1 (27.3)	98.4 (35.6)	140.8 (37.2)	109.6 (47.7)	Unclear/high risk on at least one criterion	17.5%	Yes	Self-referred
Paxton et al (32)	Body dissatisfaction, disordered eating	42	37	BSQ	134.3 (22.5)	116.8 (35.9)	143.3 (28.9)	105.8 (34.0)	Low risk of bias on all criteria	26%	Yes	Self-referred
Kaldo et al (33)	Tinnitus	26	25	TRQ	26.4 (15.6)	18.0 (16.2)	30.0 (18.0)	18.6 (17.0)	Low risk of bias on all criteria	14%	Yes	Mixed
Schover et al (34)	Male sexual dysfunction	41	40	IIEF	27.4 (17.3)	31.3 (20.4)	26.4 (18.2)	34.4 (22.2)	Unclear/high risk on at least one criterion	20%	Yes	Mixed
Andersson et al (35)	Specific phobia (spider)	15	15	BAT	6.2 (2.6)	10.5 (1.5)	7.3 (1.6)	11.1 (1.2)	Unclear/high risk on at least one criterion	10%	No	Self-referred

[a]Five dimensions of quality were assessed (see text); in this table, the criterion of blinding of outcome assessment is disregarded in the studies assessing outcome only through self-report
INT – guided Internet-based treatment, FTF – face-to-face treatment, ITT – intention-to-treat analysis, LSAS – Liebowitz Social Anxiety Scale, SIAS – Social Interaction Anxiety Scale, FPSQ – Fear of Public Speaking Questionnaire, BSQ – Body Sensation Questionnaire, PDSS – Panic Disorder Severity Scale, BDI – Beck Depression Inventory, TRQ – Tinnitus Reaction Questionnaire, IIEF – International Index of Erectile Function, BAT – Behavioural Approach Test

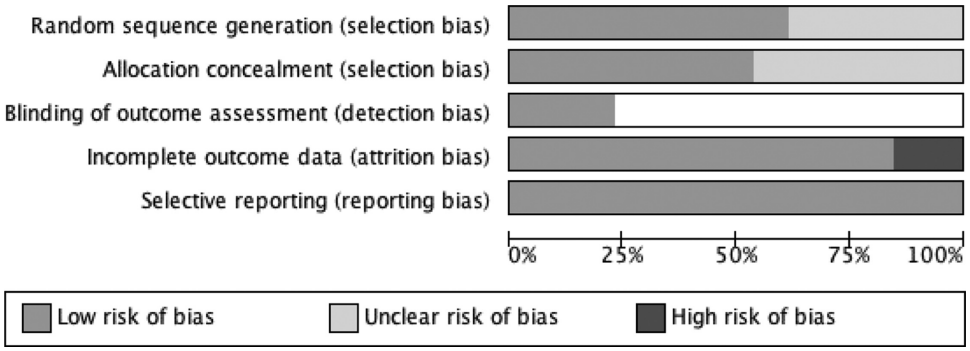

Figure 2 Estimated risk of bias across all included studies

did not search for unpublished studies. There were no restrictions regarding publication date. Searches were last updated in July 2013. We also consulted other databases (Scopus, Google Scholar and PsychInfo), and reference lists of recent studies and reviews on Internet interventions.

Two researchers read the abstracts independently and, in case of disagreement on inclusion, they discussed it amongst themselves or asked a third researcher for advice.

Each included study was assessed for quality using the criteria proposed by the Cochrane collaboration (20). Five dimensions were assessed: risk of selection bias due to the method for generating the randomization sequence; risk of selection bias in terms of allocation concealment, i.e., due to foreknowledge of the forthcoming allocations; detection bias in terms of blinding of outcome assessors; attrition bias due to incomplete outcome data; and reporting bias due to selective reporting of results. The criterion for performance bias relating to masking of participants was not used, as that form of masking is not possible in the types of treatments investigated in this review. On each dimension, the status of the studies was rated using the response options "low risk", "high risk" or "unclear". The alternative "unclear" was used when there was no data to assess the quality criterion in the original study. In studies using self-report, the criterion of blinding of outcome assessors was judged to be not applicable.

Data were analysed using Review Manager (RevMan) version 5.1.0 (20). In the main meta-analyses, we assessed the effect of guided ICBT compared to face-to-face treatment using the standardized mean difference at post-treatment (Hedges' g) as outcome, meaning that the difference between treatments was divided by the pooled standard deviation. If both intention-to-treat and per-protocol data were presented, the former estimate was used in the meta-analysis. Estimates of treatment effects were conducted both using all included studies and separately for each clinical disorder (e.g., depression). Potential differences in dropout rates between guided ICBT and face-to-face treatment were analysed using meta-analytic logistic regression.

All pooled analyses were carried out within a random effects model framework, assuming variation in true effects

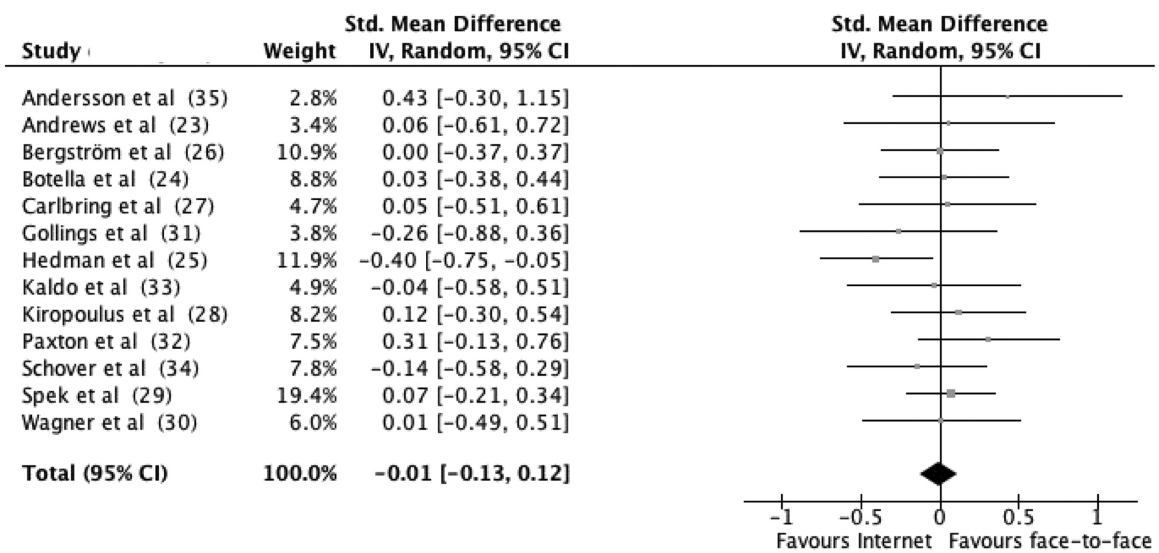

Figure 3 Forest plot displaying effect sizes of studies comparing guided Internet-based treatment with face-to-face treatment

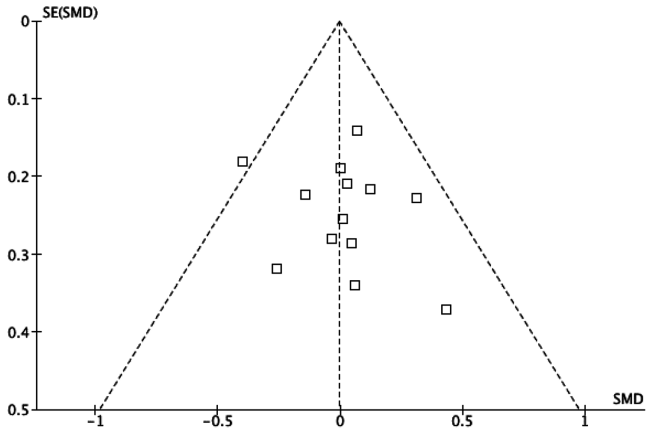

Figure 4 Funnel plot to assess for publication bias by relating effect sizes of the studies to standard errors. SE – standard error, SMD – standardized mean difference (Cohen's d)

in the included studies and accounting for the hypothesized distribution of effects (21,22). Studies were assessed for heterogeneity using χ^2 and I^2 tests, where an estimate above 40% on the latter test suggests presence of heterogeneity (21). In addition, forest plots were inspected to assess variation in effects across studies. Sensitivity analyses were conducted to assess whether study quality was related to outcome, by comparing studies judged as having a low risk of bias on all five quality criteria dimensions with the other studies (i.e., those assessed as "unclear" or "high risk" on at least one quality criterion). Publication bias was investigated using funnel plots.

Power calculations were conducted as suggested by Borenstein et al (22) and showed that, in order to have a power of 80% to detect a small effect size (d=0.3), given an alpha-level of 0.05, 14 studies with an average of 25 participants in each treatment arm were needed.

RESULTS

Of 1,286 screened studies, 13 (total N=1053) met all review criteria and were included in the analysis. Figure 1 displays the study inclusion process. All the 13 studies investigated guided ICBT against some form of CBT (individual format, n=6 and group format, n=7). In terms of conditions studied, three targeted social anxiety disorder (23-25), three panic disorder (26-28), two depressive symptoms (29,30), two body dissatisfaction (31,32), one tinnitus (33), one male sexual dysfunction (34), and one spider phobia (35). The total number of participants was 551 in guided ICBT and 502 in the face-to-face condition.

The studies were conducted by eight independent research groups and carried out in Australia, the Netherlands, Spain, Sweden, Switzerland, or the U.S.. The smallest study had 30 participants and the largest 201. Seven studies recruited participants solely through self-referral, while the remainder included participants from clinical samples or using a mix of self-referral and clinical recruitment. All studies were published between 2005 and 2013. The characteristics of each study are presented in Table 1.

When blinding of outcome assessment was included, only three studies were judged as having low risk of bias on all five quality dimensions (25,26,28). When that criterion was disregarded in the studies assessing outcome only through self-report, 7 of 13 studies were judged as having low risk of bias on all quality dimensions. Figure 2 displays the averaged risk of bias in the included studies.

In terms of dropout, meta-analytic logistic regression showed no significant difference between the two treatment formats (OR=0.79; 95% CI: 0.57-1.09), indicating that dropout did not systematically favour one treatment over the other. Tests of heterogeneity did not demonstrate significant differences in effects across treatments (χ^2=9.91; I^2= 0%; p=0.62).

A forest plot presenting effect sizes (g) of each study as well as the pooled between-group effect size of all studies is presented in Figure 3. An effect size estimate below 0 favours guided ICBT, while an effect size above 0 represents larger effects for face-to-face CBT. The pooled between-group effect size (g) at post-treatment across all 13 studies was −0.01 (95% CI: −0.13 to 0.12), showing that guided ICBT and face-to-face treatment produced equivalent overall effects.

In the three studies targeting social anxiety disorder (23-25), the pooled between-group effect size (g) was −0.16 (95% CI: −0.47 to 0.16), in favour of guided ICBT but indicating equivalent effects. In the three studies targeting panic disorder (26-28), the effect size was 0.05 (95% CI: −0.20 to 0.30), in line with the notion of equivalent effects. In the two studies targeting depressive symptoms (29,30), the effect size was 0.05 (95% CI: −0.19 to 0.30), showing equivalent effects for this condition as well.

In the two studies targeting body dissatisfaction (31,32), the effect size was 0.07 (95% CI: −0.49 to 0.62), again showing largely equivalent effects. In the only study targeting tinnitus (36), the effect size was −0.04 (95% CI: −0.58 to 0.51), suggesting no difference between the formats for this condition as well. In the only study targeting male sexual dysfunction (34), using a clinical sample of patients that had been treated for prostate cancer, the effect size was −0.14 (95% CI: −0.58 to 0.29), which is a small effect again in slight favour of ICBT. In the only study targeting spider phobia (35), the effect size was 0.43 (95% CI: −0.30 to 1.15), in favour of face-to-face treatment, but given the small size of the study not significant.

In order to estimate whether there was an association of study quality and treatment effects, subgroup analyses were conducted. In the three studies judged to have low risk of bias on all five quality criteria, the pooled effect size (g) was −0.11 (95% CI: −0.42 to 0.21), while it was 0.05 (95% CI: −0.10 to 0.19) for the other ten studies, suggesting that study quality did not affect outcomes significantly.

Figure 4 presents a funnel plot relating effect sizes on the primary outcome of the studies to the standard errors of the estimates. Effect sizes were evenly distributed around the averaged effect. Of specific interest, the lower right section of the funnel plot is not devoid of studies, suggesting that there is no major bias of the pooled effect estimate due to unpublished small studies with results favouring face-to-face treatment.

DISCUSSION

The aim of this systematic review and meta-analysis was to collect and analyse studies in which guided ICBT had been directly compared with face-to-face CBT. Altogether, the findings are clear in that the overall effect for the main outcomes was close to zero, indicating that the two treatment formats are equally effective in social anxiety disorder, panic disorder, depressive symptoms, body dissatisfaction, tinnitus, male sexual dysfunction, and spider phobia, when analysed as an aggregated cohort.

Thus, the present meta-analytic review mirrors the findings by Cuijpers et al (18), who found no differences between guided self-help and face-to-face therapies. Interestingly, there is only a minor overlap between that meta-analysis and the present one. We included the studies by Spek et al (29) and Botella et al (24), as they involved therapist contact in association with inclusion (but not during treatment). We did not include a study (included in Cuijpers et al's meta-analysis) that was judged to compare two forms of ICBT rather than ICBT vs. face-to-face treatment (37).

While there were relatively few studies on each condition, the overall number of studies and number of participants gave us power to detect differences of importance between the formats. There was a low risk of bias, including publication bias, but many individual studies were much underpowered to detect differences, and for each of the included conditions there were few studies and sometimes only one.

The results of this meta-analysis are thought-provoking both from a theoretical and practical point of view. In terms of theories about change in psychotherapeutic interventions, the results suggest that the role of a face-to-face therapist may not be as crucial as suggested in the literature (38) to generate large treatment effects. Even if factors such as therapeutic alliance are established in guided ICBT (39), they are rarely important for outcome. Indeed, understanding what makes ICBT work is a challenge for future research, as only a few studies to date have investigated mediators of outcome (e.g., 40,41).

From a practical point of view, the findings call for research on treatment preferences and effectiveness in real life settings, as most studies in this review involved self-referred participants recruited via advertisements. There are studies on treatment acceptability of ICBT showing that patient tend to appreciate the ICBT format (42-44), but also one study reporting the opposite (45). When it comes to effectiveness, there are now at least four controlled trials and eight open studies showing that ICBT works in regular clinical settings (46). However, controlled trials such as the ones reviewed in this meta-analysis all require that participants consent to being randomized to either ICBT or face-to-face treatment, a requirement that limits the generalizability of the results.

The present meta-analysis has several strengths, such as a consistent outcome across studies regarding efficacy of guided ICBT compared to face-to-face CBT, the relatively high quality of the trials included, little heterogeneity and no indication of publication bias. However, there are also limitations. First, the included studies differed substantially in terms of treatment content, not so much within studies as between ICBT programs. We endorsed a broad definition of CBT, but it would of course have been preferable to have many studies on the same program, as is the case in reviews of cognitive therapy for depression (47). Second, we compared against different formats of face-to-face therapy and it could be argued that group CBT is a suboptimal comparison (48), at least when it comes to patient preferences. Third, we analysed the primary outcome measures in the trials and did not include secondary outcomes. Indeed, the heterogeneity of clinical conditions included can be viewed as a problem on its own, but we cannot at this stage and with very few studies for each condition conclude that guided ICBT and face-to-face therapy are equally effective on all outcomes. For example, there are very few studies on knowledge acquisition following CBT and even fewer on ICBT (49), and this can be something that differs between the therapy formats (in particular in the long run). In addition, patient characteristics have not been taken into account. This is potentially important, since there are studies suggesting that different predictors of outcome (e.g., agoraphobic avoidance) are relevant when comparing face-to-face versus Internet treatment. Fourth, we only included studies on adult samples. However, a study by Spence et al (50) on adolescents is clearly in line with our findings, suggesting equivalence. Finally, we did not analyse long-term effects of the treatments. This is a possible area for future research, as the type of trials included here has the advantage that randomization can be maintained for long time periods.

ICBT has only been around for a short time and is still developing rapidly (51). A recent change is the use of mobile smart phones in treatment, and it is likely that smart phone applications and ICBT will blend in with face-to-face treatment in the near future. Finally, while we performed this review in the form of a study-level meta-analysis, there is an emerging trend to instead conduct patient-level meta-analyses with primary data (52).

In conclusion, guided ICBT has the promise to be an effective, and potentially cost-effective, alternative and complement to face-to-face therapy. More studies are needed before firm conclusions can be drawn, but the findings to date, including this meta-analysis, clearly show that guided ICBT is a treatment for the future.

Acknowledgements

G. Andersson acknowledges Linköping University, the Swedish Science Foundation and Forte for financial support.

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DOI 10.1002/wps.20151

The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neurodevelopmental Cohort

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Little is known about the occurrence and predictors of the psychosis spectrum in large non-clinical community samples of U.S. youths. We aimed to bridge this gap through assessment of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort, a collaborative investigation of clinical and neurobehavioral phenotypes in a prospectively accrued cohort of youths, funded by the National Institute of Mental Health. Youths (age 11-21; N=7,054) and collateral informants (caregiver/legal guardian) were recruited through the Children's Hospital of Philadelphia and administered structured screens of psychosis spectrum symptoms, other major psychopathology domains, and substance use. Youths were also administered a computerized neurocognitive battery assessing five neurobehavioral domains. Predictors of psychosis spectrum status in physically healthy participants (N=4,848) were examined using logistic regression. Among medically healthy youths, 3.7% reported threshold psychotic symptoms (delusions and/or hallucinations). An additional 12.3% reported significant sub-psychotic positive symptoms, with odd/unusual thoughts and auditory perceptions, followed by reality confusion, being the most discriminating and widely endorsed attenuated symptoms. A minority of youths (2.3%) endorsed subclinical negative/disorganized symptoms in the absence of positive symptoms. Caregivers reported lower symptom levels than their children. Male gender, younger age, and non-European American ethnicity were significant predictors of spectrum status. Youths with spectrum symptoms had reduced accuracy across neurocognitive domains, reduced global functioning, and increased odds of depression, anxiety, behavioral disorders, substance use and suicidal ideation. These findings have public health relevance for prevention and early intervention.

Key words: Psychosis spectrum, U.S. youths, sub-psychotic positive symptoms, neurocognition, functional impairment

(World Psychiatry 2014;13:296-305)

Psychotic-like symptoms, including attenuated paranoid delusional thinking and auditory hallucinations, occur in approximately 5-8% of the general adult population (1). In some, these symptoms never cause sufficient distress or functional impairment to necessitate help seeking (2), but in others they can precede the onset of psychotic disorders (3).

A meta-analysis of transition from subthreshold to psychotic experiences in unselected, non-help-seeking population samples reported a 0.6% one-year risk of transition to psychotic disorder (4), a much lower conversion rate than in clinically help-seeking samples (5). This is consistent with a continuum of non-clinical and clinical expressions of psychotic-like experiences in the population (1).

The psychosis spectrum (6) comprises subclinical psychotic-like experiences, threshold psychosis (delusions/hallucinations), and psychosis related symptoms including attenuated negative and disorganized symptoms. Because early attenuated symptoms frequently do not lead to disabling psychosis (7), their utility as a sole means of identifying at-risk individuals is limited. However, through longitudinal evaluation, they provide a window to examine neurobiological risk and protective factors associated with various outcomes (4).

This window may be widened by evaluating the earliest emergence of subclinical spectrum symptoms in younger people from the general population (8). Symptom onset before age 18 is a significant predictor of psychosis conversion in ultra-high risk (9) and birth cohort (7,8,10) samples. Population-based studies in children and adolescents have demonstrated higher rates of psychotic-like experiences in youths than in adults (range=5-35%), with meta-analytically derived medians of 17% in children (9-12 years old), and 7.5% in adolescents (13-18 years old) (11). Although these symptoms are likely transient in most children (8), their evolution into full psychosis may be moderated by symptom severity (4), type (3), and persistence (12,13).

Regardless of eventual psychosis, early subclinical psychotic symptoms are associated with comorbid psychopathology, including depression (5,14-16), anxiety (5), and substance use (5,12,17); impaired global functioning (18) and increased suicidality (18). Consistent with some findings of neurocognitive impairments in individuals at clinical high risk (19,20), a school-based study of children (age 11-13) in Ireland also reported an association of subclinical symptoms with impairment in processing speed and non-verbal working memory (21). Otherwise, little is known

about neurocognitive functioning associated with early emerging subclinical spectrum symptoms in the general population.

No prior study has characterized the occurrence of psychosis spectrum features in a large systematic community sample of U.S. youths. Moreover, little is known about demographic and psychopathology predictors of psychosis features in this population. We aimed to bridge this gap through the Philadelphia Neurodevelopmental Cohort, an investigation of clinical and neurobehavioral phenotypes in a prospectively accrued non-clinical sample, funded by the National Institute of Mental Health (NIMH).

METHODS

Participants

Prospective participants (N=50,293) were recruited through the Children's Hospital of Philadelphia pediatric clinics and health care network, which extends to over 30 clinical community sites in the tri-state area of Pennsylvania, New Jersey and Delaware. Participants were not recruited from psychiatric clinics, so the sample is not enriched for those seeking mental health services.

Based on electronic medical review or follow-up phone contact, potential participants from this pool were excluded if they were not proficient in English, had significant developmental delays or other conditions that would interfere with their ability to complete study procedures, or could not be contacted.

From the remaining pool, 13,598 individuals were invited, 2,699 declined, 1,401 were excluded, and 9,498 youths (age 8-21) were enrolled. The total sample for the current analyses included youths aged 11-21 (N=7,054 participants, mean age 15.8±2.7 years; 54% female; 56.3% European American, 32.9% African American, 10.8% other) enrolled between November 2009 and November 2011.

After complete description of the study, written informed consent was obtained for participants aged at least 18, and written assent and parental permission were obtained from children aged less than 18 and their parents/legal guardian. All procedures were approved by the University of Pennsylvania and the Children's Hospital of Philadelphia Institutional Review Boards.

Psychopathology measures

Probands (age 11-21) and collaterals (parent or legal guardian for probands aged 11-17) were administered a computerized structured interview (GOASSESS), including a timeline of life events, demographics and medical history, psychopathology screen, Children's Global Assessment Scale (C-GAS) (22), and interviewer observations.

Psychopathology screen was conducted through an abbreviated computerized version of the NIMH Genetic Epidemiology Research Branch Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (23,24), that was modified to collect information on symptoms, duration, distress and impairment for lifetime mood, anxiety, behavioral, psychosis spectrum and eating disorders, suicidal thinking and behavior, as well as treatment history.

Computerized algorithms determined screen positive status for each psychopathology domain based on endorsement of symptoms, frequency and duration to approximate DSM-IV disorder or episode criteria, and significant distress or impairment rated at least 5 on an 11-point scale. A self-reported lifetime substance use measure (25) was added later in the study and administered to 4,066 participants. Comparison of the diagnostic algorithms with the full criteria using data from the National Comorbidity Survey – Adolescent (23) yielded fair to excellent area under the receiver operator characteristic curve values for the major classes of disorders.

GOASSESS medical history supplemented the Children's Hospital of Philadelphia electronic medical records, and was used to identify a subgroup of physically healthy participants (no or mild physical illnesses).

Assessors underwent rigorous training, certification and monitoring.

Psychosis spectrum screen

We aimed to perform a brief screen for a broad spectrum of psychosis relevant experiences, ranging from subtle and subclinical (positive, negative and disorganized) symptoms that would not qualify for diagnosable disorders to clinically threshold hallucinations and delusions that could meet criteria for serious psychotic disorders. We thus included three screening tools to assess positive sub-psychosis, positive psychosis, and negative/disorganized symptoms. Individuals evidencing any of those symptoms were classified as "psychosis spectrum".

Positive sub-psychosis symptoms in the past year were assessed with the 12-item assessor administered PRIME Screen-Revised (26,27). Items were self-rated on a 7-point scale ranging from 0 ("definitely disagree") to 6 ("definitely agree"). The participant then rated the duration of each endorsed symptom.

Positive psychosis symptoms (lifetime hallucinations and delusions) were assessed using the K-SADS psychosis screen questions, supplemented with structured questions to reduce false positives.

Negative/disorganized symptoms were assessed using six embedded assessor rated items from the Scale of Prodromal Syndromes (SOPS, 28): avolition, expression of emotion, experience of emotions and self, occupational functioning, trouble with focus and attention, disorganized communication.

For positive sub-psychosis, given age effects on PRIME Screen-Revised score, an Age Deviant index was derived identifying children with extreme total scores ($z \geq 2$) compared to age mates. In addition, because psychosis risk may not be linearly related to total scores, such that endorsement of even one symptom at a severe level may be indicative of psychosis risk, an Extreme Agreement index was also calculated based on traditional criteria (at least one item rated 6, "definitely agree", or at least three items rated 5, "somewhat agree") (27).

Criteria for positive psychosis were hallucinations and/or delusions based on K-SADS screen, with duration of at least one day, occurring outside the context of substance use and physical illness, and accompanied by significant impairment or distress (rating of at least 5).

For negative/disorganized symptoms, an Age Deviant index was generated using SOPS z-scores. Specifically, SOPS total scores were normed within age; $z \geq 2$ cutoff reflected extreme ratings of negative and/or disorganized symptoms for age cohort.

Neurocognitive assessment

The 1-hour computerized neurocognitive battery included 14 tests assessing five neurobehavioral domains (29): executive functions (abstraction and mental flexibility, attention, working memory), episodic memory (words, faces, shapes), complex cognition (verbal reasoning, nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion intensity differentiation, age differentiation), sensorimotor speed (motor, sensorimotor).

Except for the tests designed exclusively for measuring speed, each test provides measures of both accuracy and speed. The Reading subtest of the Wide Range Achievement Test, version 4 (WRAT-4) (30) was administered first to determine participants' ability to complete the battery and to provide an estimate of IQ.

Statistical approach

First, we evaluated internal consistency (Cronbach's alpha) and age distributions of psychosis spectrum items in the total sample. Second, to minimize conflation of psychosis spectrum symptoms and experiences occurring in the context of, or attributable to, physical illnesses, we classified psychosis spectrum status, characterizing demographics and screen summary variables as well as neurocognitive function, in the subgroup of physically healthy youths. Third, we evaluated differences between psychosis spectrum and non-spectrum participants using ANOVA's and Cohen's d (quantitative variables) or chi-square (categorical variables). Fourth, logistic regression examined demographic, psychopathology and substance use predictors of spectrum status (Statistical Package for Social Sciences, SPSS, version 20).

Finally, we performed item analysis of positive sub-psychosis items comparing endorsements between groups, summarizing symptom endorsement count, and conducting multivariate analysis of variance (MANOVA) of differences in mean item ratings. Receiver operating characteristics analysis identified positive sub-psychosis items most predictive of psychosis spectrum vs. non-spectrum classification (SPSS, version 20).

RESULTS

Psychosis spectrum screen characteristics

Among the total sample of 7,054 participants, 21.0% (N=1,482) met psychosis spectrum criteria. Positive sub-psychosis Extreme Agreement was 14.6% (N=1,028). PRIME Screen-Revised mean total score was 8.0±10.7 for probands and 2.4±5.9 for collaterals; the proband-collateral pair total difference mean was 8.0±10.0, indicating that probands endorsed higher levels of sub-psychosis than reported by their caregivers.

There was a significant difference in PRIME Screen-Revised total scores across the 11-21 age groups (ANOVA: $F=13.69$, $df=10,7042$, $p<0.001$); pairwise post-hoc tests showed linear and *decreasing* total scores with age. There was also a significant age effect on SOPS items (ANOVA: $F=3.24$, $df=10,6759$, $p<0.001$), with some younger groups rated lower than older participants.

Internal consistency was high in probands (alpha=0.87) and collaterals (alpha=0.86) for the PRIME-Screen Revised, and was acceptable for the SOPS (alpha=0.70).

Characteristics of young people with psychosis spectrum features

In the subgroup of physically healthy participants (N=4,848), 3.7% reported threshold psychotic symptoms (delusions and/or hallucinations), an additional 12.3% reported significant sub-psychotic symptoms, and 2.3% endorsed subclinical negative/disorganized symptoms in the absence of positive symptoms.

Among youths classified as psychosis spectrum (N=954), 2.0% fulfilled four criteria, 8.5% three criteria, 23.0% two criteria, and 66.4% one criterion. The positive sub-psychosis Extreme Agreement was 67.6%, the positive sub-psychosis Age Deviant was 34.4%, and the negative/disorganized Age Deviant was 23.9%.

Characteristics of psychosis spectrum vs. non-spectrum participants are presented in Table 1. Gender distribution was proportional between the two groups, and although psychosis spectrum were younger, the effect was small. The psychosis spectrum group was disproportionately non-European American, and had lower WRAT-4 Reading standard scores, parental education, and global functioning.

Table 1 Characteristics of physically healthy psychosis spectrum and non-spectrum youths

	Psychosis spectrum	Non-spectrum	Test	df	Result	p	Cohen's d
N (%)	954 (20.0)	3894 (80.0)	-	-	-	-	-
Gender (% male)	47.9	45.0	Chi-square	1	χ^2=2.5	n.s.	-
Age (mean±SD)	15.2±2.7	15.8±2.7	ANOVA	1,4846	F=31.9	0.001	−0.22
Ethnicity (% European American)	37.7	58.1	Chi-square	1	χ^2=127.5	0.001	-
WRAT-4 Reading standard score (mean±SD)	97.9±17.2	103.6±16.9	ANOVA	1,4832	F=86.1	0.001	−0.32
Parental education							
Mother (years, mean±SD)	13.8±2.3	14.5±2.4	ANOVA	1,4783	F=70.8	0.001	−0.29
Father (years, mean±SD)	13.4±2.5	14.4±2.7	ANOVA	1,4437	F=93.1	0.001	−0.38
PRIME Screen-Revised							
Proband total (mean±SD)	21.4±12.9	4.3±6.1	ANOVA	1,4846	F=3557.2	0.001	2.16
Proband z (mean±SD)	1.3±1.2	−0.4±0.6	ANOVA	1,4809	F=3565.5	0.001	2.25
Collateral total (mean±SD)	4.2±8.1	1.6±4.7	ANOVA	1,3652	F=128.6	0.001	0.61
Proband-collateral pair total difference (mean±SD)	19.1±12.2	4.8±6.3	-	-	-	-	-
Threshold psychotic symptoms (%)	20.2	-	-	-	-	-	-
Hallucinations (%)	17.9	-	-	-	-	-	-
Delusions (%)	11.2	-	-	-	-	-	-
Scale of Prodromal Symptoms (SOPS)							
Total (mean±SD)	5.1±4.7	1.6±1.8	ANOVA	1,4669	F=1347.4	0.001	1.33
z (mean±SD)	0.9±1.5	−0.3±0.6	ANOVA	1,4820	F=1430.0	0.001	1.40
Trouble with focus/attention (mean±SD)	1.69±1.3	0.8±1.0	ANOVA	1,4757	F=489.7	0.001	0.84
Experience of emotions and self (mean±SD)	0.6±1.1	0.1±0.4	ANOVA	1,4803	F=595.4	0.001	0.83
Expression of emotion (mean±SD)	1.0±1.2	0.3±0.7	ANOVA	1,4740	F=447.0	0.001	0.85
Avolition (mean±SD)	0.7±1.2	0.1±0.4	ANOVA	1,4795	F=646.1	0.001	0.94
Disorganized communication (mean±SD)	0.5±0.9	0.1±0.4	ANOVA	1,4806	F=410.7	0.001	0.75
Occupational functioning (mean±SD)	0.7±1.2	0.1±0.5	ANOVA	1,4789	F=490.9	0.001	0.86
Children's Global Assessment Scale, current (mean±SD)	70.8±13.4	81.4±10.5	ANOVA	1,4807	F=697.6	0.001	−0.95

WRAT-4 – Wide Range Achievement Test, version 4

Notably, caregivers reported significantly lower positive sub-psychosis ratings than probands.

Among psychosis spectrum youths, the positive sub-psychosis items most frequently endorsed ("definitely agree") on the PRIME Screen-Revised were odd/unusual thoughts and auditory perceptions, followed by reality confusion (Table 2). The least frequently endorsed was thought control. All PRIME Screen-Revised items yielded higher ratings in psychosis spectrum compared to non-spectrum participants (MANOVA), with effect sizes greater than 0.92 and the largest group differences yielded by reality confusion, auditory perceptions, mind tricks and odd/unusual thoughts.

Receiver operator curve analysis of PRIME Screen-Revised items yielded area under the curve values ranging from 0.65 to 0.79, indicating moderate ability of items to discriminate between psychosis spectrum and non-spectrum. The most discriminating items were again reality confusion, odd/unusual thoughts, mind tricks and auditory perceptions.

Neurocognitive profiles of psychosis spectrum and non-spectrum youths

Neurocognitive profiles are presented in Figure 1. A group (psychosis spectrum, non-spectrum) x domain MANOVA (covariates were age, ethnicity and parental education) on accuracy scores showed a main effect for group (F=92.71, df=1,4550, p<0.0001) and domain (F=4.11, df=11,4540, p<0.0001), as well as a group x domain interaction (F=4.87, df=11,4540, p<0.0001). Psychosis spectrum youths showed a mild but significant decrease in performance accuracy across neurocognitive domains compared to non-spectrum.

The MANOVA on speed scores showed a main effect for group (F=10.21, df=1,4503, p=0.0014) and domain (F=4.75, df=13,4491, p<0.0001), and a group x domain interaction (F=6.97, df=13,4491, p<0.0001). Psychosis spectrum showed slower responding in some but not all domains.

Table 2 Item analysis of PRIME Screen-Revised in physically healthy psychosis spectrum vs. non-spectrum youths

	Psychosis spectrum endorsing "Definitely agree"	Psychosis spectrum	Non-spectrum	Pairwise F following significant MANOVA			ROC		
PRIME Screen-Revised item	%	Item mean±SD	Item mean±SD	F	p	Cohen's d	AUC	95% CI lower	95% CI upper
I think that I have felt that there are odd or unusual things going on that I can't explain (Odd/ unusual thoughts)	17.6	3.06±2.19	0.90±1.45	1334.81	0.001	1.33	0.77	0.75	0.79
I have had the experience of hearing faint or clear sounds of people or a person mumbling or talking when there is no one near me (Auditory perceptions)	17.5	2.19±2.45	0.25±0.89	1558.80	0.001	1.44	0.72	0.70	0.74
I think that I may get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams (Reality confusion)	16.4	3.08±2.17	0.77±1.37	1677.88	0.001	1.48	0.79	0.78	0.81
I think that I may hear my own thoughts being said out loud (Audible thoughts)	11.1	1.85±2.23	0.29±0.91	1113.47	0.001	1.22	0.69	0.67	0.71
I believe that I have special natural or supernatural gifts beyond my talents and natural strengths (Grandiosity)	10.3	1.76±2.20	0.26±0.89	1074.51	0.001	1.19	0.69	0.67	0.71
I think that I might feel like my mind is "playing tricks" on me (Mind tricks)	9.7	2.14±2.19	0.36±0.97	1410.89	0.001	1.37	0.73	0.71	0.75
I have had the experience of doing something differently because of my superstitions (Superstitions)	8.0	1.91±2.12	0.44±1.10	872.26	0.001	1.08	0.70	0.67	0.72
I wonder if people may be planning to hurt me or even may be about to hurt me (Persecutory/ suspicious)	6.1	1.56±2.01	0.27±0.86	911.30	0.001	1.10	0.68	0.66	.070
I think that I might be able to predict the future (Predict future)	5.2	1.45±1.97	0.33±0.95	645.84	0.001	0.92	0.66	0.63	0.68
I have thought that it might be possible that other people can read my mind, or that I can read other's minds (Mind reading)	4.9	1.29±1.93	0.22±0.80	692.86	0.001	0.96	0.65	0.63	0.67
I may have felt that there could possibly be something controlling my thoughts, feelings, or actions (Thought control)	3.8	1.37±1.85	0.21±0.73	922.45	0.001	1.11	0.67	0.65	0.70

ROC – receiver operating characteristic analysis of PRIME Screen-Revised items, AUC – area under the curve, indicating the ability of the item to discriminate between psychosis spectrum and non-spectrum cases, CI – confidence interval

Predicting psychosis spectrum classification from psychopathology and substance use

The prediction success of psychosis spectrum vs. non-spectrum based on demographic and clinical correlates was 84.6% (psychosis spectrum=27.7%, non-spectrum=96.6%; false positive=2.8%, false negative=12.6%) (Table 3). Receiver operator curve analysis revealed a moderate fit of the model.

Significant predictors of psychosis spectrum included male gender, younger age, and non-European American ethnicity. Psychosis spectrum was significantly predicted by depression, mania, specific phobia, social phobia, agoraphobia, obsessive-compulsive, post-traumatic stress, oppositional

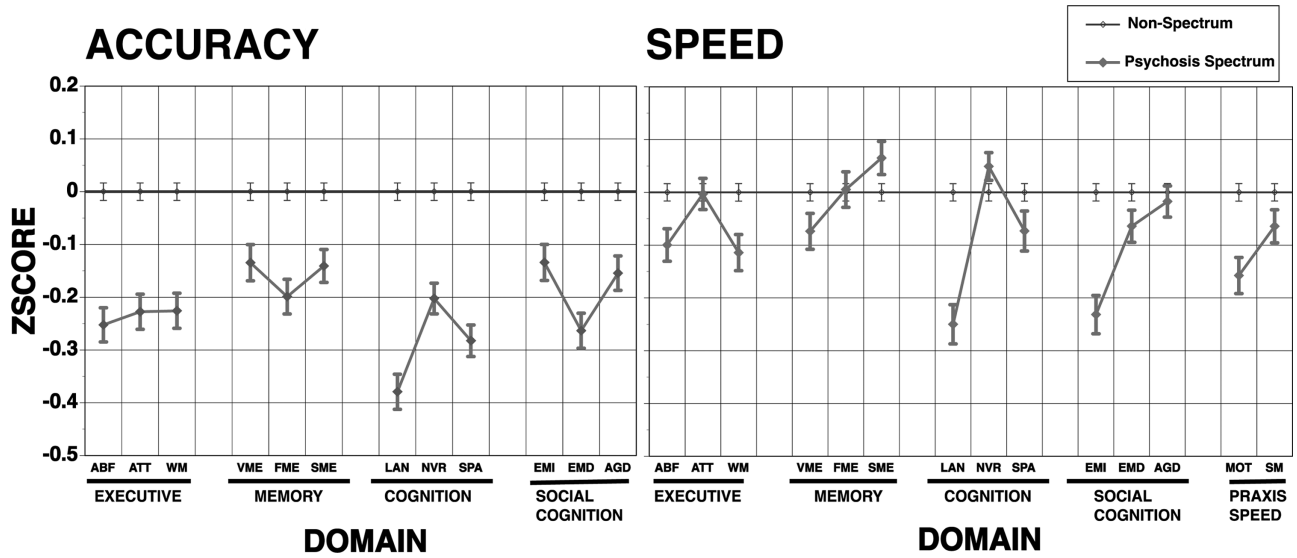

Figure 1 Computerized Neurocognitive Battery profiles of psychosis spectrum and non-spectrum physically healthy youths. ABF – abstraction/flexibility, ATT – attention, WM – working memory, VME – verbal memory, FME – face memory, SME – spatial memory, LAN – language, NVR – non-verbal reasoning, SPA – spatial processing, EMI – emotion identification, EMD – emotion differentiation, AGD – age discrimination, MOT – motor, SM – sensorimotor

defiant, and attention deficit/hyperactivity domains. Moreover, a third of psychosis spectrum youths endorsed passive thoughts of death and dying, more than 20% endorsed suicidal ideation, and both were significant predictors of psychosis spectrum group membership.

Ever talking with a professional (school counselor, psychologist, social worker, psychiatrist or other) for "feelings or problems with mood or behavior" was more likely, but not significantly, in psychosis spectrum than non-spectrum youths (65.7% vs. 44.1%). The odds of inpatient hospitalizations and functional impairment were significantly higher in psychosis spectrum (Table 3). On a follow-up item administered only to those who had not received treatment (and therefore not included in the model), 23.1% of non-help-seeking psychosis spectrum (N=84/363) compared to 9.9% of non-help-seeking non-spectrum (N=251/2538) youths reported that others suggested they seek help but they had not done so (Pearson chi-square=62.4, df=1,2901, $p<0.001$).

The substance use measure was introduced later in the study, and was therefore available on a smaller subsample (N=2,733). To verify that the psychopathology results were comparable in this smaller subset of participants, we re-ran the model including only them, and it yielded similar results (omnibus model chi-square=547.59, $p<0.001$, df=26; prediction success overall=84.3; area under the curve=0.81, 95% CI: 0.79-0.83), except that depression (Wald chi-square=1.31; odds ratio=1.22), social phobia (Wald chi-square=3.55; odds ratio=1.28), obsessive-compulsive disorder (Wald chi-square=2.81; odds ratio=1.64) and inpatient hospitalizations (Wald chi-square=2.76; odds ratio=0.56) fell short of significance. Finally, including ethnicity in interaction with each psychopathology variable did not improve fit, and only eating disorders (Wald chi-square=4.96; odds ratio=1.20) produced significant interactions with ethnicity.

Logistic regression to predict psychosis spectrum classification from demographics and substance use in the subsample with these data was significant, and prediction success overall was 81.5% (Table 3). However, although specificity was high (non-spectrum=99.5%), sensitivity was low (psychosis spectrum=3%; false positive <1%, false negative =18%). Receiver operator curve analysis revealed that the model classified groups above chance.

Significant demographic predictors were consistent with those observed in the psychopathology model, except that paternal education was a predictor, and gender was not. Among substances, Wald criterion suggested that tobacco and over-the-counter medication were significant contributors to prediction.

DISCUSSION

This is the first large, systematic study of a non-clinical sample of U.S. youths that evaluated psychosis spectrum symptoms, including attenuated and threshold positive psychotic, and negative/disorganized symptoms. Previous community studies of mental disorders in U.S. youths have not included assessment of psychotic symptoms and their correlates (31,32).

The high frequency of psychosis spectrum symptoms, consistent with findings from studies conducted in other countries, and their association with reduced neurocognitive and global functioning, suggests that psychosis spectrum screening should be part of a comprehensive evaluation of psychopathology in youths in general population

Table 3 Bivariate logistic regression predicting psychosis risk status (psychosis spectrum vs. non-spectrum) from psychopathology and substance use

	Psychosis spectrum	Non-spectrum					95% CI	
	%	%	B	Wald chi-square	p	Odds ratio	Lower	Upper
Psychopathology (N=4,665)								
Demographics								
Gender			−0.24	6.70	0.010	0.79	0.66	0.94
Age			−0.06	13.88	0.001	0.94	0.91	0.97
Ethnicity			0.52	27.16	0.001	1.68	1.38	2.05
Mother education			−0.03	1.75	n.s.	0.97	0.93	1.02
Father education			−0.03	2.47	n.s.	0.97	0.93	1.01
WRAT-4 Reading			−0.01	3.93	0.047	0.99	0.99	1.00
Mood								
Depression	26.9	9.6	0.28	4.55	0.033	1.32	1.02	1.71
Mania	2.1	0.3	1.08	4.22	0.040	2.94	1.05	8.24
Anxiety								
Generalized anxiety	5.2	1.6	0.07	0.07	n.s.	1.07	0.66	1.73
Separation anxiety	6.9	3.8	−0.06	0.10	n.s.	0.94	0.64	1.37
Specific phobia	43.5	28.7	0.19	3.97	0.046	1.21	1.00	1.45
Social phobia	36.0	17.8	0.39	15.13	0.001	1.48	1.21	1.80
Panic	3.1	0.8	0.40	1.45	n.s.	1.49	0.78	2.86
Agoraphobia	14.8	3.4	0.78	24.46	0.001	2.19	1.61	2.99
Obsessive-compulsive	7.9	1.5	0.63	8.12	0.004	1.88	1.22	2.90
Post-traumatic stress	22.0	8.4	0.30	5.18	0.023	1.35	1.04	1.75
Behavior								
Attention deficit/hyperactivity	29.8	11.9	0.50	19.20	0.001	1.64	1.32	2.05
Oppositional defiant	44.4	25.3	0.42	17.66	0.001	1.52	1.25	1.84
Conduct	17.5	4.3	0.12	0.58	n.s.	1.13	0.83	1.54
Eating (anorexia or bulimia)	3.4	1.1	0.33	1.26	n.s.	1.39	0.78	2.49
Morbid thoughts								
Thoughts of death/dying	32.6	12.0	0.69	36.58	0.001	2.00	1.60	2.50
Suicidal ideation	20.1	5.5	0.37	5.78	0.016	1.45	1.07	1.96
Treatment								
Talked with professional	65.7	44.1	0.13	1.81	n.s.	1.14	0.94	1.39
Psychiatric medications	18.6	7.1	0.17	1.49	n.s.	1.19	0.90	1.57
Inpatient hospitalization	6.7	2.1	−0.50	4.21	0.040	0.61	0.38	0.98
Global Assessment Scale			−0.04	104.55	0.001	0.96	0.95	0.97
Substance use (N=2,733)								
Demographics								
Sex			−0.14	1.95	n.s.	0.87	0.71	1.06
Age			−0.11	19.60	0.001	0.90	0.86	0.94
Race			0.68	36.25	0.001	1.98	1.59	2.47
Mother education			−0.06	5.10	0.024	0.94	0.89	0.99
Father education			−0.05	4.60	0.032	0.95	0.90	1.00
WRAT-4 Reading			−0.01	7.92	0.005	0.99	0.98	1.00

Table 3 Bivariate logistic regression predicting psychosis risk status (psychosis spectrum vs. non-spectrum) from psychopathology and substance use *(continued)*

	Psychosis spectrum	Non-spectrum					95% CI	
	%	%	B	Wald chi-square	p	Odds ratio	Lower	Upper
Substance (ever used)								
Tobacco	23.4	17.3	0.72	15.72	0.001	2.06	1.44	2.94
Alcohol	29.5	30.4	−0.17	1.17	n.s.	0.84	0.62	1.15
Marijuana	22.0	18.1	−0.02	0.01	n.s.	0.98	0.67	1.43
Stimulants	4.4	2.5	0.00	0.00	n.s.	1.00	0.53	1.88
Tranquilizers	2.8	1.1	0.58	1.98	n.s.	1.78	0.80	3.97
Downers	2.1	0.8	0.39	0.64	n.s.	1.48	0.56	3.90
Inhalants	6.7	3.6	0.39	2.99	n.s.	1.48	0.95	2.31
Over-the-counter medication	12.6	8.5	0.36	4.31	0.038	1.44	1.02	2.03
Cocaine	2.5	0.8	0.51	1.27	n.s.	1.67	0.69	4.04
Psychedelics	2.1	0.9	0.55	1.41	n.s.	1.74	0.70	4.31
Opiates	2.0	1.3	−0.35	0.50	n.s.	0.70	0.27	1.87
Steroids	1.6	1.2	−0.03	0.01	n.s.	0.97	0.42	2.25

WRAT-4 – Wide Range Achievement Test, version 4, CI – confidence interval

and pediatric settings. However, the lack of specificity of psychosis spectrum symptoms is evident from the high rates of comorbid mental disorders, that were nearly double than in the U.S. general population (31,32). Follow-up of psychosis spectrum youths will enable us to identify factors associated with transient psychotic experiences from the small minority in whom they presage the subsequent development of psychotic disorders in adulthood.

Among physically healthy young people, 12.3% reported positive sub-psychotic symptoms. The most discriminating and widely endorsed attenuated positive symptoms were unusual thoughts and auditory perceptions, as observed in other populations (11,33). An additional 3.7% of participants (20.2% of psychosis spectrum) reported threshold psychotic symptoms, similar to meta-analytically derived rates of psychotic symptoms in the general adult population (4%) (1). This comparability could reflect our requirement that threshold positive psychosis include significant distress/impairment, which offers a useful link between clinical and non-clinical psychotic experiences (1).

Consistent with prior population samples (11), younger participants endorsed higher levels of sub-psychotic positive symptoms. A minority of youths (2.3%) reported experiencing only negative/disorganized symptoms without positive symptoms, an important finding since prior work suggests that negative/disorganized symptoms in combination with positive symptoms predict poor functioning and help-seeking behavior (3).

Gender differences in psychotic-like experiences have varied in population studies (34). In our sample, being male was significantly predictive of psychosis spectrum, possibly reflecting earlier onset of clinically significant psychotic symptoms in males. Even when controlling for parental education and reading level, the psychosis spectrum group was disproportionately non-European American, and ethnicity was a significant predictor of spectrum status, consistent with prior studies of ethnic minorities (12). However, ethnicity may be confounded with urbanicity, a possibility we can pursue with ethnographic indicators.

Importantly, although caregivers of psychosis spectrum youths reported higher levels of sub-psychotic symptoms than caregivers of non-spectrum youths, they substantially under-reported symptoms compared to their children. Possibly, caregivers can better gauge "normality" and therefore are more accurate or appropriately conservative in their reports. However, several studies suggest that adolescents tend not to confide psychotic-like experiences to their caregivers or clinicians (10,35,36).

Among a comprehensive array of psychopathology domains, the odds of significant symptoms of depression, mania, anxiety (specific and social phobia, agoraphobia, obsessive-compulsive, post-traumatic stress), and behavioral (attention deficit/hyperactivity, oppositional defiant) disturbance were higher in youths with psychosis spectrum. Substance use, including cannabis, has been associated with risk for psychosis (37). In our cohort, only tobacco and over-the-counter medication were predictors of psychosis spectrum membership. The lack of significant effect for other substances may be due to the high rates of "ever use" of those substances in both psychosis spectrum and non-spectrum youths in this U.S. cohort. Alternatively, although the "ever use" criterion is highly heritable and developmentally informative (25), it may not be as sensitive to specific impairing or prolonged patterns of use associated with psychosis risk.

Global functioning was reduced in psychosis spectrum youths, and highly predictive of psychosis spectrum status.

Similarly, suicidal ideation was higher, and reported by more than 20% of youths with psychosis spectrum symptoms. Quite concerning is that, despite these distress indicators, help seeking was not predictive of spectrum status, and psychosis spectrum caregivers appear unaware of the symptoms.

The psychosis spectrum state, which is predicted by distressing comorbid psychopathology, substance use, morbid thoughts of death and dying, and functional impairment, will ultimately remit, stabilize, or resolve into a disorder (or disorders) (5). Our results underscore the public health relevance of psychosis spectrum features in a U.S. youth cohort and the potential to intervene at an early stage. By showing associated features, including decreased neurocognitive accuracy, similar to those observed in schizophrenia patients, they also support the concept of a psychosis continuum.

Although we have not yet examined the predictive validity of our psychosis spectrum assessment approach, prior work has shown high sensitivity and specificity of the PRIME screen in young adult clinical (27) and non-clinical (college student) samples (26). Internal consistency of our PRIME Screen-Revised was high as in prior reports (26,38), and our rate of screen positives based on traditional (extreme agreement) criteria (14.6%) is similar to a study of older adolescents (18.4%) (38). The structured administration of selected items from the SOPS by multiple interviewers to accommodate the high participant volume, and the use of only six scale items to screen negative and disorganized symptoms, may have reduced sensitivity to clinically significant symptoms or yielded a high level of false positives in these domains (1). Additionally, the rationally derived psychosis spectrum criteria based on extreme agreement or age deviant responding are only a first step in deriving cut-points for this assessment. A just completed comprehensive diagnostic 18-month follow-up study of 300 psychosis spectrum and 200 typically developing participants indicates acceptable sensitivity and specificity of subsequent clinical high risk status assessed via comprehensive evaluation.

Ongoing follow-up will assist in evaluating the predictive validity of the psychosis spectrum screen and contribute to the limited available information about the use of at-risk criteria in children and adolescents (8). Moreover, as noted by others (1,15,33), incorporating mood, anxiety and other psychopathology dimensions will allow a fuller evaluation of the developmental and predictive significance of observed comorbidity.

Finally, while our results indicate that psychosis spectrum characteristics are common in young people in the U.S., and predicted by comorbid psychopathology, substance use, suicidal ideation and poor global functioning, our evaluation of predictors was limited to demographic and clinical variables. Although the fit of resulting models was adequate, other variables are likely to improve prediction of spectrum status.

The Philadelphia Neurodevelopmental Cohort is a public domain resource for the scientific community that will allow investigation of a wealth of other potential predictors, including phenomenology, brain structure and function, and genomics.

Acknowledgements

The authors thank the participants of this study, and all the members of the recruitment, assessment, and data teams whose individual contributions collectively made this work possible. The study was supported by RC2 grants from the National Institute of Mental Health: MH089983 and MH089924 (Gur and Hakonarson) and K08MH079364 (Calkins).

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DOI 10.1002/wps.20152

Definition, assessment and rate of psychotherapy side effects

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Psychotherapy is often seen as a first line treatment, because patients and therapists consider this mode of treatment harmless in comparison, for instance, to drug treatment. This assumption is supported by the fact that there are only limited scientific reports on psychotherapy side effects (1,2). There is, however, some evidence which suggests that psychotherapy can have frequent or serious negative consequences, like all effective treatments (3-5).

There are several reasons why awareness of psychotherapy side effects is limited and research on this issue is insufficient. First, the psychotherapist is the "producer" of treatment and therefore responsible, if not liable, for all negative effects, which results in a perceptional bias towards positive rather than negative effects (6). Second, psychotherapy does not only focus on symptoms but also on social behavior, so that the spectrum of possible negative effects is much broader than in pharmacotherapy (7). Third, there is even no consensus on what to call negative: for instance, when evaluating a manuscript on psychotherapy side effects, a reviewer wrote: "a divorce can be both positive and negative, and crying in therapy can reflect a painful experience but can also be a positive and therapeutic event". Fourth, there is a lack of differentiation between side effects and therapy failure or deterioration of illness (8). Fifth, there are no generally accepted instruments for the assessment of psychotherapy side effects and no rules on how to plan scientific studies or monitor side effects in randomized controlled clinical trials (2).

DEFINITION AND ASSESSMENT OF SIDE EFFECTS

There are indeed some instruments for the assessment of negative psychotherapy effects, although they are not widely used. They include the Vanderbilt Negative Indicator Scale (9), the Inventory of Negative Effects (10), the Unwanted Events and Adverse Treatment Reaction Checklist for Psychotherapy (11,12) and the Experience of Therapy Questionnaire (13). Learning from the assessment of side effects in pharmacotherapy, a distinction must be made between side effects, unwanted events, adverse treatment reactions, treatment failure, malpractice effects, side effect profile, and contraindications.

The assessment of side effects must start with the recording of "unwanted events". These are events which occur parallel to or in the context of treatment and which are burdensome to the patient and/or his environment, independent of whether they are unavoidable or even necessary to reach a treatment goal. Scares in surgery or crying in psychotherapy may be unavoidable or even necessary, but if there is a new treatment without this burden to the patient, the old procedure may no longer be ethically appropriate. The UE-ATR checklist (11) provides a list of areas where to look for unwanted events (Table 1).

"Adverse treatment reactions" are all unwanted events which are caused by the treatment. This requires the ascertainment of a causal relation between the unwanted events and the ongoing treatment. In many cases it will not be possible to make a final decision about the cause of an unwanted event. Therefore, a probability rating should be made: e.g., unrelated, probably unrelated, possibly related, probably related, definitely related to the treatment.

Side effects are adverse reactions which are caused by a correct treatment, while malpractice effects are the consequence of an inappropriate treatment. Therefore, a decision must be made on the quality of treatment. Good treatment causes side effects, bad treatment malpractice effects, a distinction which is a prerequisite for the decriminalization of side effects.

Side effects which occur routinely when applying a special type of treatment constitute the "side effect profile" of that treatment. These regularly occurring side effects must be taken into account in planning the therapy, and patients should be informed about the side effect profile before starting treatment. "Contraindications" are serious side effects which must be expected in special types of patients and which render not applicable that type of treatment in those patients.

Finally, the clinical impact of side effects must be assessed. Based on intensity, duration and patient's impairment, a rating of severity is needed. For instance: mild, without consequences; moderate, distressing; severe, in need of countermeasures; very severe, lasting negative consequences; extremely severe, hospitalization required; or life threatening. A suicide would be "extremely severe"; a lay off at work "very severe"; an increase in anxiety "severe"; discussions with one's spouse "moderate"; crying in therapy "mild".

EMPIRICAL DATA ON PSYCHOTHERAPY SIDE EFFECTS

At present, it is not possible to report precise data on the rate and type of side effects of different forms of

Table 1 Areas where to look for unwanted events in psychotherapy (see 11,12)

Emergence of new symptoms
Deterioration of existing symptoms
Lack of improvement or deterioration of illness
Prolongation of treatment
Patient's non-compliance
Strains in the patient-therapist relationship
Very good patient-therapist relationship, therapy dependency
Strains or changes in family relations
Strains or changes in work relations
Any change in the life circumstances of the patient
Stigmatization

psychotherapy. Only very few papers were found when searching in PsycINFO and PubMed, from 1954 until now, for journal articles which have in their title the key word "psychotherapy" in combination with "side effects" (PsycInfo: 12, PubMed: 9), "negative effects" (PsycInfo: 9, PubMed: 4), or "adverse events" (PsycInfo: 2, PubMed: 3). A thorough screening of randomized controlled trials of psychological interventions for mental and behavioral disorders (2) found 132 eligible trials. Only 21% indicated that some type of monitoring of harms had been done, and only 3% provided a description of adverse events as well as the methods used for collection.

An example is the study by Scheeringa et al (14) on trauma-focused cognitive behavior therapy (CBT) for post-traumatic stress disorder (PTSD) in 3 to 6 year old children. They used the Adverse Events Checklist, an 8-item yes/no checklist covering suicidality, homicidality, serious disability, hallucinations, worsening of any previous symptom, appearance of any new symptom, and exposure to new domestic violence, plus an "other" category. Four possible adverse events were reported in 40 patients in the intervention group, while no information was provided for the waiting list control group. Negative events were the worsening of a pre-existing fear of the dark, and the development of enuresis or encopresis. No clear relation to treatment could be established by interviewing children's mothers.

Another example is the study by Piacentini et al (15) on behavior therapy for children with Tourette's syndrome. They compared 61 patients receiving the intervention to 65 children in a supportive therapy group. Adverse events were monitored at each therapy session. Therapists asked about recent health complaints, behavioral changes, visits for medical/mental health care, need for concomitant medications, change in ongoing medications, and hospitalizations. They also offered the opportunity for spontaneous report of any other problem. Affirmative responses prompted further inquiry concerning the onset, severity and outcome of the adverse event and measures taken to address it. Two hundred adverse events were reported during 10 weeks. Of these, 193 were rated as mild or moderate and 7 as severe (broken bones, n=3; concussion, n=1; neck pain, n=1; neck injury, n=1; nausea and vomiting, n=1). None of the severe events was considered treatment related.

In a randomized controlled trial of treatment for PTSD related to childhood abuse (16), skills training in affect and interpersonal regulation (STAIR) plus exposure (N=33) was compared with STAIR plus supportive treatment (N=38) and supportive plus exposure treatment (N=33). Under the heading "adverse effects", it was reported that the percent of participants who dropped out or experienced a worsening of symptoms was significantly higher in the support/exposure group.

Rosen et al (17) conducted a randomized clinical trial to determine the effect of a money management-based therapy on substance abuse or dependence. Unexpectedly, patients assigned to the treatment were more likely to be assigned a representative payee or a conservator than control participants during the follow-up period (ten of 47 vs. two of 43). This is an example of the large spectrum of possible unwanted events.

The few controlled studies document the difficulty of assessing psychotherapy side effects. In particular, it is difficult to discriminate between treatment related side effects and other negative events. The data regularly show lower "side effect rates" in the intervention group as compared to the control groups. To our knowledge, there is no study which explicitly discriminates between unwanted events, adverse treatment reactions, malpractice effects, treatment failure and side effects. Furthermore, it has to be considered that there are many types of psychotherapy and that results from one approach cannot be generalized to the field at large.

There are few specific side effects which have gained special attention. In a controlled study by Sijbrandij et al (18), subjects who had underwent a psychological trauma received emotional debriefing or educational debriefing or no debriefing. There was no difference in the general outcome between treatments. However, in subjects with high baseline hyperarousal, there were significantly more PTSD symptoms at 6 weeks than in control participants after emotional debriefing. This result has been confirmed by other studies (19). Another example of a specific side effect is the generation of false memories: it is well known that psychotherapy can lead to the development of subjectively convincing "memories" of something which never happened, for instance sexual abuse (20,21). The frequency of this side effect is unknown, but it must be sufficient to justify the existence of a False Memory Syndrome Foundation in the U.S..

Another way to estimate side effects of psychotherapy are patient and therapist surveys. In a survey with 1504 patients, using a specifically developed questionnaire with 61 items, Leitner et al (22) found significant differences between treatment modes. Patients reported "burdens caused by therapy" in 19.7% of cases when treated with CBT, 20.4% with systemic psychotherapy, 64.8% with

humanistic psychotherapy, and 94.1% with psychodynamic psychotherapy. Examples of burdens are that patients felt overwhelmed in therapy, were afraid of the therapist, or were afraid of stigmatization.

An example of a therapist survey is provided by Löhr and Schmidtke (23). They contacted 418 CBT therapists by mail, 232 of whom filled in a questionnaire. Therapists estimated that on average 8% of patients left their spouse after treatment, which in 94% of cases was regarded as not to be due to the intervention.

In summary, there is an emerging consensus that unwanted events should be expected in about 5 to 20% of psychotherapy patients (3-5,12). They include treatment failure and deterioration of symptoms, emergence of new symptoms, suicidality, occupational problems or stigmatization, changes in the social network or strains in relationships, therapy dependence, or undermining of self-efficacy. Rates may vary depending on patient characteristics (suggestible persons), diagnosis (personality disorders), patient expectations (social benefits), severity of illness (severe depression), therapist characteristics (demanding) or special therapeutic techniques (exposure treatment, self-revelation) (13,21).

CONCLUSIONS

Despite the lack of sound empirical data, one can conclude that psychotherapy is not free of side effects. Negative consequences can concern not only symptoms, like an increase in anxiety, or course of illness, like enduring false memories, but also negative changes in family, occupation or general adjustment in life. Consequences like job loss or divorce can be lasting, costly and detrimental for the patient and his/her environment.

As therapists and scientists alike are to some degree salesmen of "their" treatment, they are as trustworthy as pharmaceutical companies. They have good intentions and conflicts of interest as well. Like in pharmacotherapy, structures are needed to safeguard good clinical practice.

As side effects must be discriminated from malpractice, protocol adherence and quality control in psychotherapy is of utmost importance. Psychotherapists who implement idiosyncratic therapies will have to deal with a reversal of burden of proof when it comes to adverse treatment reactions.

As psychotherapy side effects are multifold and sometimes difficult to detect, good, practical and generally accepted assessment instruments are needed. Therapists should be trained in the recognition, evaluation and documentation of side effects, and learn how to plan treatment taking possible negative consequences into account.

It should be mandatory for all controlled clinical trials in psychotherapy research to thoroughly look for unwanted events and side effects. More reliable data are needed in order to allow an estimate of the true risks of psychotherapy.

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DOI 10.1002/wps.20153

Cultural inroads in DSM-5

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A lot has been said and written about the relevance of well-conceived cultural concepts in the diagnostic assessment of all kinds of patients, in nosological elaborations and in treatment interventions, particularly with psychiatric patients (1). The resulting gains in prevention and public health impact and enhancement of quality of life indicators have also been broadly discussed. These perspectives have been strengthened in the last two or three decades, notwithstanding the notable progress of neurosciences and basic laboratory research (2). Yet, in terms of concrete accomplishments, all these accurate definitions, powerful and passionate advocacy efforts, and scholarly cogent arguments have moved clinical practice only slightly above the level of byzantine exchanges.

In the diagnostic field, facts such as globalization and diversity, buttressed by massive internal and external migrations across the world, and technological advances reachable by the masses in all countries and continents, have made the need for a comprehensive cultural understanding of patients' lives, their symptoms, family history, beliefs and existential suffering, an almost mandatory requirement. Furthermore, realities such as poverty, inequities, racism, political restlessness, collective stress and disasters shape up clinical pictures, help-seeking modalities and the subsequent provider-patient relationship frames with an unmistakable cultural stamp (3).

That is probably why the American Psychiatric Association, the representative psychiatric organization of the United States, the world's most diverse country, initiated in the late 1960s the work of renewing the Diagnostic and Statistical Manual of Mental Disorders (DSM), hinting first at the need of including cultural items in its third version, and giving them a slightly wider, yet still unfairly insufficient, room in DSM-IV and in its revised text, DSM-IV-TR (4).

WHAT WAS CULTURAL IN DSM-IV?

The spokespeople of these DSM versions attempted to present them as innovative documents that included an outline for a cultural formulation (OCF) and a glossary of 25 "culture-bound syndromes" (CBS), formally admitted for the first time in a classification system. Without denying these features, what was not publicized, perhaps for being too obvious, was the fact that the additions were relegated to Appendix I of DSM-IV, the next-to-last in the thick volume, and that this was just a minimal portion of a substantial piece of scholarship and a set of significant suggestions made, after at least two years of deliberations, by a consulting group of distinguished psychiatrists, ironically appointed by the DSM Task Force leadership itself.

These circumstances, however, explain only in part the limited utilization of and meager research conducted on the DSM-IV cultural components. Very few academic or training centers, mainly in Canada, the U.S. and Europe, faced up to the tasks of exploring the feasibility, usefulness and practical applicability of the OCF or the nosological validity of the CBS (5,6). Soon, criticisms about the ontological and practical unfitness of ethnographic approaches (the five narrative areas of the OCF) in the fluid, time-limited course of diagnostic interviews in different clinical settings, started to appear. The actual impossibility to quantify the information, the limited manualization, the obsolescent definitions of CBS presented in a categorical frame, and the still unclear connections between the clinical data and specific aspects of the pharmacological or psychotherapeutic management of many patients were cited as additional limitations (7).

CULTURAL INROADS IN DSM-5

Strengthening the structure and broadening the scope of a document like DSM and, more specifically, making cultural inroads in a *medical* diagnostic instrument whose main purpose is to provide convincing solidity to a decisive clinical step, requires tenacity and patience, among other ingredients. From the beginning, the DSM-5 Committee made explicit pronouncements about the value of culture in diagnosis, with cross-cultural variations in disorder expression as a point of departure. Yet, it was clear that the mission of the Gender and Cultural Issues Study Group, appointed around 2007-2008, was enormously complex, and that the interests of several of its members differed, at times significantly. The idea that culture implied only race and ethnicity (gender was perhaps a related but still independent concept, judging from the name of the Study Group) seemed to predominate and so, the initial discussions focused mostly on epidemiological aspects of just those topics. It was after about two years of deliberations (early 2010) that a Cultural Issues Work Subgroup was created and charged (with the full support of the DSM-5 Committee leadership) to focus on a more genuine and thorough set of cultural diagnostic features.

The guiding mentality of the Work Subgroup was unequivocal: to ensure a recognizable presence of cultural components in the manual, materialized not only in cogent declarations, "statements of principle" or colorful descriptions but,

most importantly, in norms, guidelines, demonstrations and instruments to be used, actively and effectively, in clinical practice. The work took shape gradually, as the size of the subgroup grew from half a dozen to about twenty members with the addition of a number of international advisors. Available research was examined through a close reassessment of the DSM-IV-TR's contents, literature reviews, assessment of existing data banks and sharing of clinical information about the use of OCF (8).

The input of organizations such as the Society for the Study of Psychiatry and Culture, the Group for the Advancement of Psychiatry, the World Association of Cultural Psychiatry, and the Latin American Group of Transcultural Studies provided a valuable influx of diversity. Phone conversations, periodic conference calls, electronic exchanges, face-to-face meetings in professional and scientific events, and an endless traffic of text drafts and reviews were frequently used communication lines.

These deliberations gradually centered around three areas that, in the end, became the pillars of the cultural composition of the new manual (9), in addition to brief suggestions of cultural aspects for each group of disorders: an introductory text outlining the cultural aspects of DSM-5, the elaboration of what were called "cultural concepts of distress", and the preparation, structuring and field trial testing of the Cultural Formulation Interview (CFI) (6-9).

Introductory text

Definitions of *culture* as a social matrix of the whole human experience and a factor of neurobiological development, *race* as a tenuous but pervasive catalogue of identity including physical and physiognomic characteristics that nourish at times ideologically biased interpretations, and *ethnicity*, based on belonging to a society, people or community with common historical, geographic, linguistic or religious roots, precede comments on how culture influences the diagnostic process. However, details of the main cultural variables and of the weight of culture in a general definition of mental disorders are missing here and in other sections of the manual. Similarly, mentions of culture as a pathogenic/pathoplastic element, a supportive/therapeutic agent, a help-seeking/compliance determinant or, ultimately, a prognostic factor were not included (10).

Cultural concepts of distress

As a result of the re-examination of the DSM-IV's glossary of culture-bound syndromes, three more precise and useful concepts have been included. The "boundedness" feature was drastically challenged as its implication of uniqueness has been weakened by migrations and the subsequent broadening of geo-demographic areas. Concepts of illness previously considered "indigenous" have been incorporated in contemporary descriptions (and vice versa). Instead, distress becomes the common conceptual umbrella for three distinctive items: a) *cultural syndromes*: these are entities that cluster co-occurring symptoms, may or may not be recognized as an illness within the culture, but occur, are relevant in the societies of origin and may be noticed by an outside observer; DSM-5 includes only nine of these conditions, adequately supported by research; b) *cultural idioms of distress*: a relatively new name for an old concept (11), these are linguistic terms, phrases or even colloquial ways of talking about suffering, shared by people from the same culture; they are considered neither mental/emotional illnesses nor diagnostic or nosological categories; while their listing is useful – and includes crying styles, body postures, somatic manifestations, etc. – there is agreement on the need to approach them in a more systematic, empirical way; c) *causal explanations*: a needed remnant of Kleinman's rich "explanatory models" concept (12), these convey deeply ingrained views and beliefs about what the patient and his/her family consider the etiology of the reported symptoms, illness or distress; they can be part of folk classifications of disease used by laypeople or healers but, beyond their formal presentation, they may also entail an anticipation of the patient's trust, faith, hopes and expectations.

Cultural Formulation Interview (CFI)

Considered the most refined product of the Subgroup's work, the CFI is both a revised version of DSM-IV's OCF (with specific changes in the five sections of the latter), and a set of semi-structured questionnaires. In its primary format, it has a total of 16 questions that operationalize cultural definitions of the clinical problem, perceptions of cause, context and support, and treatment factors (including self-coping and help-seeking patterns). Each section and most of the questions have additional probes to clarify or deepen the initial responses. The clinical usefulness of the CFI can be expected in any cross-cultural encounter which is, ultimately, what every diagnostic interview entails.

The CFI was used in field trials conducted in seven centers in North America and five in three other continents. The trials included feedback from patients and clinicians about the instrument, through debriefing meetings conducted by the research team. The tool's feasibility, acceptability and utility measures were quite satisfactory (13). In the end, the Work Subgroup created a total of 12 supplemental modules focused on different areas (levels of functioning, social networks, psychosocial stressors, religion and spirituality, etc.) and population subgroups (such as immigrants, refugees, children and adolescents, the elderly, caregivers, etc.), to be used whenever the clinician or the evaluating center felt the need to gather additional data.

The main recommendation is to conduct the CFI at the beginning of any diagnostic evaluation. In the interview's form, the interviewer is given specific instructions as to

areas to explore and questions to ask. A smooth transition to the rest of the interview is suggested, keeping in mind the depth, detail and duration required by the individual case. The use of a "telescoping" modality, based on the observed interview flow (i.e., overall emphasis on cultural issues vs. particular attention to aspects or details of the inquiry) is also encouraged.

DISCUSSION

Agreeing on the importance of culture and cultural factors in psychiatric diagnosis is not guarantee of its full acceptance or consistent consideration in clinical practice. The multifaceted impact of these factors on availability, accessibility and acceptability of mental health and general medical services still leaves out issues of affordability and accountability (14). Neglecting them may lead to non-contextual, therefore irrelevant, clinical information, diagnostic biases and errors, therapeutic disengagement, insufficient coping strategies or uncertain outcomes. Medical educators also must adopt a basic cultural approach if they want to form professionals comprehensively equipped to deal with psychiatric patients in the contemporary world (15). To take for granted cultural sources is a form of condescension; broadening the inroads made so far can only be successfully accomplished through an adequate instrumentalization of the diagnostic process, the first step in the clinical evaluation of every patient.

There are reasons to assume that the cultural innovations in DSM-5, even though placed for the most part in Section III of the manual, reflect a degree of acceptance and commitment. This does not mean that the product is problem-free. Specific mentions of individual strengths and weaknesses, and of risk and protective factors are missing, in spite of the strong cultural load of such features. Moreover, a variety of obstacles or difficulties in their implementation emerge. The disposition of many clinicians to adopt the philosophy and the pragmatics of the CFI, for instance, remains to be seen. Didactic training and familiarity with the new cultural concepts of distress and their use and application in real life cases imply drastic curricular changes. Proof of the applicability of the new instrument in international, indeed global settings is a tall, yet indispensable order. The issue of time and duration of the transactions on cultural areas during the interview cannot be overlooked, more so if the supplemental modules are considered. Last but not least, the pervasive notion that this is still a USA-inspired (or imposed?) demand requires honest discussions by the many sides involved – the whole world and its medical, psychiatric and public health agencies.

Clearly, extensive research addressing all these topics will be needed. Locally perceived connections between cultural categories may help identify missing patterns of comorbidity and underlying biological substrates of psychopathology. Active search of concomitances with existing entities (of Western facture) needs to continue: depressive and anxious entities, as well as somatization disorders, may yet well lodge some of the remaining cultural syndromes (7,8,13,14). The use of interpreters to address crucial language and communication issues, particularly among immigrant, refugee and young age patients, must also be seriously addressed (16).

Answers to these questions lie in the future. However, it is important to remember that, whether we like it or not, the future is here, now, in this era of Orwellian features. Funding research (preferably multisite), the highest hand in this process, is a clear responsibility of those in positions of power. In the case of the CFI alone, its use in different clinical settings (inpatient, outpatient, consultation/liaison, community and rural services, age-based centers, the newest integrated or behavioral medicine units, etc.) must be tested. And to compare the cultural outreach of DSM-5 with ICD-10's or 11's, as well as to evaluate whether neuroscience-based diagnostic approaches such as the Research Domain Criteria (RDoC) of the U.S.. National Institute of Mental Health (17) could be compatible with a culturally-based clinical thinking, are tasks too crucial for us to afford ignoring them.

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DOI 10.1002/wps.20132

DSM-5 cross-cutting symptom measures: a step towards the future of psychiatric care?

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The notion that psychiatric disorders occur along dimensional continua rather than as categorical entities has long been debated. Research and clinical evidence have illustrated that a categorical diagnostic schema does not accurately reflect the full realms of clinical concerns in many patients, such as the presence of subthreshold anxiety or psychotic symptoms in individuals with major depressive disorder that cause or exacerbate impairment and distress (1,2). In some instances, clinicians are forced to diagnose two or three separate disorders, typically using the "not otherwise specified" label, in order to facilitate treatment for their patients (3).

In the absence of a fully dimensional diagnostic schema, the integration of dimensional assessments of psychiatric symptomatology may be clinically useful in providing valuable information for our current understanding of mental disorders and the issue of co-occurring symptoms and conditions (1). In addition, the integration of categorical diagnoses and dimensional assessments of psychiatric symptoms may also facilitate the identification and fine-tuning of psychiatric endophenotypes, as emphasized in the Research Domain Criteria, for the various mental disorders (4).

The DSM-5 Task Force and Work Groups developed and proposed the incorporation of dimensional measures – i.e., self-(i.e., adult and child/adolescent) and informant-report (i.e., parent/guardian) versions of the DSM-5 Cross-Cutting (CC) Symptom measures – to help address the issue of co-occurring symptoms across mental disorders (5-8). This paper discusses the benefits of the DSM-5 CC Symptom measures and identifies areas for further research and development.

BRIEF BACKGROUND OF THE DSM-5 CROSS-CUTTING SYMPTOM MEASURES

The self- and informant-reported versions of the DSM-5 CC Symptom measures were developed by the DSM-5 Task Force and Work Groups to serve as a "review of mental systems" in each patient who presents for mental health evaluation and treatment. The measures assess the presence and severity of 12-13 psychiatric symptom domains that cut across diagnostic boundaries (7,8). These include depression, anger, mania, anxiety, somatic symptoms, sleep disturbance, psychosis, obsessive thoughts and behaviors, suicidal thoughts and behaviors, substance use (e.g., alcohol, nicotine, prescription medication, and illicit substance use), personality functioning, dissociation, and cognition/memory problems in adults. Many of the same domains, except for personality functioning, dissociation, and cognition/memory problems, are also assessed in children/adolescents, along with inattention and irritability. The co-occurrence and severity of these symptoms have been shown to significantly affect the prognosis and treatment of many mental disorders (1,2,9-11).

The items on the DSM-5 CC Symptom measures do not relate to any specific disorder and as such are not intended to be diagnostic or to serve as screening measures for any disorder (8). Instead, the measures were developed to be used as adjunct tools "to give clinicians quantitative ratings that characterize patients in a way that is simple, useful, and clinically meaningful" (8). It is hoped that the information from these measures will inform clinical decision-making and treatment. For instance, the ability to characterize patients has the potential to lead to customizable treatment plans and improvement in treatment outcomes. However, future studies are needed to explore if and how these measures inform clinical decision-making.

The DSM-5 CC Symptom measures are operationalized at two levels. Level 1 consists of a 23-item (adults) or a 25-item (children/adolescents) measure of the presence and severity of symptoms over the past two weeks (7,8,12). The items, with the exception of suicide ideation, suicide attempts, and substance use in children/adolescents, are rated on a 5-point scale (i.e., 0=none/never; 1=slight/rare; 2=mild/several days; 3=moderate/more than half the days; and 4=severe/almost daily), with higher scores indicating greater frequency of occurrence or greater degree of severity. The suicide ideation, suicide attempts, and substance use items on the child/adolescent version of the scale are scored on a yes/no basis.

Items scored as 2 or greater (i.e., mild/several days) or with a "yes" trigger the completion of a more detailed assessment of that symptom domain using the associated self- or informant-reported DSM-5 Level 2 CC Symptom measure. Level 2 CC measures inquire about the presence and severity of symptoms within pure psychiatric domains during the past seven days (e.g., the Altman Mania Scale for a more detailed assessment of mania, given the respondent endorsed the Level 1 mania item at a score of 2 or greater).

The intent is for all patients, regardless of DSM diagnoses, to complete the DSM-5 Level 1 and 2 CC Symptom measures routinely either at each clinic visit or at clinically-indicated intervals but prior to meeting with their clinicians. This would enable clinicians to track the presence, frequency of occurrence, and severity of overall psychiatric symptomatology in their patients over time across diagnoses,

even in those areas not directly related to the patient's primary diagnosis. This will also allow for the identification of heterogeneity within diagnoses, which is important for future research and understanding of mental disorders.

The measures were field tested in the DSM-5 field trials and demonstrated mostly good-to-excellent test-retest reliabilities (7) and strong clinical utility from patient and clinician perspectives (12,13).

DSM-5 CROSS-CUTTING ASSESSMENT: ADVANTAGES AND POTENTIAL AREAS FOR GROWTH

A number of benefits to these cross-cutting measures should be recognized. The measures are easy to administer, score, and interpret, especially in the electronic form. Even in their pencil-and-paper form, detailed instructions for scoring, scoring summary sheets, and interpretation of scores are provided to facilitate their use (5,6). They were easily incorporated in busy clinical settings in academic centers and the community and solo and small group practices in the DSM-5 field trials and pilot studies (12-14), which provides some support for their use in routine clinical care. The measures are freely available for download and use from DSM-5 Online Assessment Measures (5).

The measures are, for the most part, self-report and self-administered, which facilitates patient engagement in their own assessment and care. Similarly, there are informant versions of the measures that allow parents and guardians to become actively involved in their children's care and provide a way to open lines of communication with clinicians. As such, the incorporation of these measures into Section III of DSM-5 indicates the move towards a more patient-centered rather than a top-down approach to the assessment and care of vulnerable populations. This is important, and timely, given that patient-reported outcomes speak directly to the U.S. Patient Protection and Affordable Care Act's recent mandate that clinicians engage in patient-centered, measurement-based quality care (15).

Although the use of dimensional measurement in psychiatric treatment is not new and has been found to be clinically useful (16,17), it is still not standard clinical practice. However, as psychiatry moves towards a more measurement-based model of care, the availability and use of these measures can provide a standardized way for clinicians to assess and quantify patients' symptom profiles over time. This is particularly true if the measures are completed at regular intervals, as clinically indicated and recommended by DSM-5 (5,6).

The multi-domain nature of the Level 1 and 2 CC Symptom measures is a major strength. Use of the measures, as proposed by the DSM-5 Task Force and Work Groups, has the potential to allow clinicians and researchers to gain better understanding of how different combinations of these cross-cutting symptoms at varying levels of severity may present across diverse diagnoses, and their potential impact on patient outcomes. Lastly, and very importantly, the DSM-5 CC Symptom measures could also provide the field with a standardized way to communicate about comorbidity, remission, and recovery and lead to more customized treatments to match different symptom profiles over time.

The DSM measures have valuable potential to shift the way psychiatric care is conducted in the U.S., but they also offer an opportunity to consider what further research is needed to maximize their potential. During the DSM-5 pilot studies and field trials debriefing sessions, clinicians pointed out that in busy clinical settings, especially with new patients with limited documentation of symptoms and illness history, the possibility existed that the DSM-5 CC Symptom measures would be used as screeners for specific disorders, a use for which they were not intended or tested (12,14). This observation emphasizes the need for focused clinician education on the proper use and interpretation of the measures.

Many of the Level 1 CC Symptom measure items were derived from existing patient-reported measures (7,8,12) with sound psychometric properties. For example, the two Level 1 items for depression were taken from the 2-item Patient Health Questionnaire – a validated screening measure for depression (18). The derivation of some items from psychometrically-sound existing scales does not automatically translate into a psychometrically-sound DSM-5 Level 1 CC Symptom measure. Although the DSM-5 field trials provided promising evidence of the test-retest reliability of the items and some evidence of convergent validity, further studies of the psychometric properties of the measure are warranted. This need is heightened for items that were newly developed by the respective DSM-5 Work Groups (e.g., the two personality functioning items and the dissociation item). That they demonstrated good test-retest reliabilities (7) is a first and important step in this process.

Level 2 measures are available for some but not all Level 1 domains. DSM-5 developers wanted to ensure that all Level 2 measures were accessible to clinicians and researchers without cost. The lack of suitable freely available assessments explains why some Level 2 measures were omitted (e.g., dissociation and cognition/memory problems for adults). DSM-5 developers included Level 2 items only after careful consideration and discussion, but it may be useful in the future to contemplate whether development and inclusion of Level 2 measures for *all* domains could be beneficial.

Psychosis and suicidal ideation and behaviors are two domains on the adult Level 1 CC Symptom measure without self-report Level 2 measures, although they do have clinician-completed Level 2 measures (8). For psychosis, the clinician-completed measure might be warranted when impaired insight – a common symptom in psychosis – is present (19). Impaired insight can significantly impact the self-reporting of psychiatric symptoms, compliance with treatment, and prognosis in psychosis and across all mental disorders. As such, the inclusion of a Level 1 insight domain with associated Level 2 measures to the battery of DSM-5 CC Symptom measures may be beneficial in the future.

Information on the clinical utility of the DSM-5 CC measures was derived primarily from the use of electronic

versions of the measures, including electronic completion, scoring, and transmission of results (14). In the DSM-5 pilot study, only a partial electronic version was used (i.e., completion only), yet patients and clinicians still found the measures clinically useful (12). The feasibility and clinical utility of the pencil-and-paper versions still need to be demonstrated, though the positive findings on their electronic counterparts bode well.

Psychometrically sound and valid paper-and-pencil versions of these measures are important for places in the U.S. and around the world that do not have ready access to electronic technology. However, an electronic platform will facilitate the speed and convenience of administration if they are to be adopted for use in future psychiatric care, underscoring the importance of the results from the DSM-5 field trials (7,14).

CONCLUSIONS

In summary, efforts to include a standardized and freely available battery of dimensional measures into DSM-5 represent an important step in moving the field away from a rigid, categorical conceptualization of psychopathology. Further refinements to the DSM-5 CC Symptom measures are warranted, as indicated by field trial testing (7,13,14), but the existing battery dovetails nicely with ongoing efforts supported by the National Institute of Mental Health's Research Domain Criteria project to better integrate basic science and neurobiology – including the use of dimensional assessments of observable and neurological symptoms – into the psychiatric nosology (4). Dimensional assessments also may provide a way to reduce diagnostic complexity and comorbidities by giving clinicians a better way to capture gradients within a disorder – such as co-occurring symptoms – rather than forcing them into categorical decision-making.

These dimensional assessments map on nicely with the mandates of the US Patient Protection and Affordable Care Act (15) and may offer a glimpse into what the future of psychiatric care will look like. As refinements on these measures continue, the goal is to move the field closer to a more accurate and fully informed understanding of mental disorders and the experiences of the individuals who live with them.

Acknowledgements

The authors would like to acknowledge Drs. Farifteh F. Duffy (Director, Quality of Care Research, American Psychiatric Association), William E. Narrow (Interim Director, Division of Research, American Psychiatric Association), Holly C. Wilcox (Associate Professor, Department of Child and Adolescent Psychiatry, Johns Hopkins Medical Institute), and Helena C. Kraemer (Professor Emerita, Stanford University School of Medicine) for their critical review of earlier drafts of the manuscript. Also, they would like to acknowledge the research and editing support provided by Ms. Keila Barber, MHS in the preparation of this manuscript.

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DOI 10.1002/wps.20154

Uncomplicated depression is normal sadness, not depressive disorder: further evidence from the NESARC

We write to update the results of our recent paper (1) suggesting that uncomplicated depressive episodes are not in fact disorders and should be excluded from the diagnosis of major depressive disorder (MDD). We also address some concerns expressed about our claims.

The concept of "uncomplicated depression" is essentially a generalization to all stressors of the "bereavement exclusion" that appeared in DSM-IV (and was eliminated in DSM-5). Uncomplicated depression is defined as a response to a stressor that satisfies current DSM-5 five-symptoms-for-two-weeks criteria for MDD but is better explainable as a normal distress response, as evidenced by the fact that it lasts no longer than six months and does not include any of the following pathosuggestive symptoms: marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, and psychomotor retardation. Uncomplicated episodes thus contain only depressive symptoms common in general distress reactions (e.g., sadness, moderate withdrawal or role impairment, decreased interest in usual activities, insomnia, decreased appetite, difficulty concentrating, fatigue).

THE INITIAL STUDY AND ITS REPLICATION

In our recent paper (1), using longitudinal data from the Epidemiological Catchment Area (ECA) study (2), we found that in those with lifetime uncomplicated MDD at baseline, the one-year recurrence rate (3.4%) was not significantly different from the background MDD incidence rate in those who never previously had MDD (1.7%), but both were dramatically lower than recurrence rates in other ("complicated") MDD (14.6%). Thus, in terms of recurrence risk, uncomplicated MDD is different from other MDD but indistinguishable from no-MDD-history. We concluded that "consideration should be given to eliminating uncomplicated episodes as a class from MDD diagnosis".

However, that study had several limitations. We (3) therefore replicated and broadened the analysis using an entirely different, more recently collected longitudinal community data set – the National Epidemiological Survey on Alcohol and Related Conditions (NESARC, 4) – that allowed a more clinically meaningful 3-year follow-up window and use of an expanded set of three clinically important validators (depression recurrence, suicide attempt, generalized anxiety disorder (GAD)), as well as other advantages in measuring impairment and clinical significance. Due to data-set limitations, only single-episode uncomplicated cases could be evaluated in this study.

The results were that people with single-episode uncomplicated major depression had rates during follow-up of MDD recurrence (6.9%), GAD (4.3%), and suicide attempt (0.1%) that were not significantly different from background rates for those who never had MDD (6.1%, 2.7%, and 0.3%, respectively), but were dramatically and significantly lower than rates for both single-episode complicated cases (19.5%, 7.8%, and 0.8%, respectively) and multiple-episode cases (27.1%, 11.2%, and 1.7%, respectively) (3). The results were not explainable by group differences in severity or treatment rates. Given the replication's success, we concluded that uncomplicated MDD is a benign condition that is typologically distinct from the rest of MDD, thus supporting our earlier thesis that uncomplicated MDD is in fact a form of normal sadness.

However, in a commentary on the replication, Maj (5) expressed some concerns about the evidence provided by our study. These previously unaddressed concerns are now considered.

CONCERN 1: QUALITY OF REMISSION WAS NOT EVALUATED

In MDD, the quality of remission, and especially the number of residual depressive symptoms, is important both because subthreshold depression is harmful in itself and such symptoms predict recurrence and may indicate a latent pathology. Yet, Maj notes, our studies did not report the residual symptom levels among those not experiencing MDD during the follow-up. To address this concern, we analyzed the average number of MDD symptom groups experienced during follow-up by individuals in each of our baseline MDD groups who did not have recurrences during the follow-up period.

In each of the four baseline wave 1 lifetime MDD history groups, the mean number of residual symptom groups experienced by those who had no wave 2 recurrences during the 3-year follow-up period was: 0.37 (95% CI: 0.35-0.39) for the no lifetime MDD history group (N=25,514); 0.49 (95% CI: 0.34-0.65) for the lifetime uncomplicated single episode group (N=379); 0.75 (95% CI: 0.65-0.85) for the lifetime complicated single episode group (N=1,756); and 1.00 (95% CI: 0.91-1.10) for the lifetime multiple episodes group (N=1,876).

Thus, there is not a significant difference in the number of symptoms during follow-up between the no-MDD-history group and the uncomplicated single episode MDD group. There is no "residual symptom" problem indicating implicit pathology or risk of recurrence among the uncomplicated group above the non-MDD baseline. In contrast, the complicated single episode and multiple episode groups both experienced significantly higher residual symptom levels than the no-history and uncomplicated single episode groups. In sum, recovery in uncomplicated depression generally returns to population baseline levels of depressive symptoms, which is unlike the recoveries of those with other MDD.

CONCERN 2: THE LENGTH OF THE FOLLOW-UP PERIOD WAS TOO SHORT

Maj (5) also argued that the 3-year follow-up may have been too short to detect recurrences in uncomplicated cases because recurrence after recovery can occur after longer intervals. He noted, for instance, that in the National Institute of Mental Health (NIMH) Collaborative Depression Study, the median time to first recurrence of MDD in people who had fully recovered from their index episode was over 4 years (6).

However, the baseline NESARC data used in our study were lifetime MDD data at interview 1. Thus, the duration of the follow-up was not just three years. In fact, many of the individuals classified with lifetime MDD at wave 1 had not had their last MDD episode for some years prior to the wave 1 interview, so the average time interval since recovery was potentially much greater than three years. Thus, to address Maj's concern, we calculated for each of our MDD groups the average time from the end of the last episode to the wave 1 interview to obtain a more accurate approximation of the time intervals from the last episode to the outcome reported for wave 2.

The mean years of remission prior to wave 1 assessment for each group were: 9.1 (95% CI: 7.9-10.3) for the lifetime uncomplicated single episode group (N=417); 9.1 (95% CI: 8.6-9.6) for the lifetime complicated single episode group (N=2128); and 3.9 (95% CI: 3.6-4.2) for the lifetime multiple episodes group (N=2501).

Thus, the average time from the end of the last episode to the beginning of the wave 2 follow-up period was lengthy, about nine years for both uncomplicated and complicated single-episode cases and about four years for multiple episode cases. This substantial time interval is more than enough for elevated recurrence rates to emerge during the examined 3-year window, and such elevated rates did occur for the single-episode complicated cases but not for the uncomplicated cases at the same 9-year average time since the baseline episode.

CONCLUSIONS

Our recent replication and extension (3) of our earlier results (1) supports the predictive validity of the uncomplicated versus complicated depression distinction across stressors, supplementing a previous study supporting concurrent validity (7). A course with elevated recurrence relative to population baselines is generally considered the single most salient identifying feature of depressive disorder versus normal sadness (8) and a primary rationale for inferring underlying dysfunction (9), yet no such elevation occurs for uncomplicated depression.

The evidence thus supports two conclusions. First, uncomplicated depression is not similar to, and is typologically distinct from, major depressive disorder. Second, given the lack of differences between uncomplicated depression and no history of MDD in crucial negative sequelae including recurrence, suicide attempt, and GAD, uncomplicated depression is best interpreted as an intense normal emotional episode. The additional analyses presented here in response to Maj's (5) concerns regarding quality of recovery and duration of follow-up substantially strengthen the support for these conclusions.

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DOI 10.1002/wps.20155

Public attitudes towards psychiatric medication: a comparison between United States and Germany

Psychiatric medication (PM) is becoming more and more popular, which is reflected in rising prescription rates in most Western countries. However, absolute prescription rates differ between countries (1), and there also seem to be country differences in public attitudes towards PM (2-4). Representative population surveys suggest that PM is particularly popular in the U.S., but it is unclear whether this is a true difference or merely the result of different questionnaire wording or survey methodology.

Knowing whether public attitudes in the U.S. differ from other countries would be of particular interest, because only in the U.S. (and New Zealand) direct to consumer advertising (DTCA) of prescription drugs is legal. DTCA may be associated with more positive views on PM among the general public. The effect of DTCA on consumer attitudes and behavior has been discussed critically (5), but a direct cross-country comparison of public attitudes towards medication is lacking. Here we report the results of a study comparing public attitudes towards PM in the U.S. and Germany, using data from the U.S. General Social Survey (GSS) 2006 and from a population survey conducted in Germany in 2011.

Two population-based random samples in the U.S. (N= 1,437) and in Germany (N=1,223) received identical questions on PM during a fully structured face-to-face interview (see 4,6 for details on sampling and interview methodology). The questions on attitudes towards PM were first used in the GSS (6). For the German survey, items were translated according to World Health Organization guidelines (7). Six statements assessed views on harms and benefits of PM, and four enquired whether the respondent would take doctor-prescribed PM in various situations, ranging from personal trouble to acute depression or anxiety.

Responses were recorded on five-point Likert scales, which we combined into three categories for our analyses: agree or likely, undecided, unlikely or disagree. A fourth category was "don't know". We then calculated multinomial logit regression models for all items, comparing the predicted probability for choosing each category between countries. Analyses controlled for respondents' gender, age, and years of education, holding all control variables at their mean for the combined sample. We computed 95% confidence intervals (CI) for the predicted country difference with the delta method to establish significance. We multiplied probabilities by 100, so they can be read as percentages. We report country differences in agreement, which were all significant ($p<0.05$).

In the U.S., perceptions of potential harm of PM were much lower than in Germany. The statement that PM is harmful to the body was endorsed by 58% of respondents in Germany versus 27% in the U.S. (predicted difference: −31%). In Germany, 72% agreed that taking these medications interferes with daily activities, versus 44% in the U.S. (predicted difference: −28%).

More people in the U.S. expected benefits from PM. The statement "taking these medications helps with day-to-day stresses" was endorsed by 81% in the U.S. versus 75% in Germany (predicted difference: 6%). In the U.S., 75% of respondents expected that PM makes things easier in relations with family and friends, versus 65% in Germany (predicted difference: 9%). Expectation that medication helps people control their symptoms was only slightly higher in the U.S. (84 vs. 80%), and slightly less respondents in the U.S. endorsed that PM helps people feeling better about themselves (65% vs. 71%).

Respondents in the U.S. were considerably more likely to take PM: 63% in the U.S. would take medication for symptoms of anxiety, versus 48% in Germany (predicted difference: 15%); 49% in the U.S. considered themselves likely to take medication for symptoms of depression, versus 26% in Germany (predicted difference: 23%). Similar country differences were also present in situations where taking medication is not indicated: 47% in the U.S. (versus 30% in Germany) would take PM if they didn't know anymore how to cope with the stresses of life; 30% in the U.S. (versus 14% in Germany) would take PM because of trouble in their personal life.

In summary, public attitudes towards PM are considerably more favorable in the U.S. than in Germany. It is to be acknowledged that the surveys in the U.S. (2006) and Germany (2011) were conducted in different years. However, assuming the overall trend towards more positive medication attitudes (6) had continued in the U.S. after 2006, attitudes of the U.S. participants would have been even more positive in 2011.

The U.S. and Germany differ with regard to a number of social, cultural and health care system factors, of which DTCA is only one. Also, it is worth considering that more permissive population attitudes towards medication could also have paved the way towards legalizing DTCA.

Since the FDA issued new guidelines facilitating DTCA of prescription drugs in 1997, many studies have examined potential negative consequences of this development (for a review, see 5). Although increases in antidepressant use have been reported in many countries, it has been shown that exposure to DTCA in television and print media was associated with an additional 3–10% increase in antidepressant consumption rates (8). DTCA may increase AD consumption not only for clinically relevant

depression or anxiety disorder, but also for other, subthreshold conditions where antidepressant medication use may not be indicated and where taking drugs would do more harm than good (5,9). In our study, willingness to take PM was greater in the U.S. than in Germany for all hypothetical situations, regardless of whether it was medically appropriate. Although the greatest difference was observed in depression, twice as many respondents in the U.S. than in Germany were also willing to take medication when dealing with personal trouble.

The largest between-country differences were with regard to perceived harms of PM. A potential reduction of harm awareness as a result of DTCA would be of particular concern. The two psychiatric drugs that were advertised most between 2007 and 2011 already have black box warnings for serious side effects (duloxetine: suicidality in young people; aripiprazole: mortality in dementia patients, and suicidality) (5). Several drugs outside the field of psychiatry that were promoted through DTCA in the U.S. were later withdrawn due to severe side effects, e.g. COX-2 inhibitor rofecoxib in 2004. Benefits of PM might thus be outweighed by the harm due to increased rates of side effects in persons that would not have needed medication (10).

In conclusion, our study found significant differences in public attitudes towards PM between the U.S. and Germany. People in the U.S. were more willing to take psychiatric medications, even in situations where they are not indicated, less concerned about the possible harms, and more strongly convinced of the benefits of these medications. These differences may reflect, at least in part, the effects of DTCA, but also point towards other cultural, social and health care system differences between the two countries.

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Acknowledgement

This study was funded by the Fritz-Thyssen-Stiftung (Az. 10.11.2.175).

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DOI 10.1002/wps.20169

The impact of adolescent cannabis use, mood disorder and lack of education on attempted suicide in young adulthood

Suicide is one of the leading causes of death worldwide among young people. One of the strongest predictors of completed suicide is a previous suicide attempt (1). Suicide attempts are more frequent among young people, and a suicide attempt may be a marker of a lasting trajectory of adverse mental and physical problems into middle adulthood (1,2).There is limited evidence for factors during the adolescent period and the period of transition to young adulthood that increase the risk of attempted suicide. We used a prospective cohort study design incorporating clinical interviews to determine what factors measured at ages 12-15 years are associated with attempted suicide reported at ages 19-24 years.

The methods for the baseline adolescent study have previously been described (3). Using a stratified random sampling technique, 743 students in eight mainstream schools were screened for psychopathology. Adolescents who scored above threshold on the screening instruments or who indicated the presence of significant suicidal ideation (N=140) were invited to attend for interview, along with a group of 174 controls matched for gender, school and school year. 84.3% adolescents from the "at risk" category and 54% of the control group attended for a semi-structured clinical interview, along with a parent or guardian. All 212 young people who were interviewed as young adolescents were invited to take part in a follow-up interview eight years later. Follow-up information was obtained on 168 participants (79% follow-up rate). There were no differences between responders and non-responders in age, gender, parental socio-economic status, "at-risk" status at baseline, or diagnosis of psychiatric disorder at baseline.

We collected exposure information at interview on: family and childhood risk factors (family history of psychiatric illness and experience of childhood trauma, i.e. physical/sexual abuse or witnessing domestic violence); adolescent risk factors (psychopathology, cannabis use and alcohol use); young adult risk factors (psychopathology, cannabis use, self-harm, education level and employment status). The outcome measure was lifetime suicide attempts at 19-24 years old.

Ten percent of participants had made a suicide attempt at some point in their lives up to age 19-24 years. The mean age of those attempting suicide was 20.6 years. Fifty-three percent of those who reported a suicide attempt were female. Hierarchical logistic regression models showed that adolescent mood disorder and adolescent cannabis use, young adult mood and anxiety disorders, and a low level of education were the most strongly predictive factors for making a suicide attempt when the effects of family psychiatric history, childhood trauma, alcohol use and other psychopathology were taken into account.

Adolescent mood disorder and adolescent cannabis use both independently increased the odds of a suicide attempt 7-fold (OR=7.0, 95% CI: 1.4-34.3; OR=7.5, 95% CI: 1.2-43.8), while young adult mood and anxiety disorders both independently increased the odds of an attempt 11-fold (OR=11.7, 95% CI 1.8-73.9; OR=11.1, 95% CI: 21.0-57.9). Young adults with only secondary-level education had an 8-fold increase in the odds of a suicide attempt compared to those with third-level education (OR=8.0, 95% CI: 1.1-54.4).

There is evidence that substance use disorders in adulthood increase the risk of suicidal behaviours. Here we show that any use of cannabis in the early adolescent period is a strong independent predictor of attempted suicide in young adulthood. We know that significant brain maturation continues to occur during adolescence, particularly in limbic structures such as the hippocampus; and within the prefrontal cortex important processes such as synaptic pruning, myelination and programming of neurotrophic levels are occurring at this time (4). Regular cannabis use can lead to grey matter volume reduction in a range of brain areas, including the medial temporal cortex, the parahippocampal gyrus, the insula and orbitofrontal regions (5). There is evidence of a linear association between the age at onset of cannabis use and both white matter integrity and grey matter volume, suggesting that the earlier the onset of use, the greater the toxic effects on the brain (5,6). Neuroimaging studies of people who have attempted suicide show structural and functional brain changes that are in keeping with those found in cannabis users (7). It is possible that cannabis use in early adolescence, at a vulnerable time for neurodevelopment, leads to or exacerbates ongoing dysfunctional brain changes that prime young people for a maladaptive trajectory towards young adulthood. Those most at risk for attempted suicide may have experienced accumulating risk exposures throughout childhood and adolescence and in young adulthood may lack adequate problem solving skills, as possibly indexed here by low levels of education.

The increasing awareness among the mental health community that we need to focus on early clinical intervention to protect against the worst effects of emotional distress among our young people, both on a personal and

an economic level (8), can only be acted on when we can reliably identify which young people are most at risk. The available evidence suggests that the specialist treatment of psychiatric disorder in adolescence alone is insufficient for the prevention of future suicide attempts (9). We need a more tailored approach to youth mental health and a greater awareness of the different contingencies involved in the pathway to suicidal behaviours such as accumulating risk from adolescent cannabis use, adolescent mood disorders and a lack of education.

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Acknowledgement

This work was supported by a grant from the Health Research Board HRA-PHS/2010/4.

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DOI 10.1002/wps.20170

Gambling and the enduring financial recession in Greece

The enduring nature of the economic crisis in Greece has already been linked to adverse health effects (1). Congruent with this, previous work from our research team has shown a gradual increase in the prevalence of major depression and suicidality in the country during the period 2008-2011 (2-4).

In 2013, we conducted a nationwide telephone survey, following the same methodology of previous surveys (2-4), in order to identify the general population's strategies for tackling increasing financial demands. A random and representative sample of 2,188 people were interviewed about their financial difficulties, ways of dealing with financial strain, and the presence of major depression and suicidality. A major depression diagnosis was ascertained by the pertinent module of the Structured Clinical Interview (5), while financial burden was assessed through the Index of Personal Economic Distress (2).

Interestingly, 2% of the population reported that they resort to gambling in order to deal with financial distress. A series of univariate analyses were performed to identify the variables that bore a statistically significant association with gambling: they were gender, educational status, employment status, financial distress and working hours. A logistic regression analysis with the aforementioned variables entered as predictors and gambling as the outcome variable (binary: yes/no) indicated that financial distress and working hours were the only variables exerting an independent effect on gambling. In particular, for every unit increase in the Index of Personal Economic Distress, respondents were 1.12 times more likely to gamble in order to deal with financial strain (OR=1.12, 95% CI: 1.03-1.23). Furthermore, participants who reported working more than 40 hours per week were roughly 7 times more likely to gamble than those who reportedly work less (OR=7.34, 95% CI: 2.03-22.91).

A non-significantly lower prevalence of major depression was found among respondents who reported they gamble as a way of dealing with financial difficulties (0.9% among those who gamble vs. 16.3% among those who do not, df (1)=0.63, $p>0.05$). With regard to suicidality, 0% of people who reported that they gamble experienced suicidal ideation, in contrast to 2.6% among people who do not gamble: df (1)=1.15, $p>0.05$).

Although differences were not significant, these data suggest that gambling offers an alternative to the dead-end created by the grim financial reality in Greece, buffering to some extent against hopelessness, a strong risk factor for major depression, suicidality and suicide (6-8). However, the existing literature suggests that, when gambling turns into its pathological form, it progresses through four stages: winning, losing, desperation and hopelessness (9). Thus, while it seems initially to offer a solution, it may subsequently lead to the same dead-end it wishes to avoid.

These data add to the growing literature (10,11) about the impact of recession on the mental health of the Greek population and the need for actions which are tailored to the specific characteristics of each population subgroup.

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DOI 10.1002/wps.20156

Depression: a silent driver of the global tuberculosis epidemic

Depression is a common comorbid condition for patients with tuberculosis (TB) (1-3), and is associated with higher morbidity and mortality (4,5), antibiotic drug resistance (1,3,6), and community transmission. Depressed individuals with TB are less likely to seek care promptly, if at all, and once in treatment are significantly less likely to take medications consistently and/or completely (2,4,7). These treatment irregularities can lead to drug resistance, morbidity and mortality. Therefore, depression may be an unrecognized driver of the TB and multidrug resistant TB (MDR-TB) epidemics.

MDR-TB treatment is significantly more expensive, takes approximately four times as long to complete, and produces acute physical and psychiatric side effects, which makes treatment adherence and completion a considerable challenge. Since few low-income settings have the resources or capacity to deliver the specialized care that is required, ensuring prompt and complete TB management in all settings is critical to curb the global TB and emerging MDR-TB epidemics.

Using a two-stage snowball approach to reviewing the literature, first searching MEDLINE (1946-2013), PubMed (1966-2013), and PsycINFO (1806-2013) databases with key relevant search terms, then reviewing the references of those articles, we identified 31 studies from 11 countries that assessed depression prevalence among individuals with active TB. These included one low-income (Kenya), three lower-middle income (India, Nigeria, Pakistan), five upper-middle income (South Africa, Peru, Romania, Russia, Turkey), and two high-income countries (Greece, United States). The studies were of mixed methodological quality. A majority of them relied on brief screening instruments to identify probable cases of depression, seven used clinical diagnostic interviews, and two did not specify the method of assessment. Only two studies included a healthy comparison group. Sample sizes ranged from 30 to 691 (mean 158, median 100). Two-thirds were conducted among outpatient populations and the remaining among inpatients in hospitals.

The current prevalence of depression among individuals receiving treatment for TB ranged from 11.3% to 80.2%, with a mean weighted prevalence of 48.9% (95% CI 48.3%-49.6%). In the two studies that compared the prevalence of depression among TB outpatients to healthy controls, that prevalence was three to six times higher among the former. Though we expected to find consistent rates within or between countries of similar income levels, a great deal of variability was observed. The widest variation occurred within countries (India, Nigeria, Pakistan, Peru and Russia). However, in these cases, the weighted mean prevalence within countries revealed relatively narrow confidence intervals with a strong central tendency. There was little difference in rates between studies using structured diagnostic interviews versus brief screening instruments, and no single screening instrument produced higher or lower rates than any other used. The most commonly used brief screening tool, adopted in eight studies, was the Beck Depression Inventory.

Though available evidence is of mixed methodological quality, it suggests that the prevalence of depression among individuals with active TB may be equally high or higher than in people with other chronic medical conditions. However, more research is sorely needed to estimate the true community prevalence of depression among individuals with TB.

Treating comorbid depression has been associated with better TB outcomes, including medication adherence, treatment completion, and cure. A prospective controlled study in India found that TB patients who received individual psychotherapy during treatment were significantly more likely to adhere to and complete treatment and, thus, be cured of their disease (8). In rural Ethiopia, the organization of peer-led "TB clubs" increased clinic attendance and adherence, case detection, and community awareness about TB (9). In Peru, a psychosocial support group intervention was developed for MDR-TB patients which improved treatment adherence and completion, as well as social rehabilitation after treatment (1). Finally, antidepressants, in isolation or in conjunction with other therapies, have also been effectively used to treat depression among patients with TB (10).

Though TB disproportionately affects individuals in low-resource settings with few mental health specialists, a growing body of evidence suggests that non-specialist health workers can be trained to deliver basic mental health care, including case detection, symptom management and triage, and such strategies may be very useful and relevant in the context of TB.

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DOI 10.1002/wps.20134

A plea to change the misnomer ECT

Convulsive therapy was introduced by Meduna in 1933 (1), using intravenous camphor, then cardiazol. In 1938, Cerletti and Bini (2) initiated convulsive therapy using electricity, which was named electric shock treatment, then electroconvulsive therapy (ECT).

The portrayal of ECT in the media, especially the movies showing that it was used as a punitive intervention, in an inhumane way and violating the human rights of patients, has perpetuated its negative image and increased the stigma related to this therapy. It has been rarely emphasized that ECT may be a life saving measure, especially in the treatment of melancholic, psychotic and suicidal depression.

Furthermore, the term ECT is now a misnomer, since there are no convulsions with the use of anesthesia and muscle relaxants (modified ECT). The procedure just produces blinking of the eyes rather than a full body convulsion.

C. Kellner already criticized the name ECT in 1990 (3). In Egypt, we changed the name into brain synchronization therapy (BST). This has made a shift to the positive in the family awareness and patient's acceptance of the treatment. Explaining to the patient and family the procedure without referring to convulsions has been of great help (4).

In the new Mental Health Act in Egypt (2009), the term BST (of course in Arabic) replaced ECT, and it was specified that "under no circumstances should BST be given without anesthesia and muscle relaxant" and that the treating psychiatrist will be accountable if this regulation is not followed.

A group of eminent Arab psychiatrists have just finalized the preparation of "guidelines for the treatment of depression in the Arab World" and have also replaced the term ECT by BST in order to reduce the stigma and change the wrong perception of families and patients.

This letter is a plea to psychiatrists worldwide to follow us in changing the name of ECT to BST, in order to decrease the stigma associated to this therapy and to allow more patients receiving a treatment that has become unpopular also because of its name, but that, if applied in the correct manner, can be life saving.

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DOI 10.1002/wps.20143

The WPA Action Plan 2014-2017

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The activity of the WPA during the triennium of my presidency will be guided by an Action Plan which follows the objectives of the Association. These objectives include: to increase knowledge and skills about mental disorders and how they can be prevented and treated; to promote mental health; to promote the highest possible ethical standards in psychiatric work; to disseminate knowledge about evidence-based therapy and values based practice; to be a voice for the dignity and human rights of the patients and their families, and to uphold the rights of psychiatrists and to facilitate communication and assistance especially to societies who are isolated or whose members work in impoverished circumstances.

The Action Plan, which has been approved by the WPA General Assembly during the World Congress of Psychiatry held in Madrid last September, focuses specifically on two objectives – to prevent mental disorders and to promote mental health – while also pursuing the remaining objectives of better care by providing knowledge and skills for psychiatrists. As a preliminary communication, I am sharing my vision with the readers of *World Psychiatry*. A key principle is that we learn from each other and share good clinical and academic practice.

The first objective of the Action Plan is to prevent mental disorders. There is considerable evidence in the literature that nearly three quarters of mental illness in adulthood start before the age of 24 years and also that many conditions can be prevented or delayed in their onset. It has also been shown that certain factors contribute to the onset and perpetuation of mental illness, and that some of these factors are already active before a child is born.

Bearing in mind cultural and resource variations under this broad objective of the WPA, outcomes on four key themes will be delivered: gender based interpersonal violence; child sexual, emotional and physical abuse; prisoner mental health care; mental health of the groups who are most vulnerable, including the elderly, refugees and asylum seekers, people with learning disability, and lesbian, gay, bisexual, and transgender (LGBT) individuals.

Under the second aim of promoting mental health, materials will be prepared with clear plans and campaigns to deliver messages across life span and across communities.

The above five "pillars" will also have horizontal crossings which are related to the matrix. For example, gender will play an important role across all pillars. Similarly, children and the elderly will also be considered across all columns.

The outcomes will be on four levels: materials for undergraduate curriculum, materials for postgraduate curriculum, materials for continuing professional development (continuing medical education) and policy documents. Curricula will be developed in a standardized format, so that member organizations and other interested parties can access them and modify them according to their needs and resources. Task force groups will be set up to deliver all of these, and members of the WPA Executive Committee have agreed to take on specific responsibility for one or more of these tasks.

Early career psychiatrists are the future of psychiatry and will be involved at all levels. Every effort will be made to engage trainees and medical students so that the brightest individuals are not only attracted to psychiatry but also retained in the field.

In addition, virtual hubs will be established which can be accessed to retrieve policy documents, research papers and links, and clinical advice. The WPA has produced various educational materials and it is proposed to develop and build on these so that psychiatrists and other mental health professionals as well as patients and their families can access them. These hubs will be closely linked with member organizations so that their needs can be assessed and materials provided accordingly. Selected organizations will host these hubs. These hubs will also be linked with key WPA collaborating centres which will be established based on strict criteria as approved by the Executive Committee. These centres will provide materials for training, research and policy development and will lead on identifying significant materials for translation if needed and further dissemination. In addition, training materials will be produced and placed in public domains. An arm's length body created for education will deliver educational materials at all levels including assessment tools.

Additional tasks will include updating the WPA website and making it more user friendly with repository of policy documents from all member organizations and teaching and training materials for psychiatrists at all ages of practice and across different psychiatric specialties, along with patient/carer/family information leaflets on different psychiatric conditions. Furthermore, policy documents across different languages will be available in key languages including English. We also aim to translate various texts from other languages into English so that there is a fair exchange of ideas, information and knowledge.

Readers of *World Psychiatry* who are interested in being informed or wish to contribute to the above initiatives are welcome to contact the WPA Secretariat (wpasecretariat@wpanet.org) or me directly through the WPA website.

DOI 10.1002/wps.20157

Acknowledgement
This publication has been partially supported by an unrestricted
educational grant from Roche SpA,
which is hereby gratefully acknowledged