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EDITORIAL

Clinical complexity and person-centered integrative diagnosis

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Clinical complexity is emerging as a pointed indicator of the conceptual and empirical richness of psychiatry and general medicine and of the intricate challenges faced by our field. This complexity needs to be appraised, understood and formulated in attention to its various aspects and levels in order to inform adequately the development of crucial clinical tools such as an effective diagnostic model. A broad model relevant to this concern is being outlined under the term of person-centered integrative diagnosis (PID) (1,2).

UNDERSTANDING CLINICAL COMPLEXITY

Clinical complexity is a protean term encompassing multiple levels and domains. Illustratively, a prominent concern in health care involves multiplicity of disorders and conditions experienced by a person along with their cross-sectional and longitudinal contexts. Also relevant are the diversity of severity levels and courses of clinical conditions. Financial-related complexity includes case-mix definitions and their implications for reimbursement. Further noteworthy are the plurality of values of people experiencing health problems and seeking help for them (3).

A major form of clinical complexity is *comorbidity*, which is widely recognized as a common feature of regular clinical care. While recognizing the spurious use that has been made sometimes of this term, as when two facets of the same condition have been taken as separate disorders, there are many situations where clearly different clinical conditions, such as circulatory problems and depression, are identified as requiring specific attention.

The need to systematically address comorbidity in general medicine was highlighted by Feinstein (4), who is credited with coining this term. He defined it as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study". The broadness of "additional clinical entities" under his concept of comorbidity reached physiological conditions requiring clinical attention such as pregnancy.

Comorbidity can be noted among conditions in the same chapter of the International Classification of Diseases (ICD), such as that on mental disorders. It can be noted as well among conditions in different ICD chapters. It can be argued that comorbidity can also apply to the concurrence of disorders and social conditions of clinical significance, such as trauma and child abuse. The intricacy of comorbidity may also be extended to the involvement of multiple sectors such as mental disorders, general medical disorders, and clinically relevant social conditions, a situation that has been referred to as *hypercomorbidity* by the Workgroup on Comorbidity of the World Health Organization (WHO) (5).

The US National Comorbidity Survey (6) revealed that 79% of all ill people had comorbid disorders, and that over half of the lifetime disorders identified were concentrated in 14% of the population studied. Comorbidity is particularly common in the elderly, and with worldwide advancing of population age it is becoming a major global health concern.

Comorbidity is associated with serious implications for clinical care, due to its impact on both diagnosis and treatment. Comorbidity may interfere with the identification of the index disease by creating significant difficulty in symptom attribution, leading to delay or incorrect nosological diagnosis. The course of the index disorder may be adversely affected by comorbid conditions, leading to increased disability and mortality as well as to higher family and societal burden and suffering. Comorbidity may also lead to limitations in treatment planning, implementation and outcome.

Conventional health care paradigms focusing just on disease and immediate care are often regarded as inadequate. This is particularly true when comorbid conditions are noted. The WHO Comorbidity Workgroup concluded that person-centered care offers the most promising approach when comorbid conditions are involved, by facilitating coordination and integration of services. A person-centered approach would also facilitate attention to the positive aspects of health, such as resilience, resources, and quality of life. This is important for clinical treatment, prevention, rehabilitation and health promotion.

PERSON-CENTERED INTEGRATIVE DIAGNOSIS

The need for person-centered care in response to clinical complexity (from comorbidity to patient values) and other developments in the health field has been recently addressed by the WPA through an Institutional Program on Psychiatry for the Person (IPPP) (7,8). The program is aimed at promoting a psychiatry of the person, for the person, by the person, and with the person. One of its components involves clinical diagnosis, dedicated to collaborating with WHO in the development of ICD-11 and to the design of PID (1).

To be noted as background of these developments is WPA's extensive record on classification and diagnosis. An illustrative contribution is the International Guidelines for Diagnostic Assessment (IGDA) (9). The record also encompasses long-standing collaboration with the WHO, which has been displayed through a number of major conferences and congresses and the publication of two monographs in *Psychopathology* (10,11). Collaboration has also taken place with national and regional psychiatric associations, such as the American Psychiatric Association (12), the Chinese Psychiatric Society (CCMD-3) (13), the Cuban Psychiatric Society (GC-3) (14), the French Psychiatric Federation, and the Latin American Psychiatric Association (GLADP) (15).

The construction of the PID theoretical model has been carried out by the IPPP workgroup through a number of meetings in 2006 and 2007, most recently a major conference in London co-organized by the UK Department of Health. Emerging features of the PID model include its being a diagnosis of health (of both illness and positive aspects of health), involving collaborative and empowering engagement of patients, and serving as informational basis for prevention, treatment, rehabilitation, and health promotion. Strategically, the PID model has a bio-psycho-sociocultural framework, articulates science and humanism, utilizes all pertinent descriptive tools (categories, dimensions, and narratives) in a multilevel structure, and engages clinicians, patients and families in a diagnostic partnership.

Building on the above mentioned PID model, a PID guide or manual will be developed with the following phases: preparation of the first draft of the PID guide (during 2008), evaluation (reliability, validity and feasibility) of the draft (2009), completion and publication of the PID guide (2010), and its translation, implementation and training (2011 and following years).

CONCLUDING REMARKS

Clinical complexity denotes the richness of our field and represents a pointed challenge to our professional responsibilities. WPA is responding to it through the IPPP and the PID model and guide, in collaboration with all its institutional components, including the Global Network of National Classification and Diagnosis Groups, and growing links with major international medical and health organizations.

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Neurobehavioral sequelae of traumatic brain injury: evaluation and management

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Traumatic brain injury (TBI) is a worldwide public health problem. Over the last several decades, improvements in acute care have resulted in higher survival rates. Unfortunately, the majority of survivors of moderate and severe TBI have chronic neurobehavioral sequelae, including cognitive deficits, changes in personality and increased rates of psychiatric illness. These neurobehavioral problems are understandable in the context of the typical profile of regional brain damage associated with trauma. This paper presents an overview of the neurobehavioral sequelae of TBI and outlines issues to consider in the evaluation and management of these challenges.

Key words: Traumatic brain injury, neurobehavioral sequelae, regional brain damage, cognitive deficits, personality changes

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Traumatic brain injury (TBI) is a universal public health problem. A recent review of epidemiological studies in Europe suggests an incidence of 235 hospitalized cases (including fatalities) per 100,000 population (1). In the US, the incidence is estimated at 150 per 100,000 population (2). Less data is available from other regions of the world, but TBI is acknowledged as a significant problem worldwide. Of note is that the incidence rates are calculated from hospitalized cases only, and do not include injured individuals who do not seek or have access to care. Thus, the actual incidence of injury is probably 3 to 4 fold larger than the quoted numbers. Most studies suggest that the incidence rates for TBI are greatest in the second and third decades of life, with a secondary increase in the elderly stemming from falls (2,3). Males are more likely to suffer a TBI than females (2,3).

In developed countries, there has been a reduction in the mortality rates associated with TBI over the last several decades, generally attributed to improved systems of trauma care and improved motor vehicle safety design. Many individuals with mild traumatic brain injury and virtually all individuals who survive moderate and severe TBI are left with significant long-term neurobehavioral sequelae (4-6). Thus, the reduction in TBI-associated mortality rates (7) has led to a significant increase in the number of individuals with long-term neurobehavioral disorders related to TBI (8,9).

Brain trauma can be caused in a number of ways, including mechanisms which penetrate the substance of the brain (e.g., projectiles) and those that do not. This paper focuses on non-penetrating injuries. Despite different contexts and instruments, the physics and biomechanics underlying damage to the brain from non-penetrating injuries have some common features. This results in certain brain regions being at greater risk for damage than others and allows for some general statements to be made about typical profiles of brain injury associated with trauma. The assessment and treatment of the neurobehavioral sequelae of TBI follow logically from an understanding of this injury profile.

RELATIONSHIP OF PROFILE OF INJURY TO NEUROBEHAVIORAL SEQUELAE

There are two broad categories of forces that result in brain injury: contact (or impact) and inertial (acceleration or deceleration). Contact injuries result from the brain coming into contact with an object (which might include the skull, or some external object). Contact mechanisms often result in damage to scalp, skull, and brain surface (e.g., contusions, lacerations, hematomas) (10). Frequent sites of such injury are the anterior temporal poles, lateral and inferior temporal cortices, frontal poles, and orbital frontal cortices.

Inertial injury results from rapid acceleration or deceleration of the brain that produces shear, tensile, and compression forces. These forces have maximum impact on axons and blood vessels, resulting in axonal injury, tissue tears, and intracerebral hematomas. These mechanisms also produce more widespread or diffuse injury (diffuse axonal injury) to white matter. Particular areas of vulnerability include the corpus callosum, the rostral brainstem, and subfrontal white matter (10).

Many injuries result from a mixture of both forces, and injury from both occurs immediately (referred to as primary injury), and may also evolve over time (secondary injury). Secondary injury is caused by a variety of factors, such as hypoxia, edema, and elevated intracranial pressure. In addition, mechanical distortion of the neurons results in massive release of neurotransmitters, with subsequent triggering of excitotoxic injury cascades (11). Although this probably occurs throughout the brain, the excitotoxic cascades and other forms of secondary injury such as hypoxia/ischemia have a disproportionate effect on certain brain regions, such as the hippocampus, even in the context of an otherwise fairly mild injury (12).

The emergence of explosive devices (particularly "improvised explosive devices") as primary mode of attack in the conflicts in Iraq and Afghanistan, as well as in other regions of political unrest, has called attention to the effects of "blast injury". Explosions generate a rapidly moving wave of over-

heated, over-pressurized air, followed by a low pressure trough. These waves are particularly damaging to air and fluid filled organs and cavities, and can be associated with significant brain injury as well (13-15). At this time it is not known whether the effects of blast injury on the brain are related to the mechanical effects of the pressurized wave, with distortion of vascular tissue, neural tissue or both, the inertial effects of being buffeted by the alternating high and low pressure events, or some other mechanism. It is clear that other injury mechanisms often come into play, including impact mechanisms (coming into contact with an object), inertial (rapid acceleration/deceleration of the brain), and penetrating injuries from shrapnel or debris.

Thus, the typical profile of injury involves a combination of primary injury (occurs at time of application of force) and secondary injury (evolves over time subsequent to the primary injury) as well as a combination of focal and diffuse injury. Furthermore, although the damage may be diffuse or multifocal, there are certain brain regions which are highly vulnerable to injury and account for the high rate of challenging behavior and probably the increased rates of psychiatric illness that are associated with TBI. These include the frontal cortex and sub-frontal white matter, the deeper midline structures including the basal ganglia, the rostral brainstem, and the temporal lobes including the hippocampi.

In addition to the profile of regional brain injury described above, there is evidence that neurotransmitters with important roles in maintaining cognitive and behavioral homeostasis are altered in TBI. For example, there is significant dysfunction of catecholaminergic systems associated with TBI (16-18). There is also evidence of altered central cholinergic tone (19-23) following trauma. The cholinergic system plays an important role in many cognitive domains, particularly memory and attention (24) and may play a role in the genesis of mood disorders, particularly depression (25). The serotonergic system is activated in TBI, with increased levels of serotonin particularly evident in areas of significant tissue damage and in association with lowered regional cerebral glucose utilization (10,26-28).

CHANGES IN COGNITION

Initial and persistent cognitive deficits are the most common complaints after TBI (29,30) and the major hindrance to normalization in the areas of independent living, social readaptation, family life, and vocational endeavors (31,32). Several cognitive domains are predictably impaired, including frontal executive functions (problem solving, set shifting, impulse control, self-monitoring) (33,35), attention (36,37), short-term memory and learning (38-43), speed of information processing (44,45), and speech and language functions (46-49). Obviously, these are not completely independent domains, and there is typically a mixture of deficits of varying degrees across domains.

CHANGES IN PERSONALITY

Survivors and family/caregivers frequently describe alterations in emotional and behavioral regulation as "changes in personality". This takes two different forms: exaggeration of pre-injury traits, or fundamental changes in response patterns. Within the latter category, careful inspection usually reveals that this can be further parsed into alterations in the frequency or intensity of predictable responses to environmental cues or stimuli, or unpredictable response patterns. Several common clusters of symptoms that characterize the "personality changes" are recognizable.

One problem area is that of *impulsivity*. This may be manifest in verbal utterances, physical actions, snap decisions, and poor judgment flowing from the failure to fully consider the implications of a given action. This is closely related to the concept of stimulus boundedness, in which the individual responds to the most salient cue in the environment or attaches exaggerated salience to a particular cue, without regard to previously determined foci of attention or priorities.

A second problem area is that of *irritability*. Survivors may be described as more irritable or more easily angered. Although a particular cue might be perceived as a legitimate aggravation, the response is characteristically out of proportion to the precipitating stimulus. Responses can range from verbal outbursts to dangerous aggressive and assaultive behavior. This modulatory deficit differs in intensity, onset, and duration from the pre-injury pattern for any given individual.

A third area is that of *affective instability.* Survivors and family/caregivers frequently describe exaggerated displays of emotional expression, out of proportion to both the precipitating stimulus and the pre-injury range of response to similar stimuli. Cues that previously elicited momentary sadness now precipitate weeping or crying. Events which in the past might provoke a frown or reply laced with irritation now result in loud angry verbal outbursts associated with marked sympathetic arousal. Additional characteristics include a paroxysmal onset, brief duration, and subsequent remorse. This phenomenon occurs in other central nervous system disorders and has been called pathological affect, affective lability, pseudobulbar affect, and affective incontinence (51).

The burden of the above changes in personality and behavior is often complicated by a surprising and at times devastating *lack of awareness* of these changes (52,53). The injured individual may be unable to appreciate that his or her behavior is different, in stark contrast to family/caregivers, who are painfully aware that the injured individual has changed in fundamental ways and will often provide detailed lists of these changes. Alternatively, an individual with TBI may have a vague sense that he or she is different or "not who I used to be" and yet struggle to define the specific ways in which his/her behavior or personality differs from prior to the injury. Individuals with TBI are less like-

ly to be aware of changes in behavior and executive function than changes in more concrete domains such as motor function (54). Furthermore, the degree of awareness has been found to correlate with functional and vocational outcome in many (55-58), though not all (59), studies. The literature suggests that lack of awareness of illness is not simply a function of global cognitive deficits, but perhaps is more related to frontal-executive dysfunction (60,61). In individuals with TBI, this dimension is frequently the focus of family/caregiver concern, yet is often not recognized by the individuals themselves (8,62-66). Even when the individual admits to some difficulties, he or she is often unable to predict the implications of these deficits in current or future social situations.

Another problem area is that of *apathy*. The underlying deficit associated with apathy is in the realm of motivated behavior (67). Although not as overtly disturbing as some of the other changes described above, it can be a focus of concern and is frequently the reason that injured individuals fail to progress in rehabilitation programs. It is often misinterpreted as laziness or depression and may be linked somewhat paradoxically to aggression when attempts to engage the individuals in activities in which they have little interest can precipitate assaultive behavior (68).

Apathy is quite common after TBI. Kant et al (69) found that it occurred (mixed with depression) in 60% of their sample. Andersson et al (70) found that almost half of their individuals with TBI had significant degrees of apathy. Deficits in motivated behavior can occur in association with injury to the circuitry of "reward" (68,71). Key nodal points in this circuitry include the amygdala, hippocampus, caudate, entorhinal and cingulate cortices, the ventral tegmental area and the medial forebrain bundle. Catecholaminergic systems, particularly the mesolimbic dopaminergic system, appear to play critical roles in the modulation of the reward system (68,71).

RELATIONSHIP OF PROFILE OF INJURY TO PERSONALITY CHANGES

A full discussion of the neuroanatomical substrates of the above behaviors is beyond the scope of this paper. However, the link between the injury profile in a typical TBI and some of these behaviors is fairly simply understood. Five major frontal-subcortical circuits have been identified, of which three have significant roles in non-motor forms of behavior (72). Each of these three circuits can affect motivated behavior, though in somewhat different ways. Damage to the dorsolateral prefrontal cortex and its circuitry impairs executive functions such as working memory, decision making, problem solving and mental flexibility. Damage to the orbitofrontal cortex and related nodal points impairs intuitive reflexive social behaviors and the capacity to self-monitor and self-correct in real time within a social context. Damage to anterior cingulate and related circuitry impairs motivated and reward-related behaviors. Damage to medial temporal regions impairs other aspects of memory and the smooth integration of emotional memory with current experience and real-time assessment of stimulus salience. The frontal-subcortical circuits responsible for these critical domains of higher intellectual function and empathic, motivated, nuanced human behavior are highly vulnerable to injury in the typical TBI.

RELATIONSHIP OF TBI TO PSYCHIATRIC DISORDERS

In addition to the changes in cognition, behavior, and personality described above, a significant body of evidence suggests that TBI results in an increased relative risk of developing various psychiatric disorders, including mood and anxiety disorders, substance abuse and psychotic syndromes (73-76). For example, Kopenen et al (76) studied 60 individuals 30 years after their TBI and found that almost half (48%) developed a new Axis I psychiatric disorder after their injury. The most common diagnoses were depression, substance abuse, and anxiety disorders. Rates of lifetime and current depression (26%; 10%), panic disorder (8%; 6%), and psychotic disorders (8%; 8%) were significantly higher than base rates found in the Epidemiologic Catchment Area (ECA) study (77). Hibbard et al (74) studied 100 adults on average 8 years after TBI. A significant number of individuals had Axis I disorders prior to injury. After TBI, the most frequent diagnoses were major depression and anxiety disorders (i.e., post-traumatic stress disorder (PTSD), obsessive-compulsive disorder and panic disorder). Almost half (44%) of individuals had two or more disorders. More recently, this group reported a longitudinal study of 188 individuals enrolled within four years of injury and assessed at yearly intervals on at least two occasions (78). Once again, they found elevated rates (compared to population base rates as reported in the ECA study) of psychiatric disorders (depression and substance abuse) prior to injury. Subsequent to TBI there were increased rates of depression, PTSD, and other anxiety disorders. This was particularly true of those with pre-injury psychiatric disorders. Furthermore, the rates were greatest at the initial assessment point after injury and stabilized or decreased over time. Van Reekum et al (75) carefully reviewed the literature on the relationship of TBI to a variety of psychiatric disorders and, using the ECA data for baseline rates, concluded that TBI was associated with an increase in the relative risk for several psychiatric disorders. Others have also reported increased indicators of psychiatric illness after TBI and increased medical costs associated with those indicators (79,80).

As with any potentially disabling condition, individuals with TBI report a variety of symptoms in different domains (discouragement, frustration, fatigue, anxiety, etc.). Not all of these symptoms will rise to the level of a disorder. However, constellations of symptoms that are consistent and sustained over time (usually weeks), and that are of suffi-

cient severity to interfere with social or occupational function or quality of life, are legitimately considered disorders. In the studies cited above, standardized criteria encompassing those principles were used and thus argue strongly that TBI acts as a gateway for the development of many psychiatric disorders. The consistent observation that individuals who sustain a TBI have higher base rates of psychopathology prior to injury also suggests that there is a reciprocal interaction: psychopathology predisposes to TBI, and TBI in turn predisposes the individual to develop psychiatric disorders.

In addition to the psychiatric disorders noted above, a concern has been raised about the relationship of TBI to dementia. Many individuals with TBI who have significant impairments in memory and executive function meet the DSM-IV definition of dementia. However, the larger issue is whether exposure to a TBI increases the risk of a progressive dementing disorder such as Alzheimer's disease later on. At this time it is not possible to say definitively whether TBI, particularly mild TBI, is a risk factor for that disease. This topic has been recently reviewed by Jellinger (81), who concluded that both Alzheimer's disease and TBI are associated with abnormalities in amyloid and tau protein deposition, and that several epidemiological studies have suggested either that Alzheimer's disease occurs with increased frequency in individuals with TBI or that the age of onset of the disease is reduced after TBI relative to non-injured controls. It may be that the reduced cognitive reserve associated with TBI facilitates earlier symptom manifestation of dementia in individuals destined to develop Alzheimer's disease (82).

NEUROPSYCHIATRIC ASSESSMENT

It is clear from the above that a careful assessment of neurobehavioral problems should be an important component of the evaluation and rehabilitation of individuals with TBI. Furthermore, the pattern of sequelae should make sense from the injury. The process of elucidating the profile of brain injury, evaluating the profile of current signs and symptoms, and mapping the latter onto the former to assess goodness of fit is essentially the work of the neuropsychiatric evaluation. Signs and symptoms which are not accounted for by the profile of injury must be explained on another basis or the profile of injury should be re-assessed.

It should be taken into account, however, that the cognitive deficits which frequently accompany a TBI alter the neuropsychiatric assessment, particularly the history taking. The presence of short-term memory deficits, problems with sequencing events in time, and difficulties with self-monitoring and self-awareness can make it very challenging for an individual to give a clear and consistent history. This puts the onus on the clinician to identify other sources of information (family members, friends, employers, primary medical/school/vocational records) that can help clarify the history and current clinical picture.

The assessment of the effects of an injury must start with a thorough understanding of what the individual was like prior to the injury. In the absence of such information, there is a significant risk of misattributing life-long traits, characteristics, and behaviors to the brain injury. Ideally, such baseline information is obtained shortly after the injury. The more time that passes from the point of injury, the greater the tendency to (mis)attribute more and more to the injury.

Once the baseline picture is complete, the clinician is positioned to accurately assess the changes that have occurred since the time of the injury. It is important to carefully review the functional domains that are frequently affected by injury, including cognition, personality, mood regulation, speech/language, mobility, and higher order domains such as vocational performance, major role performance within the family or equivalent context.

It is important to emphasize that temporal association does not guarantee causality. There are several ways that neurobehavioral change can be associated with brain injury. Change may be a direct effect of the insult to neural tissue with subsequent disruption of the functions subserved by the damaged tissue. Alternatively, the change may reflect the development of a new illness or disorder that is the driving force behind the behavioral change. Moreover, behavioral change could be caused by the meaning of the accident or injury, being a reaction to a loss of self-esteem due to disfiguring injury, loss of mobility, or unemployment. Finally, changes in environment such as living situation, change in caregivers, or change in routine or flow of daily life can have an enormous impact on the behavior and adaptation of an individual with brain injury or other neuropsychiatric illness. An individual showing new, aggressive outbursts associated with a change in residential care may be better served by further training of the residential provider rather than by the massive use of medications. On the other hand, if this patient has clear evidence of orbitofrontal damage, it may be that his threshold for tolerating frustration is so lowered that treatment will require both medication approaches and environmental manipulation.

The proper assessment and formulation of the relative weighting or contribution of each of the above factors to the genesis of the challenging behaviors frames what can be termed a neurobiopsychosocial paradigm. It differs from more traditional psychiatric assessments with respect to the critical importance placed on understanding the profile of regional brain injury, and the array of complex behavioral circuitry that this profile would reasonably disrupt. Thus, the work of the neuropsychiatric assessment can be summarized as the process of matching the profile of brain injury with the changes that have occurred in cognition, behavior, and overall function, and gauging the "goodness of fit" between predicted and actual outcomes. This is followed by an interpretative process whereby the clinician assigns relative weights to the various contributions made by the neural, biological, psychological, and social components. Treatment interventions should flow logically from

this formulation. It is important to point out that even experienced clinicians can make mistakes in this process, due to the complexity of clinical presentations and the incomplete data available. Thus, the final critical component to this process is the regular re-evaluation of intervention efficacy. Each formulation should be hypothesis driven and each intervention flow logically and in an empirically testable fashion from this formulation (e.g., "I believe the increase in aggression is due to depression, thus I will prescribe antidepressants"). Poor or incomplete response to the intervention should prompt a re-evaluation and formulation of a new and testable hypothesis. It is acceptable to be wrong, it is not acceptable to engage in sloppy thinking.

PRINCIPLES IN TREATMENT

Due to cognitive and sensorimotor deficits associated with TBI, clinical presentations of common psychiatric disorders may not meet standard diagnostic criteria as outlined in the DSM. Thus, it is reasonable to have "relaxed fit" criteria when making a diagnosis in individuals with TBI. It is important to point out that there are two broad factors that contribute to the neurobehavioral sequelae of TBI: the injury induced changes in personality and the increased rate of psychiatric disorders. A problem arises when the latter presents as a heightening or worsening of the former. For example, it is quite common for an individual with TBI to have a baseline of increased irritability or lowered frustration tolerance. It is also quite common for these traits to be exaggerated in the presence of a superimposed episode of depression or mania (or some other psychiatric disorder). If the clinician does not carefully tease out the post-injury baseline and clearly ascertain whether there is a change, it is easy to misinterpret the challenging behavior.

It is best to have a clear sense of what is causing the challenging behavior before designing a treatment plan. Yet, many clinicians are inclined to prescribe antipsychotics or selective serotonin reuptake inhibitors without knowing, or at least formulating a hypothesis for what they are treating. This is a symptomatic approach, similar to treating a fever associated with a bacterial infection with acetaminophen but not antibiotics. In the neuropsychiatric arena, the symptomatic approach should be one of last resort after having carefully ruled in or out the presence of an Axis I disorder (e.g., depression, mania, psychosis), neuromedical conditions that would account for the behavior (e.g., complex partial seizures, pain, iatrogenic complications, medication side effects), or factors in the environment that are causing the change in behavioral symptoms.

There are times, for example when data is difficult to obtain or when the neurological deficits through which challenging behaviors are being expressed are severe, that one is at a loss to account for the etiology of a given behavior or behaviors, and thus not clear about a treatment strategy. A fallback position is to conceptualize the cluster of behaviors as if they were a particular syndrome or as if they represented what Tariot et al (83,84) have termed a "behavioral metaphor". For example, an individual expressing increased negativism, loss of interest in activities, and/or self-destructive or self-injurious behavior might be conceptualized as having a depressive syndrome and thus could reasonably be prescribed an antidepressant regimen. An individual with increased irritability, increased arousal and activation, and a significant reduction in sleep might be conceptualized as having an irritable manic-like syndrome and thus reasonably started on a mood stabilizer. The critical issue is that these are testable hypotheses and should be treated as such. Target behaviors and baseline frequencies should be identified prior to treatment and an adequate but time-limited trial prescribed. It should be clearly decided what the endpoint is and, if the desired goal is not attained, the medication should be discontinued and an alternative conceptual scheme considered.

Individuals with cognitive impairment have a heightened sensitivity not only to medications, but to the environment in which they live. *Stimulus boundedness* refers to the tendency to be very sensitive to events in the immediate environment, perhaps related to difficulty with components of attention, including complex, selective, and sustained attention, and resultant problems in prioritizing incoming stimuli and in gating out stimuli that would ordinarily be deemed of secondary importance. At its essence this may be a problem assigning or decoding proper salience to the constant influx of environmental cues and stimuli.

Fondness for routine refers to the sensitivity of individuals with cognitive deficits to changes in routine or schedule. This may relate to the afore-mentioned deficits in executive function, in which difficulties with problem solving and mental flexibility can be quite apparent. Individuals will often respond with anxiety, irritability, or even catastrophic reactions to these changes in routine.

Injured and non-injured individuals alike base much of minute to minute and long-term decisions and actions on their predictions of what response a given action will produce. Increasing the probability of favorable responses and decreasing the likelihood of undesirable responses are powerful forces in shaping behavior. Individuals existing in an environment in which the same behaviors elicit different responses from different people or the same people at different times can become confused, anxious, and agitated.

It is critical to carefully consider the above factors when performing a neuropsychiatric assessment. To ignore the environment and factors that may be provoking challenging behaviors will greatly reduce the efficacy of any prescribed medication, even if it is the proper one. On the other hand, without the properly prescribed medication, even massive efforts at applying behavioral analysis and environmental manipulation may be in vain. The therapeutic issue then should not be "Do we prescribe a drug, or write a behavioral plan?". The question is better framed as "Which medicine prescribed in the context of what

changes in environment and strategies for shaping behavior has the best potential for success?".

CONCLUSIONS

Attention to the diagnosis and management of the neurobehavioral sequelae of TBI can serve a critical role in advancing the rehabilitative process. It requires a knowledge and understanding of the profile of regional structural and neurochemical injury associated with the typical TBI and how that profile predicts the common neurobehavioral sequelae. Careful assessment requires an accurate description of the individual's functional and neurobehavioral status prior to the injury and how that has changed subsequent to the injury. It is helpful to be aware of the problems in diagnosis in individuals who have a fluctuating behavioral baseline, who may have significant cognitive deficits, or in whom the usual connection between internal feeling state and external behaviors may be uncoupled. Treatment should follow from a clearly articulated diagnostic scheme and should be time-limited and re-evaluated in the presence of poor or incomplete response.

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Advances in endophenotyping schizophrenia

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The search for the genetic architecture of schizophrenia has employed multiple, often converging strategies. One such strategy entails the use of tracing the heritability and neurobiology of endophenotypes. Endophenotypes are quantifiable traits not visible to the eye, which are thought to reflect an intermediate place on the path from genes to disorder. Endophenotype abnormalities in domains such as neurophysiology or neurocognition occur in schizophrenia patients as well as their clinically "unaffected" relatives, and reflect polymorphisms in the DNA of schizophrenia spectrum subjects which create vulnerability to developing schizophrenia. By identifying the single nucleotide polymorphisms (SNPs) associated with endophenotypes in schizophrenia, psychiatric neuroscientists can select new strong inference based molecular targets for the treatment of schizophrenia.

Key words: Schizophrenia, endophenotypes, neurophysiology, neurocognition, vulnerability genes

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The endophenotype concept was introduced to the field of psychiatric genetics 34 years ago by Gottesman and Shields (1), linked to the use of the glucose tolerance test (GTT) as an endophenotype for diabetes. Endophenotypes, such as the GTT, are heritable biomarkers that are not observed by the naked eye. After a long latency period, interest in the endophenotype approach has become remarkably strong. This exponential growth of interest in the "endophenotype strategy" (Figure 1) undoubtedly reflects the usefulness of deconstructing the complex phenotypes of "fuzzy" DSM psychiatric disorders into their pathophysiological and genetic components (2-4).

When implemented in psychiatric research, endophenotypes are quantifiable traits that are conceptualized as being "closer" to gene-based neurobiological deficits than an illness itself, but are significantly associated with and may cosegregate with the illness. These endophenotypes can be measured objectively and reliably in the laboratory (1,3,5,6). In this broad context, endophenotypes show: a) heritability; b) state independence (i.e., they exhibit test-retest stability, with impairments evident in patients that are not due to medications, and are observed regardless of illness state); and c) elevated rates of deficits in close non-affected biological relatives (e.g., first-degree relatives). Compared to clinical psychiatric diagnoses, it is hypothesized that endophenotypes are usually simpler, more easily quantified, closer to gene expression and neural circuitry disturbances, and more amenable to gene discovery. We are cognizant that the use of the terms "endophenotype" versus "intermediate phenotype" is being debated in the literature (7) but, based on the established use of "endophenotype", we will maintain our use of this term, as described above.

In this paper, we will often refer to the Consortium on the Genetics of Schizophrenia (COGS), the first multi-site, large scale family-based effort to apply a comprehensive endophenotype approach to schizophrenia in probands and their families (8). The COGS strategy is comparable to the identification of vulnerability genes and substrates in type-2 diabetes, noted by Jim Neel 30 years ago to be a "geneticist's graveyard" (9).

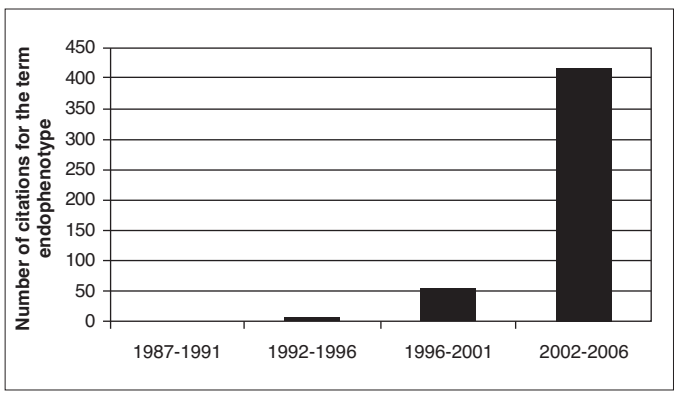

Figure 1 The growing importance of the endophenotype strategy in psychiatry, as seen in the increase of the number of citations from 1987 to 2006

THE PROMISE OF THE ENDOPHENOTYPE STRATEGY AS APPLIED TO SCHIZOPHRENIA

The endophenotype strategy, as applied to schizophrenia, follows a series of steps that are expected to ultimately lead to novel treatments (10). Step 1 is clinical observation (e.g., schizophrenia patients don't "gate" irrelevant information and are subject to "sensory overload" and cognitive fragmentation) (11). Step 2 is laboratory-based, quantifiable measurement of the Step 1 traits (e.g., Bleuler's observation that distractibility was a hallmark of schizophrenia laid a foundation for laboratory-based measures that quantify the failure to inhibit responses to repetitive stimuli) (12). In Step

3, studies demonstrate the level of heritability and genetic basis of the trait via family and association studies. In Step 4, model organism and brain imaging studies clarify the neurobiological basis of the trait, and specific molecular variations are identified, which can serve to explore novel molecular targets for pharmacotherapies. Step 5 is drug development.

Thus, endophenotypes offer a "window" on genetically mediated vulnerability to developing schizophrenia. In this context, Steps 1-3 may take 10 to 20 years to refine, test, replicate and provide a viable platform for the family and genetic studies that follow (3). Once a familial-transmitted endophenotype is identified, it is of interest to see if it co-segregates with the disorder itself. While these family based studies are carried on, it is often the case that model organism (13) and brain imaging studies identify the neural substrate dysfunction that underlies endophenotypic dysfunctions.

It is widely assumed (and confirmed) that schizophrenia has a polygenic basis. It is possible that the common disease/rare single highly penetrant nucleotide polymorphism (SNP) hypothesis is accurate for some schizophrenia patients (14). This would mean that single, highly penetrant mutations are myriad and that each case or family with schizophrenia has a single mutation in the neural circuit underlying a key endophenotype, whose disruption could result in a "final common pathway" of schizophrenia. The (not exclusive) alternative is that in the remaining (majority of cases) there are more "ancient" and more common mutations characteristic of multiple families with schizophrenia, and vulnerabilities associated with gene carriers may act alone or "add up" for genetic loading for mild to severe forms of the disorder. It seems most likely that some (e.g., 10% or less) of schizophrenia is accounted for by the rare SNP hypothesis, although this is merely a well informed guess at the present time.

SELECTION OF NEUROPHYSIOLOGICAL AND NEUROCOGNITIVE CANDIDATE ENDOPHENOTYPES

The use of endophenotypes for genetic studies of the kind described above requires large family and patient samples and multisite collaborations to achieve sufficient statistical power. Endophenotype measures must be reliable and suitable for administration to large numbers of participants. The COGS chose 6 well-established neurophysiological and neurocognitive measures to be primary endophenotypes. Then, based on initial heritability analyses (8), six Penn Computerized Neurocognitive Battery (CNB) measures were added. All twelve COGS measures show between-site reliability and heritability (3,8,15-17). In addition, these endophenotypes have significant relationships to functional status and outcome, pointing to possible molecular targets for therapies once association studies identify the molecular deficits underlying these endophenotype abnormalities. We will focus in this paper on neurophysiological and neurocognitive endophenotypes, but many other areas (e.g., metabolic, neurodevelopmental) pose similar risks and rewards.

Neurophysiological endophenotypes

The importance of inhibitory deficits in schizophrenia derives from the clinical observation that patients are unable to "screen out" trivial stimuli and focus on salient aspects of the environment (11,18,19). Inhibitory functions of sensory gating, sensorimotor gating, and oculomotor control are strong determinants of this ability to "gate" stimuli, and are assessed via measures of P50 suppression, prepulse inhibition of the startle response (PPI), and the antisaccade task. The importance of these inhibitory measures also resides in the fact that they are understood at neurobiological (and in some cases, molecular) levels, based on extensive human and model organism studies.

Studies initiated by Freedman and colleagues, and replicated by others, have identified P50 suppression as an important endophenotype of schizophrenia (3,20-25). In response to the presentation of paired auditory "clicks", there is normally an 80% diminution of the second P50 wave relative to the first, and this is attributed to the activation of inhibitory neural circuitry by the first auditory stimulus. P50 suppression is likely regulated by wide-ranging neural circuitry, prominently involving hippocampal structures (26). Brain cholinergic systems regulate some of these gating deficits, as suggested by findings that P50 suppression abnormalities in schizophrenia patients (27) and their family members (28) resolve temporarily after administration of nicotine. The use of P50 suppression as a candidate endophenotype for genetic studies is further supported by the identification of significant linkage of P50 suppression with a genetic marker in the promoter region of the alpha-7 subunit of the nicotinic receptor (29). This finding is the first to link a candidate endophenotype in schizophrenia to a specific marker.

Prepulse inhibition (PPI) occurs when a weak sensory event (prepulse) normally inhibits the startle reflex to an intense, abrupt stimulus. Since 1978 (30), PPI deficits have been consistently identified in schizophrenia patients (31). As is true for deficits of P50 suppression, PPI deficits extend beyond patients to their clinically unaffected relatives (32,33), and schizotypal (non-psychotic, unmedicated) patients (32,34). PPI deficits correlate with distractibility (35), with quantitative measures of thought disorder (36) and with impaired function in schizophrenia patients (37). Much is known about the neural regulation of PPI by elements of cortico-striato-pallido-thalamic circuitry in humans and animal models (31,38,39). PPI may become a particularly valuable tool for screening novel therapeutic agents based on molecular targets identified by COGS (37,38,40).

Oculomotor measures are quite robust schizophrenia endophenotypes. Measures of saccade control (rapid redirection of gaze to locations of interest), primarily those associated with saccadic inhibition, effectively differentiate schizophrenia subjects from controls at very large effect size levels (41). Saccadic performance in schizophrenia patients is characterized by an increased proportion of antisaccade er-

rors (42). Importantly, patients' performance is normal on tasks measuring basic saccades to a newly appearing target.

Central inhibitory deficits detected by neurophysiological measures such as P50 gating, PPI and antisaccade performance are not specific to schizophrenia. Normal inhibition in these measures is regulated by specific forebrain circuits, and these circuits in turn are controlled by a large number of genes. For example, PPI deficits are detected in Huntington's disease (43), 22q11 deletion syndrome (44) and fragile-X syndrome (45), and in animal models of each of these disorders (45-47).

In their immediate connection to neuronal mechanisms, neurophysiological endophenotypes are a much stronger signal for the presence of disorder-related genes, compared to more variable and complex clinical phenotypes. The COGS strategy is to leverage this more direct physiological signal to identify genes responsible for aberrant brain mechanisms.

Neurocognitive endophenotypes

Neuropsychological deficits are detectable in genetic high-risk subjects (48) and adult, non-psychotic relatives of schizophrenia probands, with effect sizes of ~0.3-0.5, compared to 1.0 in schizophrenia patients. These impairments in genetic high-risk subjects are not confounded by psychosis or medications, and their presence in high-risk children and adolescents provided strong support for a neurodevelopmental model of pre-psychotic vulnerability for schizophrenia (49). There is substantial evidence that measures of sustained attention or vigilance, verbal declarative memory and working memory are valid endophenotypes in schizophrenia. Continuous performance tests (CPTs) are widely used measures of deficits in sustained, focused attention and are prominent indices of neurocognitive deficits in schizophrenia (50-53). Deficits in detection of target stimuli are evident in CPT simple simultaneous discrimination and successive discrimination (54-59). CPTs without working memory burdens detect deficits (52,60), as do CPT versions with perceptual or working memory loads, which are more sensitive to subtle deficits (51,52). Effect sizes for discrimination of schizophrenia patients from controls range from 0.45 to 3.30 (2). A longitudinal study of children of schizophrenia patients has found that those who later developed schizophrenia spectrum disorders had shown CPT deficits at age 12-13 (61). Positron emission tomography (PET) activation studies with the degraded stimulus CPT support the role of cortical-striato-thalamic pathways in the deficits observed in schizophrenia (62).

Verbal episodic or declarative memory is one of the most impaired neurocognitive functions in schizophrenia (63,64). It is evident in neuroleptic naïve patients (65,66) and persists after psychotic episodes (67). While schizophrenia patients have impaired rates of encoding and forgetting, the primary deficit is in encoding and organization of information (68,69). Verbal memory deficits are found among relatives of schizophrenia patients (70,71). The deficits implicate left temporal-hippocampal dysfunction (66,67,72-74), and dysfunction in a prefrontal-temporal limbic network (74,75). Reduced hippocampal volumes among relatives of patients and smaller hippocampal volumes in multiplex versus simplex relatives and controls is consistent with the hypothesis that increased genetic loading for schizophrenia affects the neural substrates of verbal memory (76,77).

Schizophrenia patients show significant deficits on measures of working memory. The letter-number span (LNS), used as a COGS endophenotype (78), yields large separation between patients and controls, with effect sizes of 1.4 (78) and 1.9 (79). This task requires subjects to categorize stimuli into classes (numbers vs. letters) as well as order stimuli within class, and to retrieve this information. Working memory is also deficient among first-degree relatives of schizophrenia probands, as detected with both verbal (80) and spatial tasks (81). The New York High Risk Study reported that childhood scores on a verbal working memory factor successfully predicted later schizophrenia-spectrum psychoses among offspring of schizophrenia mothers, further supporting its relevance as an endophenotype for schizophrenia (82).

In addition to these three neurophysiological endophenotypes, the COGS identified six measures from the Penn CNB to be viable endophenotypes. The selection of these measures as endophenotypes was based on their large effect sizes, deficits in unaffected relatives, reliability across test sites and strong evidence of heritability (8). The Penn CNB provides measures of accuracy and speed for several neurobehavioral domains (83). Deficits in CNB performance have been related to clinical features of schizophrenia (69) and the tasks are also used in functional neuroimaging, permitting inferences about neural substrates.

GENETIC LINKAGE AND ASSOCIATION STUDIES IN SCHIZOPHRENIA

Family, twin, and adoption studies have consistently indicated that, although schizophrenia is highly heritable, its genetic etiology is complex. Genome-wide searches found that susceptibility genes for schizophrenia may exist in relatively broad regions of multiple chromosomes (84,85). Linkage analyses have produced enticing but variable results. No genome-wide scans have included enough families to conclusively establish a linkage. Meta-analytic studies suggest that susceptibility genes for schizophrenia may exist in chromosomes 6p, 10p, 13q, 15q, 18q, and 22q (86). Several candidate genes have been implicated in the susceptibility to develop schizophrenia, including dysbindin-1 (DTNBP1), neuregulin-1 and catechol-O-methyl transferase (COMT). However, the causal variants have not been definitively identified. Recently, Mutsuddi et al (87) noted that five replication studies with independent Caucasian samples reported different risk alleles and haplotypes than the original DTNBP1 study (88). In all six studies, the Caucasian sam-

ples had haplotype patterns and frequencies that were consistent with the HapMap Centre d'Etude du Polymorphisme Humain and Utah (CEU) samples. Thus, it is unlikely that population differences contributed to the observed pattern of results. Mutsuddi et al concluded that the association between schizophrenia and DTNBP1 remains uncertain. In summary, current molecular methods, such as linkage and association analyses, have not clearly or indisputably identified definitive causative genes for schizophrenia (89). Therefore, it is necessary to develop new approaches to better understand the genetics of this disorder.

Which evolving strategies are likely to illuminate the genetic basis of schizophrenia? First, family studies can yield linkage information regarding where in the genome a "signal" for schizophrenia is located. Complementary to this strategy, the COGS utilizes endophenotypes found in schizophrenia to identify linkage regions that are associated with these specific neurophysiological and neurocognitive deficits that "run" in schizophrenia families. Next, the COGS has developed a custom 1536-SNP chip (Illumina) in order to examine the association of candidate gene SNPs to endophenotypes, where the SNPs are chosen on the basis of understanding the neural and genetic substrates of these endophenotypes. Lastly, whole genome association studies utilizing extensive interrogations of the genome can examine many DNA loci (e.g., 300,000 or 1,000,000) to see which specific "unselected" SNPs are strongly associated with either schizophrenia or endophenotype deficits or both. The burgeoning power of the whole genome association strategy is now being realized via the use of large scale replication strategies with multiple samples, a time consuming but necessary endeavor that has been authoritatively endorsed (90,91) and successfully employed for gene finding in type-2 diabetes (92). Still, approaches such as the COGS SNP chip have the advantage of selecting candidate SNPs based on model organism, brain imaging and neural substrate studies, and can be utilized with smaller sample sizes since they are *not* atheoretical and the SNP selection is neurobiologically guided by extensive studies.

GENETIC ANALYSES: HERITABILITY *VS.* "MAPABILITY"

It is important to recognize the distinction between heritability and "mapability" in genetics. For example, height is among the most heritable of human phenotypes but, because it is highly polygenic, it would be a daunting task to comprehensively "map" its genetic basis. In contrast, the COGS endophenotypes were carefully selected for their likely ease of mapability. For some (e.g., P50 suppression, PPI), mapability has already been accomplished (29). With the significant levels of heritability of all COGS endophenotypes, we have strong reason to believe that mapability and gene discovery will be quite feasible. This will position us to identify therapeutic targets. This approach is already being utilized with P50 suppression, where SNPs in the promotor region of the alpha-7 nicotinic receptor (29) already led to the development and initial clinical trials of alpha-7 nicotinic agonists for the treatment of schizophrenia (10).

COGS CUSTOM 1536 SNP CHIP FOR SCHIZOPHRENIA

We have constructed an innovative gene chip, containing 1536 SNPs in 94 genes of relevance to schizophrenia, that were chosen based on knowledge of biological systems, as well as an extensive review of published association and linkage studies. Many of these genes have also been reputed to be involved in P50 suppression, PPI and neurocognitive functioning. These genes cluster into several domains and pathways, including cell signal transduction, amino acid metabolism, and glutamate, serotonin, dopamine, and GABA receptor signaling. We have also used the ingenuity pathway analysis (IPA) software to aid in the visualization of the underlying molecular mechanisms and biological processes that connect many of these genes and may contribute to disease susceptibility. A path diagram that details the interactions of 42 of the 94 genes on the COGS chip can be constructed. Knowledge of such gene by gene interactions will be accommodated in association with other analyses. In order to efficiently interrogate these genes, we have chosen to use haplotype-tagging SNPs, which, when available, derive solely from Caucasian populations, since our sample is primarily Caucasian. Of the 1427 tagging SNPs that were selected for 89 of the genes, many also had reported associations in the literature. For the five genes for which tagging SNPs were not available, 29 SNPs were chosen for even coverage. We have also included an additional 80 SNPs that were reported to be associated with schizophrenia in the literature, many of which had been replicated by separate groups. The SNPs from this chip will be utilized for association analyses of our endophenotypes for schizophrenia in 143 of our COGS families for which local, site-specific DNA samples have been collected (93). This COGS SNP chip will also be of interest to other groups studying schizophrenia and related phenotypes.

ACCOMMODATING MEDICATION EFFECTS

Many of the above-mentioned endophenotypic measures appear to be relatively immune to antipsychotic medication effects. Nonetheless, investigators can take advantage of three complementary strategies to accommodate and/or assess medication effects in their analyses: a) statistically assess differences, if any, between medicated and unmedicated individuals, by treating medication status as a grouping factor; b) perform a sensitivity analysis of findings by making worst (or best) case assumptions about the unmedicated phenotypic values for individuals on medication; and c) use a novel method for considering possible unmedicated values for

medicated individuals, which exploits estimated probability distributions for these values obtained from existing clinical trials data where subjects have been measured both on and off treatment. This last approach has been developed by Schork and colleagues and has some parallels to imputation methods for missing data (94-96). Given information about a subject's medicated endophenotype value, age, gender and other characteristics, one estimates the distribution of possible unmedicated values. These values are then weighed by the probability that the individual has the assumed unmedicated value in subsequent analyses. Mathematically, this can be achieved by integrating over the unknown unmedicated values using the estimated probability distribution for that value. Also, recent CATIE-based reports indicate that these cognitive endophenotypes are *not* powerfully influenced by the administration of even atypical antipsychotic medication (97,98). Clearly, these converging strategies are very useful in accounting for medication effects on endophenotypes and, in combination, offer an acceptable strategy to deal with a problem ubiquitous in biomedical genetics research.

CONCLUSIONS

The endophenotype strategy is a powerful and effective means for identifying vulnerability genes in schizophrenia. The probability of discovering genetic variations that predispose to schizophrenia (vulnerability genes) is greatly enhanced by the methods discussed in this overview. If too many genes are involved in complex oligogenetic (to say nothing of gene-environment) interactions, the probability of finding the genetic basis of complex diseases decreases dramatically (Figure 2). In addition, for common disorders (e.g., incidence of about 1% or more), some portion of endophenotypically relevant, disease gene polymorphisms may be *de novo* (99,100). The requisite large scale patient and family platforms necessary to conduct these studies often involve considerable expense and effort. Despite these challenges, the identification of abnormal endophenotypes, their underlying genetic architecture and the corresponding strong inference based molecular targets offers the promise of great rewards. These rewards center on ultimately finding effective new treatments, which may provide inestimable dividends in terms of decreasing the terrible disease burden that schizophrenia imposes on patients and their families.

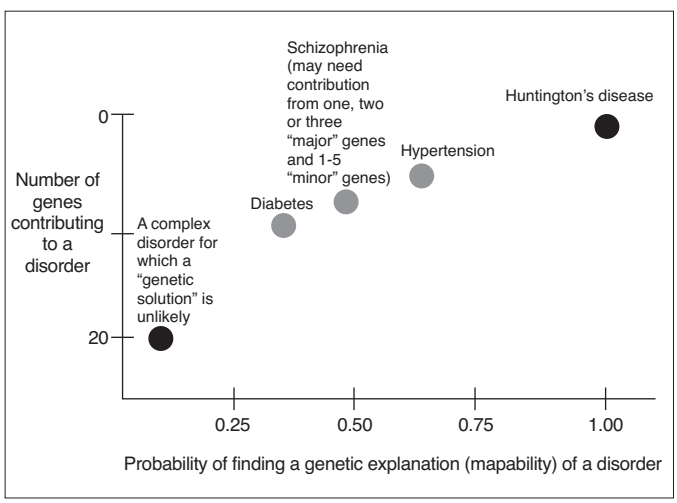

Figure 2 Probability of finding a "genetic explanation" for a disorder as a function of the number of vulnerability genes and gene-gene interactions

APPENDIX

The investigators of the Consortium on the Genetics of Schizophrenia include: Monica E. Calkins, Raquel E. Gur, Ruben C. Gur and Bruce I. Turetsky (University of Pennsylvania); Dorcas J. Dobie, Allen D. Radant and Debby W. Tsuang (University of Washington-Seattle); Robert Freedman and Ann Olincy (University of Colorado Health Sciences Center); Kristin S. Cadenhead and Ming T. Tsuang (University of California, San Diego); Michael F. Green, Jim Mintz and Keith H. Nuechterlein (University of California, Los Angeles); Larry J. Seidman and William S. Stone (Harvard University); Larry J. Siever and Jeremy M. Silverman (Mount Sinai School of Medicine).

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Autism in infants: an update

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Although autism is a disorder of very early onset, knowledge on how it is first expressed in infancy has, until recently, remained limited. In recent years new strategies of research, including prospective studies, have substantially increased our knowledge regarding autism in infants. Research findings have suggested the very early emergence of significant differences in social information processes. In addition to having important implications for research, these findings also offer new opportunities for screening and early identification and, hopefully, for improved outcome.

Key words: Autism, infancy, diagnosis, social development

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In his original report on autism, Leo Kanner (1) indicated his belief that the disorder was congenital in nature. Subsequent work has confirmed that, while a small proportion of children seem to develop the disorder after some months of normal development (2), symptoms emerge within the first two years of life in a vast majority of cases (3). Indeed, many of the skills not expressed by older individuals with autism are readily mastered by typically developing infants (4). Early onset would also be consistent with the impressive body of work supporting a genetic basis for the condition (5).

Somewhat paradoxically, our knowledge on autism as it is first expressed remains limited. This is unfortunate for several reasons. First, it makes it more difficult to disentangle the complicated impact that autism has on various lines of development, i.e., to focus on particular processes and sequences of development which go awry. In addition, there is now a strong suggestion that early diagnosis and intervention may significantly improve outcome (6). It is possible that, if a diagnosis of autism could be made very early in life, intervention could begin much sooner. In this paper we review current knowledge of autism in the first months of life, with a focus on diagnostic and developmental issues, and discuss areas important for advancing future research.

CLINICAL PRESENTATION IN INFANCY

Various problems have, until recently, limited our knowledge of autism as it is first expressed in infancy. Of the first 11 patients described by Kanner (1), only one was below age 3 years, and over half were above 4 years of age. Until recently, it was relatively common for the diagnosis to be made around age 4, even when parents were worried for several years before (7). As a result, much of the available research on early development was based on parental retrospection or, less commonly, reviews of home videotapes (8,9). The first longitudinal studies of young children referred for a possible differential diagnosis raised interesting questions about expression of autism in the first years of life (10). As more information on early development of children with autism has become available, it has generally confirmed Kanner's original emphasis on disturbed social development as the major clinical hallmark of the condition. Infants with autism appear to have limited eye contact, social attention and responsiveness (11), are less likely to engage in vocal or motor imitation (12), and may have problems with regulation of arousal and unusual responses to sensory stimuli (12).

Until relatively recently, the most frequent source of information on early development was that provided by retrospective parents' reports, which are complicated to interpret for a number of reasons. It is clear that many parents are seriously concerned about the child's development in the first year of life, and almost 90% are so concerned by age 2 (13). Common concerns include observations of social deviance or oddity, worries that the child may be deaf, and that the child's language fails to progress. Prospective data, for instance derived from high-risk populations, are clearly needed (14), although, when such data are available, it will be important to consider them in light of the rapid pace of change in infancy (i.e., the meaning and significance of particular behaviors may have important developmental correlations). For example, an early preoccupation with visual stimulation (staring at fans) may gradually transform itself into the repetitive stereotyped behaviors more frequently observed between ages 2 and 3 years. Similarly, contextual and situational variables become much more important in evaluating infant behaviors, e.g., the effects of arousal or novelty may impact the behaviors of interests more dramatically.

As noted above, one important complication in the study of infants with autism is the observation that in some cases (about 20%) early development is reported to be generally within normal limits. A clear consensus on the significance of regression in autism has not yet emerged, although Rogers (15) emphasized that subtle delays may precede more obvious skills loss. The advent of prospective studies of high-risk samples of younger siblings of children with autism should help to validate the phenomenon, and establish whether children with regression do or do not con-

stitute a specific subgroup that requires further, but separate, study.

An important approach to overcoming the lack of direct access to infants with autism is retrospective analysis of videotapes. This approach has its limitations, but a series of such studies have now generally confirmed the early emergence of developmental differences in infants later found to have autism. For example, a review of videos of infants up to 6 months suggested that those later diagnosed with autism exhibited less social visual attention, smiled and vocalized less commonly, and engaged in less object exploration (11); interestingly, abnormalities were not observed in terms of repetitive behaviors. Slightly older infants (8 to 12 months of age) have been noted to be less likely to respond to their own names (9,16). However, while failure to respond to name might be an indicator that a 12 month old child would benefit from a further evaluation for a possible diagnosis of autism, passing the "name calling" test does not mean that the child is not at risk of developing the disorder. Osterling et al (17) found that 12 month old infants with autism, compared to infants with mental retardation, differed with respect to orientation to name, while comparison to a nondelayed group showed differences in other areas, including repetitive behaviors, use of gestures, and looking at objects held by people.

By ages 6 to 12 months, differences become more pronounced in the area of communication, including a general lack of orientation towards verbalization in general and to their own name in particular. Infants with autism are less interested in people at a time when most infants begin to more fully integrate object exploration with social interaction and become more clearly intentional. On the other hand, some behaviors frequently reported by parents have not so clearly emerged as areas of difference using videotaped analyses (e.g., difficulties in arousal regulation). Such problems may be less specific to autism; alternatively, the failure to find differences may have more to do with the nature of the available videotaped materials.

Research on the development of toddlers (ages 1 to 3) with autism is greater in quantity than that on infants, and is relevant to work on infancy in that it highlights areas which may serve as precursors of behaviors later observed. In general, the data indicate that differences from typical peers are readily observable to parents and others by at least age 30 months. The behaviors that differentiate children with autism from those with developmental delay include both person-to-person behaviors (anticipatory postures, turn taking, intensity of eye contact) and behaviors which involve some aspects of joint attention (e.g., pointing to materials, following the point of another person or giving objects). In addition, limited affective responses and unusual sensory and motor behaviors are more frequently observed (3). Other areas of difficulty include abnormal play and limited response to speech (18,19). In general, the results (based on both parent report and observation/assessment) indicate that between the second and third birthday higher levels of more "typical" autistic behaviors are present, so that a diagnosis can be made with greater certainty by that time (20).

DIAGNOSTIC ISSUES

Since Kanner's first description of autism (1), the diagnostic concept has undergone modification based on research and clinical work, while retaining important historical and conceptual continuities with Kanner's description (21). Kanner emphasized the centrality of the social difficulties as well as the presence of a set of unusual behaviors he subsumed under the term "insistence of sameness" or "resistance to change". These behaviors included unusual movements and mannerisms as well as problems in dealing with change and novelty. This approach was generally retained in the DSM-IV, where the final definition of autism was based on a large multinational field trial (13) including information on nearly 1000 cases seen at over 20 sites around the world. Of these cases, over 300 were less than 5 year of age (although most were aged between 3 and 5). The final diagnostic approach provided reasonable coverage over the range of syndrome expression in autism and was applicable from early childhood (i.e., around age 3) through adulthood. At the time the DSM-IV was formulated, there was much less concern about the diagnosis of autism in infants and it appeared that the approach derived worked satisfactorily by age 3. Examination of some of the DSM-IV field trial data for children under age 5 did reveal a few items with stronger developmental correlates. In general, such items were discarded since they would not be applicable to the entire range of syndrome expression. For example, attachment to unusual objects has low sensitivity (0.50) but high specificity (0.90), so that, when it is observed, it has high predictive power for autism but only in this younger age group.

The applicability of current (DSM-IV) approaches to the diagnosis of autism in infants and very young children has been questioned on several grounds: for instance, some of the criteria are not clearly applicable to infants, reducing the potential pool of available criterion items (22).

Another approach has focused on the development of screeners and checklists. Such instruments provide an important alternative to the more detailed DSM type diagnostic approach, but entail a somewhat different set of concerns or constraints: for instance, overdiagnosis may be much less of a concern than underdiagnosis; time constraints and issues of efficiency are important as is ease of use and the degree of training required for use (23). Level 1 screeners are intended to identify children likely to have disability from typical peers, while Level 2 screeners focus more specifically on differentiating children at risk for autism from those with other difficulties. The latter are typically intended for more specialized settings. Screeners to date have not focused on children under 1 year.

DIRECTIONS FOR THE FUTURE AND IMPLICATIONS FOR CLINICAL SERVICES

Recent work employing new approaches to the study of social attention has begun to emerge and has important potential for contributing to both screening and early diagnosis. These findings build on the observation that older individuals with autism exhibit highly unusual patterns of attending to people (24). Similar results have now been obtained with toddlers (25). These results are consistent with the general lack of salience of social motivation and interest (26). Another approach has used automatic attention cuing (27) to further clarify differences in early gaze processing. The use of strategies based on these techniques may offer important new approaches to early screening that are more physiologically based.

As diagnostic and screening methods improve, more and more infants will be referred for assessment and treatment. It remains unclear what services will best be employed in treatment. The recent US National Research Council Report (6) has summarized work relevant to somewhat older, i.e. preschool, children, while there is uncertainty about models of service provision that will be most appropriately provided to infants. However, the potential for focusing on remediation in the earliest months of children's lives does provide the possibility for substantially improved outcomes.

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Should cognitive impairment be included in the diagnostic criteria for schizophrenia?

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Neurocognitive impairment is considered a core component of schizophrenia, and is increasingly under investigation as a potential treatment target. On average, cognitive impairment is severe to moderately severe compared to healthy controls, and almost all patients with schizophrenia demonstrate cognitive decrements compared to their expected level if they had not developed the illness. Compared to patients with affective disorders, cognitive impairment in schizophrenia appears earlier, is more severe, and is more independent of clinical symptoms. Although the DSM-IV-TR and ICD-10 descriptions of schizophrenia include several references to cognitive impairment, neither the diagnostic criteria nor the subtypology of schizophrenia include a requirement of cognitive impairment. This paper forwards for consideration a proposal that the diagnostic criteria include a specific criterion of "a level of cognitive functioning suggesting a consistent severe impairment and/or a significant decline from premorbid levels considering the patient's educational, familial, and socioeconomic background". The inclusion of this criterion may increase the "point of rarity" with affective psychoses and may increase clinicians' awareness of cognitive impairment, potentially leading to more accurate prognosis, better treatment outcomes, and a clearer diagnostic signal for genetic and biological studies. Future research will need to address the validity of these possibilities. The reliable determination of cognitive impairment as part of a standard diagnostic evaluation will present challenges to diagnosticians with limited resources or insufficient expertise. Cognitive assessment methods for clinicians, including brief assessments and interview-based assessments, are discussed. Given the current emphasis on the development of cognitive treatments, the evaluation of cognition in schizophrenia is an essential component of mental health education.

Key words: Schizophrenia, neurocognition, cognitive impairment, diagnosis

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Neurocognitive impairment in schizophrenia is clinically relevant and profound. Patients with schizophrenia perform 1½ to 2 standard deviations below healthy controls on various neurocognitive tests. The severity of this impairment is greatest in the domains of memory, attention, working memory, problem solving, processing speed, and social cognition (1). These deficits are present prior to the initiation of antipsychotic treatment (2) and are not caused by psychotic symptoms in patients who are able to complete cognitive testing, which includes the overwhelming majority (3). Many of the various cognitive deficits in schizophrenia have been shown to be associated with functional outcomes such as difficulty with community functioning, difficulty with instrumental and problem-solving skills, reduced success in psychosocial rehabilitation programs (4), and the inability to maintain successful employment (5). Cognitive deficits are better able to explain important functional outcomes such as work performance and independent living (6) than positive or negative symptoms.

The importance of cognitive deficits in schizophrenia goes beyond their severity and relation to functional outcomes. Cognitive deficits are present in some patients with schizophrenia prior to the onset of psychosis and are correlated with measurable brain dysfunction more than any other aspect of the illness. Perhaps most importantly, cognition is increasingly considered as a primary target for treatment (7-10).

Despite the relevance of cognitive impairment to biology, function, and treatment in schizophrenia, it is not included in the DSM-IV-TR or ICD-10 criteria. It is noteworthy, however, that the first sentence of the description of schizophrenia in DSM-IV-TR includes four references to cognitive disturbances: "the characteristic symptoms of schizophrenia involve a range of *cognitive* and emotional dysfunctions that include perception, inferential thinking, language and communication, *behavioral monitoring*, affect, *fluency* and productivity of thought and speech, hedonic capacity, volition and drive, and *attention*" (11). Thus, it is clear that cognition was important to the schizophrenia experts who authored DSM-IV-TR, but a method for including this fundamental aspect of the illness in the diagnostic criteria for schizophrenia has not been determined. This article raises the question of whether cognitive impairment should be included in the diagnostic criteria for schizophrenia, and forwards a proposal for consideration that severe cognitive impairment should be part of the criteria for schizophrenia in DSM-V and ICD-11 (12). In addition, a research agenda for determining the validity and usefulness of including cognitive impairment as part of the criteria for schizophrenia will be discussed.

The following criterion is proposed for consideration in the diagnostic criteria for DSM-V and ICD-11 schizophrenia: "A level of cognitive functioning suggesting a consistent severe impairment and/or a significant decline from premorbid levels considering the patient's educational, familial, and socioeconomic background". If these diagnostic systems focus less on specific criteria in favor of a completely dimen-

sional approach (13), the above recommendation could be easily revised to include cognitive impairment as one of the key dimensions.

This proposal will be considered in the context of several issues, including the evidence for diagnostic differences in cognition, the clinical importance of recognizing cognitive impairment in schizophrenia, and the assessment challenges that would be produced by such a change in the criteria.

DIAGNOSTIC DIFFERENCES IN COGNITION

The ability of a diagnostic refinement to improve the distinction between two entities and thus create an increased non-overlap between them is considered to be a crucial determinant for inclusion (14). Thus, the first question to be considered is whether adding the above definition of cognitive impairment to the criteria for schizophrenia will help define a "point of rarity" with other diagnostic entities, particularly affective disorders.

Diagnostic differences in severity of cognitive impairment

The cognitive experts in the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project concluded that "schizophrenia and schizoaffective disorder share a similar pattern of cognitive impairments, which is distinct from patterns in major depression, bipolar disorder, and Alzheimer's dementia" (10). The group came to this conclusion based upon previous work suggesting that patients with schizophrenia demonstrate a pattern of deficits that is more profound than those in major depression and bipolar disorder, is more stable over the course of illness, and is less related to other symptoms and clinical state. Patients with schizophrenia have more profound impairment on all of the cognitive tests that were measured in each diagnostic group. The deficits of schizophrenia have also been shown to be more severe than those in affective disorders in other comparisons (10,15). A meta-analysis comparing the performances of patients with schizophrenia and bipolar disorder concluded that the cognitive performance of patients with schizophrenia is about 0.5 SD more impaired, even when patient groups are matched on the severity of their clinical symptoms. Deficits in patients with schizophrenia were found to be especially profound on tests of verbal fluency, working memory, executive control, visual memory, mental speed, and verbal memory (15).

Studies of patients with first episode schizophrenia and affective disorder appear to support the meta-analyses completed on more chronic patients. In an epidemiological study of all first admission psychotic disorders in Suffolk County, New York, patients who received a diagnosis of schizophrenia at 24 months follow-up (n=148) were found to have significantly greater cognitive deficits compared to those first episode psychotic patients who were diagnosed with bipolar disorder (n=87) and depression (n=56) 24 months later. Again, the differences between schizophrenia and affective psychoses were particularly profound with regard to memory, executive functions, and mental speed tasks (16). These results support the predictive validity of the new cognitive criterion, and suggest that cognitive information at first episode may aid in the decision of whether an individual's later diagnosis will be in the affective or schizophrenia spectrum.

Diagnostic differences regarding relation of cognitive impairment to clinical state

Although patients with affective psychoses also have cognitive impairment, in these patients cognitive deficits are more strongly associated with clinical symptoms and state-related factors than they are in patients with schizophrenia (17,18). In a study of patients with schizophrenia or bipolar disorder who were assessed when psychotic at baseline and then 8 months later when remitted, only the bipolar patients improved in their cognitive performance (19); the patients with schizophrenia showed the same level of cognitive impairment at follow-up. Similar data have been reported in first episode samples. First episode patients with affective psychoses perform similarly to those with first episode schizophrenia, but patients with non-psychotic affective disorders perform significantly better than both psychotic groups (20). Thus, although the cognitive deficits of affective disorders may be profound in some cases, these deficits are related to clinical symptoms. In contrast, cognitive impairment in patients with schizophrenia has been repeatedly demonstrated to be uncorrelated with psychotic symptoms (3,21-23). This absence of correlation is partially due to the distinct longitudinal differences between psychotic symptoms and cognition: the symptoms of schizophrenia vary over time in almost all patients, leading to low stability coefficients over time (24), while the stability of cognitive deficits in all domains is very high, with test-retest coefficients ranging between 0.70 and 0.85 even in patients tested one year apart following their initial treatment for psychosis (24). Thus, although there are cognitive deficits in affective disorders, they fluctuate in parallel with other symptom changes. In schizophrenia, however, they appear to be the most stable aspect of the disorder.

Prevalence of cognitive impairment in schizophrenia versus other diagnostic entities

If cognitive impairment is to be considered a part of the diagnosis of schizophrenia, it will be important to demonstrate that its prevalence among patients with schizophrenia is higher than in other diagnostic groups. Little comparative work has been done to address this issue. However, almost all patients with schizophrenia may demonstrate some measure of cognitive impairment. In comparing patients with schizophrenia and healthy controls on the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (25), the distribution of a large number of patients with schizophrenia (n=575) is shifted about 2

SDs below the 540 healthy controls from the standardization sample (25,26). Although there is significant overlap between these two distributions, there are very few healthy controls at the lower ends of this distribution and very few schizophrenia patients at the upper ends. Traditional neuropsychological criteria for cognitive impairment would identify those individuals who performed better than one SD below the healthy control mean as "unimpaired" (27-29). By these criteria, about 20% of the patients in this study would be considered to have cognitive functions in the normal range. However, it is possible that many of the individuals at the upper end of this schizophrenia distribution have demonstrated cognitive decline compared to what their cognitive functions would have been if they had never developed the illness.

Although this conjecture can never be proven, it is strongly supported by the differences between patients with schizophrenia and controls regarding the relationship of current cognitive functions to antecedent factors such as parental education and reading scores. In healthy controls, current cognitive ability is clearly predicted by antecedent factors such as maternal education and reading score (30). The healthy controls whose mothers had greater education had higher cognitive functions. Due to the natural variability of cognitive performance among healthy controls, about half of the individuals performed above expectations while half performed below expectations. However, almost all of the patients with schizophrenia in this sample performed below the expectations established by maternal education. Thus, it is likely that the overwhelming majority of patients with schizophrenia have some measure of cognitive deficit compared to what their level of cognitive function would have been if they had never developed the illness. These types of analyses will need to be completed on other diagnostic groups to compare the prevalence of cognitive impairment relative to expectations between patients with schizophrenia and other diagnoses.

Early cognitive decline in schizophrenia compared to other disorders

Although most patients with schizophrenia show some cognitive decline based upon what would have been predicted by antecedent factors, patients with schizophrenia, on average, start out at a lower baseline prior to the onset of the illness. Children who will eventually develop schizophrenia demonstrate cognitive impairment compared to healthy controls and children who later develop affective disorders (31,32). However, individuals who will eventually develop schizophrenia also demonstrate decline on scholastic measures between early childhood and late adolescence (32). The presence of cognitive deficits or cognitive decline during adolescence has been found to predict the conversion to schizophrenia in a variety of samples (32-39). Thus, patients with schizophrenia appear to begin life with cognitive performance that is slightly worse than their peers. As childhood progresses, cognitive performance tends to worsen in these children. By the time psychosis develops in late adolescence or early adulthood, they perform substantially worse than their healthy peers. Although patients with affective disorders also demonstrate cognitive impairment in adulthood, it appears as though these individuals do not show as much impairment prior to the adult onset of their disorders (31).

The literature reviewed above supports the notion that the severity and longitudinal course of cognitive impairment in schizophrenia differ substantially from that found in patients with affective disorders. Yet it remains undetermined whether including a criterion of cognitive impairment or cognitive decline from healthy premorbid levels in the diagnosis of schizophrenia will help define a "point of rarity" with affective psychoses. If the recommended change in the diagnostic criteria for DSM and ICD is implemented, the point of rarity with other psychoses may increase. It is possible that some patients diagnosed with schizophrenia who have little or no cognitive impairment have treatment responses and courses of illness that are more consistent with a diagnosis of affective disorder. If this is the case, it will benefit clinicians to change their expectations based upon this revised diagnosis. Similarly, some patients diagnosed with affective disorders and severe cognitive impairment may follow a longitudinal course and treatment response that is more characteristic of typical patients with schizophrenia. It will be important for research studies and analyses of existing data bases to address the question of whether these diagnostic changes are validated by differences in course and treatment outcome. In addition, these studies can address whether patients whose diagnosis changes based upon the new criteria are more likely to have genetic and other biological indicators consistent with the new diagnosis.

THE CLINICAL IMPORTANCE OF RECOGNIZING COGNITIVE IMPAIRMENT

Even if the inclusion of a definition of "cognitive impairment" in the criteria for schizophrenia does not increase the point of rarity between schizophrenia and other psychotic disorders, it should be considered whether such a change would be able to "provide useful information not contained in the definition of the disorder that helps in decisions about management and treatment" (14). Psychiatrists rarely consider cognitive function in their evaluation of patients with schizophrenia. Including cognitive impairment in the criteria for schizophrenia may increase psychiatrists' attention toward a core component of the disorder that is the largest determinant of long-term functioning (7). Since cognitive impairment is also rarely considered as an important treatment target, its inclusion in the diagnosis may help to educate clinicians about the importance of cognition in their treatment options. Furthermore, representatives from the US Food and Drug Administration have indicated that the recognition of cognitive impairment in the diagnostic nomenclature would be an important step in ap-

proving a drug for a cognitive improvement indication for patients with schizophrenia (10). A large number of pharmaceutical companies and government agencies are involved in intense work to develop compounds that may improve cognition with schizophrenia. If successful, these compounds have the potential to alter the treatment of schizophrenia. However, if clinicians are not trained to recognize cognitive improvement, a potential great benefit to patients would be missed. Inclusion of cognitive impairment in the diagnostic criteria for schizophrenia may force educational systems to teach clinicians how to recognize cognitive impairment and improvement and direct treatments accordingly.

CHALLENGES IN ASSESSING COGNITION IN SCHIZOPHRENIA

The implementation of this change in diagnostic criteria will present two challenges for clinicians to collect relevant data: using reliable assessment methods for the determination of current cognitive deficits, and the collection of historical information to establish the context for the current cognitive abilities.

Cognitive assessment methods

Although formal cognitive testing is sensitive to the cognitive impairments found in schizophrenia, the resources required to complete full neuropsychological evaluations are often prohibitive. However, resource requirements have not kept cognitive impairment out of the diagnostic criteria for other disorders of cognition, such as Alzheimer's dementia and attention-deficit/hyperactivity disorder (ADHD), which do not require formal cognitive testing. Brief assessment may help reduce the burden of collecting cognitive performance data, but psychiatrists frequently are pressed to find enough time even to complete standard clinical evaluations. If cognitive paradigms were developed that were able definitively to separate diagnostic entities, a case could be made that this testing is essential to patient diagnosis and treatment planning. Unfortunately, however, as discussed above, we are not yet at this stage. Thus, the methods for establishing the presence of cognitive impairment in schizophrenia for diagnostic purposes will need to be established. A few possible methods are outlined below.

Brief assessment

Almost all of the variance in cognitive composite scores can be accounted for by a small number of tests (3), and short batteries may be as effective in assessing general cognitive deficits as lengthy ones (36,37). Thus, clinicians may be able to develop the capacity to assess cognitive impairment in schizophrenia without overwhelming time requirements. However, education and training in the use of standardized cognitive tests for clinicians will be essential to assure that the assessment procedures are completed in a manner that maintains test standardization. This aspect of training is usually included in the curriculum of clinical psychologists and neuropsychologists, but is rarely a component of education for physicians, social workers and nurses. A program for training in cognitive testing and supervision of data collection will be essential steps to increase the capacity for clinicians to assess the cognitive impairments of schizophrenia, and some psychological tests require supervision by a licensed psychologist. It will take time to work cognitive assessment training into the traditional education of psychiatrists and other non-psychologists. This training does not need to be limited to formal neuropsychological tests, and may be better aimed toward the assessment of patients' ability on practical cognitive tasks, which may have stronger direct correlations with outcome (40).

Interview-based assessments of cognition

Although the unavailability of trained testers may prohibit testing in many clinical environments, recent methodological advances have included the assessment of cognition in patients with schizophrenia with interview-based measures. Similar to ADHD assessment methods, which do not involve formal testing, these measures involve a series of questions directed toward the patient with schizophrenia and his or her relatives or caregivers. These questions address whether people with schizophrenia have cognitive deficits that impair fundamental aspects of their daily lives. For instance, some of the questions ask whether patients have difficulty remembering names, concentrating well enough to read a newspaper or book, being able to follow group conversations, and handling changes in daily routines (41,42). Interview-based assessments of cognition have historically been unreliable and have demonstrated low correlations with cognitive performance. However, these measures have generally relied upon the reports from patients and their treating clinicians, which have been unreliable and potentially invalid (43-46). A methodology that assesses cognition with interviews of patients and caregivers, such as relatives or caseworkers, appears to have improved reliability and validity. For example, the Schizophrenia Cognition Rating Scale (SCoRS) has been found to have excellent reliability, and substantial correlations with cognitive performance and functional outcomes (41,47). One of the potential weaknesses of this methodology, however, is that reports from patients have been found to have reduced reliability if patients are the only source of information. This weakness is particularly problematic in the assessment of patients with schizophrenia, since many patients do not have an available informant who can provide information about the patient's cognitive deficits and how these deficits affect the patient's daily behavior. For example, in a study that validated the MATRICS Consensus Cognitive Battery (MCCB), the test-retest reliability coefficient (ICC) for the SCoRS collected over the course of one month was high when ratings were based upon a patient and informant as a source of information (ICC=0.82) (47). However, when patients were the only source of information, the reliability was low (ICC=0.60).

A more extensive series of questions, as found in the CGI-CoGS (42), appears to improve the reliability of patient reports up to ICC=0.80, but patients describe these longer interviews, which require up to 45 minutes per interview, as burdensome (47). A shorter, less burdensome instrument that would not require an informant and could be completed on almost all patients would be ideal, although is not currently available. Future studies should focus on this methodology, and must also determine whether interview-based assessments and brief assessments of cognition can contribute to the diagnostic separation between schizophrenia and affective psychoses.

Collection of historical information

The criterion for cognitive impairment will frequently depend upon an evaluation of a patient's longitudinal course of cognitive functioning in the context of his or her personal background, requiring clinicians to gather substantial amounts of historical information. A statement that a patient's background must be assessed was included to avoid over-diagnosing schizophrenia in individuals whose environments deprive them of the opportunity to develop cognitive skills. People with very low levels of education and socioeconomic disadvantage may perform very poorly on cognitive tests independent of a psychiatric diagnosis. Thus, the evaluation of a patient's cognitive impairment must place the cognitive data in the context of his or her background and educational history (26). On the other end of the spectrum, some patients who had demonstrated high levels of cognitive skills early in their lives may have cognitive performance that is in the "normal range" despite significant decline from high premorbid levels (30). How will diagnosticians determine how historical and demographic factors interact with a patient's illness to result in his or her current cognitive levels?

It will be important for diagnosticians to understand the average course of cognitive performance in someone with schizophrenia. During childhood and adolescence, patients who will eventually develop schizophrenia perform about 0.5 SDs below their peers who will not develop schizophrenia (31,32,34). Although there have not been sufficient data to make a definitive estimate, immediately prior to the onset of psychosis patients who are about to develop schizophrenia demonstrate cognitive performance that is about one SD below healthy controls (33,39). Diagnosticians must determine whether there has been a decline in cognitive functions from expected cognitive levels based upon antecedent factors such as parental education, early school performance, and reading level. They will also need to collect as complete a history as possible on the cognitive performance of each patient, including how the patient's current cognitive performance compares to early school performance and any academic, intelligence or cognitive testing that was performed during premorbid and prodromal periods. Further, a patient's level of cognitive performance should be compared to other members of the patient's family and sociocultural background, if available. In many cases, testing will benefit this assessment. In other cases, the amount of cognitive impairment in a patient will be clearly obvious and in direct contrast to early cognitive competence.

Longitudinal cognitive information is also important to distinguish the more transient cognitive impairment of affective disorders from the more stable cognitive impairment in schizophrenia (10,17,18). In contrast to affective disorders, the cognitive deficits in schizophrenia are expected to be present throughout non-acute periods of illness. Although this longitudinal assessment may help to differentiate schizophrenia and affective psychoses, it may also result in delays in definitive diagnoses in cases where cognitive impairment is only known to be present in the context of symptom exacerbation.

Although this historical and longitudinal data collection may initially appear to add burden, if indeed the level and course of cognitive deficit is crucial not only to diagnosis but to prognosis and treatment planning, it is likely that this "front-loading" of clinical care may eventually reduce clinical burden in the form of improved treatment response and long-term functioning.

CONCLUSION

In sum, this paper has recommended for consideration that a criterion for consistent severe cognitive impairment should be added to the DSM and ICD diagnostic criteria for schizophrenia. There are several challenges that must be met before this suggestion will be accepted. Research is needed to determine: if such a criterion will increase the point of rarity between schizophrenia and other diagnostic entities; if clinicians are able to evaluate cognition reliably with brief formal assessment instruments or interview-based methods; and if the inclusion of such a criterion will improve the value of the diagnosis of schizophrenia for prognosis, treatment outcomes, and the identification of its biological and genetic determinants.

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cluding the Brief Assessment of Cognition in Schizophrenia (BACS), and the BACS symbol coding subtest of the MATRICS Consensus Cognitive Battery (MCCB), some of which are discussed in this paper. Currently, there is no fee charged for the use of the Schizophrenia Cognition Rating Scale (SCoRS), copyrighted by Duke University, discussed in this paper; however, in the future a fee may be charged. The author has devoted much of his career to research on cognitive impairment in schizophrenia. Thus, if the suggestions of this article are carried out, he stands potentially to benefit academically and financially.

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Cognitive deficits in schizophrenia: short-term and long-term

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Richard Keefe provides a compelling case for inclusion of cognitive impairment in the diagnostic criteria for schizophrenia. From both a clinical and pathophysiological perspective, there is little doubt that cognitive deficits are a core component of the disease (1). From a nosological perspective (2), we agree that inclusion of a cognitive criterion may improve both diagnostic validity and clinical utility relative to current standards. However, we also suggest that such improvements must be balanced with an awareness of long-term consequences of such a shift.

Perhaps the most persuasive argument for inclusion is the well-replicated finding of strong correlation of cognitive abilities with functional outcomes (3). Of greatest diagnostic significance is the fact that this relationship holds true not only concurrently, but also longitudinally. For example, in a study of first-episode patients at the Zucker Hillside Hospital, global cognitive ability was the only baseline variable that was able to predict both social/vocational functioning *and* symptom remission over the subsequent five years (4). Only a small percentage (14%) of patients successfully attained a two-year period of recovery in both domains, and global cognitive performance was by far the strongest predictor ($p<0.0001$). Even in the prodromal phase, before the onset of frank psychosis, cognitive deficits significantly predict subsequent diagnosis (5). In defining diagnostic validity, Goodwin and Guze stated that "diagnosis is prognosis" (6); applied to schizophrenia, Robins and Guze declared that "good prognosis schizophrenia is not mild schizophrenia, but a different illness" (7). Assuming this model of schizophrenia is correct, a cognitive impairment requirement would enhance the diagnostic validity of the construct.

As a matter of clinical utility, placement of cognitive deficit in DSM-V would begin a much-needed process of clinical education and updating of standard psychiatric evaluation practices. The significant relationship between cognitive deficits in schizophrenia and public sector costs (8) contributes strong economic incentives towards development of treatments for cognitive deficits. In the US, governmental agencies such as the Food and Drug Administration and the National Institute of Mental Health have thrown their support behind the development of novel pharmaceutical approaches targeting cognitive enhancement as a primary endpoint (9,10). In response to this, industry is developing a range of putatively nootropic molecules, based on a wide variety of mechanisms (11). Thus, in the not-too-distant future, clinicians will need formal mechanisms by which to designate patients for such treatment, and to monitor its progress.

For several reasons, however, the immediate impact of adding a cognitive criterion may be limited, unless it initiates a more comprehensive re-evaluation of diagnostic, clinical, and research practices. First, given the strong linkage between cognitive deficits and functional impairment, it is probable that the current "B" criterion in DSM-IV captures much of the territory to be identified by the proposed cognitive impairment criterion. Second, while the cognitive deficits in schizophrenia are profound (1-2 SD below normal), the cognitive differences between schizophrenia and affective disorders are subtle (0.5 SD) and state-related, thus making it unlikely that the "point of rarity" between the two classes of illness will be substantially enhanced.

Moreover, the often insidious progress of cognitive decline, which can begin long before the manifest symptomatology, complicates the proposed diagnosis of "significant decline from premorbid levels". As noted by Keefe, it is possible for deficits to begin in early childhood (~0.5 SD) and slowly progress through the prodromal period in adolescence (an additional ~0.5 SD), with an additional precipitous decline (also ~0.5 SD) around the onset of psychosis. We have observed this modal progression in two independent studies. In a follow-back study of school records obtained from first episode schizophrenia patients, a one grade-level deficit was observed at the beginning of primary school, incrementally increasing to a two grade-level deficit by high school (12). Separately, we found that patients prodromal for schizophrenia-spectrum psychosis displayed cognitive impairments of about 1 SD on average, about half of which appeared to represent decline from earlier levels (5).

Taken together, the evidence above (and that reviewed by Keefe) suggests that cognitive deficits in schizophrenia represent a dimensional phenomenon rather than an absolute threshold. Such a conception is also consistent with recent genetic findings, which strongly point to a polygenic model in which multiple genes of small effect individually contribute to illness susceptibility via multiple pathophysiological processes (13). For example, recent evidence suggests that a variant in DTNBP1 (dysbindin), which slightly elevates risk for schizophrenia, is also associated with severity of negative symptoms and generalized cognitive deficits (14-16). At the same time, variants in DISC1 are associated with persecutory delusions and specific deficits in working memory (17,18).

Therefore, we would suggest that Keefe's proposal be considered in the context of recent suggestions for a dimensional approach to diagnostic systems (19) and clinical practice (20). Development of a brief assessment of degree of cognitive impairment suitable for clinical application, with appropriate adjustments for age, socio-economic status, and prior history, should be a priority for further research. A dimensional approach may also mitigate any

medico-legal and ethical complications which could ensue from a criterion-based categorization of cognitive impairment. In a categorical system, a diagnostic finding of "cognitive impairment" could be misinterpreted by courts or other legal entities, possibly leading to confusion with issues of competence or a paradoxical denial of certain educational or vocational opportunities. Overall, we feel that Keefe's proposal is likely to lead to improved diagnosis, prognosis, and treatment even in the context of current diagnostic standards. In the longer term, current research may lead to more fundamental changes in our diagnostic system, but the potential for unintended consequences must be clearly recognized.

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Cognition and the differential diagnosis of schizophrenia

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I agree with Richard Keefe in terms of all of the evidence he presents. I firmly believe that cognitive impairments are a cardinal symptom of the schizophrenic illness, similar to Bleuler's conception of fundamental symptoms. I also agree that more work may be required before cognitive impairments may be added to the diagnostic criteria for schizophrenia. Keefe does an excellent job in discussing the issues associated with assessment. However, we are also trying to talk about improvement of diagnostic criteria, with a goal of identifying more homogenous groups that clearly are separable (i.e., having a clear point of rarity) from other groups. One of the implications of acceptance of a Bleulerian monothetic taxonomy is that the assumption is: "all patients with schizophrenia have cognitive impairments and patients with cognitive impairments therefore have schizophrenia". This may not be a supportable statement with the evidence currently available in the field. In this commentary, I will focus strictly on the implications for classification accuracy of adding cognitive impairments to the diagnostic criteria.

Do the current diagnostic criteria already capture a group with a 100% prevalence of cognitive impairments and, if so, what would be added by including cognition as a diagnostic criterion? As clearly shown by Keefe, the current diagnostic criteria already capture a group of patients who all have the cognitive impairments described. It is not clear if additional diagnostic information or precision would be gained by requiring the assessment of a feature of the illness that is already present in all cases. In fact, this requirement has the potential of *decreasing* the reliability (and hence limiting the potential validity) of the diagnostic process. Requiring assessment of cognitive impairment would clearly raise awareness and have a positive impact, but might reduce diagnostic reliability from its current level. The trade-off between these two outcomes is a matter for further consideration.

How much would diagnostic sensitivity and specificity increase if cognitive impairments were added? This is also a particularly important question. Validity and specificity of diagnoses include at least two important attributes: the utili-

ty of the elements of the diagnostic criteria for identifying features of illness that separate from healthy people and the utility of the elements of the diagnostic criteria for separation from other illnesses.

The substantial separation from healthy controls in terms of cognitive impairments is shown quite clearly by Keefe. If the group means on a variable of interest are separated from each other by 2 SD, that implies that the lower functioning distribution and the higher functioning distribution will overlap at a level of 17%, which is quite an acceptable level of misclassification. This problem is addressed in detail by Zakzanis et al (1): they use a criterion that a deviation from normal performance associated with a similar sample overlap should provide suitable evidence of a true "syndromal" difference. By these criteria, the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) data cited by Keefe provide clear evidence that neuropsychological performance is a suitable syndrome indicator when patients are compared to healthy control samples.

The smaller differences in neuropsychological performance between different patient samples are a much more challenging issue. To examine this directly, we will consider the data from the Suffolk County Mental Health project (2) reviewed by Keefe. In that dataset, subjects with schizophrenia demonstrated a general deficit score (measuring global impairments in cognitive functioning) that averaged 1.4 (SD=0.9), while bipolar patients had an average general deficit score of 0.8 (SD=0.8). This means that the effect size for the overall difference in cognitive impairments between the group means was 0.66 [(1.4-0.8)/(0.9)]. This difference is hugely statistically significant: $p<0.0001$. At the same time, this means that about 33% of the cases with bipolar disorder are scoring within 2 SD of the schizophrenia mean and vice versa, leading to substantial overlap in samples and likelihood of misclassification of cases on the basis of neuropsychological performance alone.

It is entirely true that patients with mood disorder generally show more impairment when experiencing symptoms than when euthymic. However, there are several issues that make this situation more complicated. First, in order to perform a true differential diagnosis of schizophrenia versus mood disorder, the mood disordered patient would have to be assessed while euthymic. This may reduce the validity of assessment, because euthymic periods may be more rare in people with bipolar disorder than previously thought. Follow-up studies have suggested that people with bipolar disorder spend as much as 50% of the time *between* identified episodes experiencing symptoms (3-5). Therefore, although asymptomatic periods are associated with reduced neuropsychological impairment, these periods may be uncommon, and the modal mood state of someone with bipolar disorder may be not euthymic.

Second, recent data have shown that disability in bipolar disorder is much more prevalent and severe than clinical lore would suggest. For instance, functional recovery rates (defined only as return to premorbid functioning) in first episode cases with bipolar disorder who experienced a period of symptomatic remission are only about 40% over a three year follow-up (6), compared to less than 20% in similar patients with schizophrenia (7). This would suggest that disability is present in most cases with bipolar disorder as well as in cases with schizophrenia. For instance, the rate of marriage in people with bipolar disorder is only about 25% (8); independent living is impaired in 20-60% of cases across studies (9); unemployment rates are reported to be in the vicinity of 60% (10). These figures are slightly better than those seen in schizophrenia (11), but reflect clear functional disability. However, there have been no studies that directly measured the correlation between cognitive impairments and functional deficits.

In conclusion, cognitive impairments are present in essentially all patients with schizophrenia when diagnosed with the current criteria. These impairments clearly separate from those of healthy people, but there is considerable overlap in distributions with people with other conditions, particularly bipolar disorder. Bipolar disorder is also marked by the same aspects of disability and cognitive impairment as seen in schizophrenia, but the level of sophistication and detail in assessment that has been applied to people with schizophrenia is lacking in the study of bipolar disorder.

The only argument that I can see against including cognitive impairment as an element of the diagnostic criteria for schizophrenia is that it is already captured by the current criteria. Adding cognitive impairment might reduce the reliability of assessment by adding false negatives, but this still might be acceptable if the overall result is an increased awareness of cognitive deficits. It is also likely that cognitive impairment is as viable a diagnostic criterion for bipolar disorder as it is for schizophrenia, but the state of the research on bipolar disorder is much less well developed. Further research on the functional relevance of cognitive impairment across psychiatric conditions is clearly needed.

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Is cognitive impairment in schizophrenia ready for diagnostic prime time?

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The question of whether cognitive impairment should become one of the formal diagnostic criteria for schizophrenia reflects the wide acceptance that cognitive performance provides an important signal about the integrity of cortical function in schizophrenia. Further, the fact that cognitive impairment has a powerful relationship to functional disability suggests that the inclusion of a cognitive impairment criterion might focus clinical attention on disability reduction, the major therapeutic challenge of the illness (1). As noted by Richard Keefe, a cognition criterion might also serve to re-draw diagnostic boundaries, better establishing a "point of rarity" between schizophrenia and bipolar disorder. Such a redefinition could result in more homogeneous clinical phenotypes, possibly facilitating both genetic and treatment research. However, there are practical, statistical, and theoretical issues to consider before taking such a dramatic step.

In order for a cognitive impairment criterion to serve the purpose of clinical heterogeneity reduction, it would need to be mandatory: a patient could not get the diagnosis of schizophrenia without meeting this criterion. Therefore, validated assessment approaches designed to provide the data needed to make a yes or no decision about the presence of cognitive impairment would have to be available, and would need to be applicable across clinical settings, countries, and cultures. No such assessment tool exists, and given the work that would be involved in developing one, it is reasonable to assume that such a tool will not become available in the foreseeable future. Thus, in practical terms, it seems nearly certain that the height of the instrument development hurdle will effectively eliminate the possibility of a cognitive impairment criterion being introduced into any international diagnostic classification system in the near term.

The question remains, however, whether a cognitive criterion would help establish a useful "point of rarity" among ill patients. What is the evidence that cognitive impairment is sensitive and specific when comparing patients with DSM-IV schizophrenia to healthy controls? Consider the data on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) published by Wilk et al (2), which included 575 schizophrenia patients who were compared to the RBANS healthy control standardization sample. The patient mean standard score of 70 fell two full standard deviations (SD) below normal, a degree of impairment that exceeds the expectations established by several meta-analyses (3,4). In this unusually impaired group, if one uses a cut-off score of 85 (1 SD below normal) to define impairment, this would correctly identify 80% of patients as impaired, but would falsely diagnose 16% of controls as having schizophrenia (using the cognition criterion alone). Using a 2 SD cut score, the false positive diagnosis rate drops to 2%, but the true positive rate drops to 50% – fully half the patients fail to meet the criterion. The risk of false positives in this context is relatively unimportant: a healthy person has no other symptoms of schizophrenia, so a false positive on the cognitive criterion is of no practical consequence. The false negative problem, however, has important implications: relative to healthy controls, the 1 SD cut-off misses 20% of patients, whereas the 2 SD cut-off misses 50%. One could argue that these are not "false negatives", but represent patients with a form of illness that does not include marked cognitive impairment – they do not have the newly defined form of schizophrenia. Thus, the use of a cognitive impairment criterion results in a dramatic redrawing of diagnostic boundaries, one that might require the reclassification of 20-50% of patients with DSM-IV schizophrenia depending on the cut-off employed.

The problem becomes even more pronounced in the separation of bipolar patients from schizophrenia patients. For ease of argument, assume bipolar patients are "half" as impaired as patients with schizophrenia (there is RBANS data documenting that this is a reasonable estimate, see 5). The use of a 1 SD cut-off would result in the diagnosis of a very sizeable portion of bipolar patients as having schizophrenia, while the use of a 2 SD cut-off would still capture a significant minority of bipolar patients, with the cost of a false negative rate of 50% for DSM-IV schizophrenia patients. In short, rather than defining clear points of rarity, the use of a cognition criterion would significantly redraw the diagnostic map.

Given these concerns, what would be gained with a cognition criterion? One argument is that it would highlight cognitive impairments as a treatment target for clinicians and encourage drug development. While the cognition criterion

could foster increased clinical awareness, it cannot alter clinical care for the foreseeable future, given lack of any available treatments. Further, there is substantial industry interest in the development of cognitive enhancers, as the market for such compounds is enormous: nearly every patient with schizophrenia. Might the cognition criterion result in more homogeneous clinical phenotypes, thereby enhancing research on biological pathways and genetic risk factors for schizophrenia? This is a potential benefit that could be investigated in existing data sets where cognitive measures have been obtained along with other biological measures or treatments. The question would be whether the "schizophrenia" signal is enhanced when samples are limited to subjects demonstrating different degrees of cognitive impairment. Such supportive evidence would be needed in order to justify the effort required to overcome the measurement hurdles and implementation challenges of adding a cognitive impairment criterion to the DSM.

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Reflections on the inclusion of cognitive impairment in the diagnostic criteria for schizophrenia

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Richard Keefe outlines the reasons for including cognitive impairment as one of the criteria for the diagnosis of schizophrenia in future diagnostic manuals (DSM-V and ICD-11). First, he convincingly argues that cognitive impairment has a major impact on the lives of *almost all* individuals who meet DSM-IV and ICD-10 criteria for schizophrenia. He reminds the reader that even patients who obtain normal or almost normal psychometric scores might still be cognitively impaired, compared to their potential as predicted by their parents' intelligence and their socioeconomic context. Than he presents the advantages and stumbling blocks associated with adding cognitive impairment to future diagnostic criteria, and suggests solutions.

The first advantage Keefe identifies is help in defining a point of rarity between schizophrenia and other diagnostic entities, to reduce diagnostic overlap. The second advantage is the encouragement of the clinical, academic, regulatory, and pharmaceutical communities to develop treatments targeting cognitive impairment. The main impediment he identifies is lack of assessment instruments which on the one hand are brief and simple and on the other are sufficiently detailed and comprehensive to capture developmental and current information in a valid and reliable manner. He voices the concern that non-psychologist clinicians, who are not sensitized and trained in the assessment of cognition, might be unwilling to carve out the necessary time from the already-limited patient-clinician encounter. Since, even for the most comprehensive scales, much of the variance is accounted for by only a few items, the solution he advocates is the use of brief scales which can be quickly learned and applied by clinicians.

Keefe is correct to point out that cognitive impairment in schizophrenia differs from cognitive impairment in mood disorders, which is the main overlapping diagnostic group, in terms of prevalence, severity and course. However, the differences are neither large nor consistent, and it is unclear by how much the inclusion of cognitive impairment as a criterion would reduce the diagnostic overlap. Furthermore, cognitive impairment is present in almost all psychiatric diagnostic categories, some of which overlap with schizophrenia in manifestations other than cognitive impairment (e.g., severe personality disorders, drug abuse, obsessive-compulsive disorder). Moreover, there is considerable overlap between schizophrenia with severe cognitive impairment and mild mental retardation with unusual ideation, and the inclusion of cognitive impairment as a criterion for schizophrenia might only enhance the overlap.

There is little doubt that the inclusion of cognitive impairment as a diagnostic criterion would increase awareness and focus on it the attention of all stakeholders. Whether this would hasten the development of treatments targeting cognitive impairment is less certain. Increased awareness might help divert budgets and other resources to education and rehabilitation programs focused on cognitive enchantment. Since education and rehabilitation activities have a incremental and cumulative effect, more budgets and resources might benefit cognition. However, the development of a pharmacological intervention targeting cognitive impairment is an endeavor waiting for a conceptual breakthrough, rather than the incremental assigning of

more funds which would result from increased awareness.

Cognitive impairment in schizophrenia may have more in common with cognitive impairment occurring in most other mental disorders than with schizophrenic psychosis *per se* (1,2). Cognitive attributes and predisposition to psychosis are partially inherited traits in schizophrenia patients. However, whether these traits co-segregate and follow common pathophysiologic pathways is far from certain. The lack of correlation between the severity of cognitive impairment and psychosis, and the fact that cognitive impairment appears before and persists after psychosis, are consistent with the idea that they are independent. Conceptually, therefore, it would take the same breakthrough to treat cognitive impairment in schizophrenia as it would take to improve cognitive functioning in any individuals, mentally ill or not, whose performance is 1.5 to 2.5 SDs below norms or expected performance. This major scientific endeavor could hardly benefit from the inclusion of cognitive impairment as a criterion for schizophrenia.

I would not be too concerned with the willingness of those who treat schizophrenia (psychiatrists, nurses, social workers, and others) to learn and devote time to the assessment of cognition. The relentless efforts of researchers like Keefe and others over the past 15 years have already sensitized clinicians to the issue of cognitive impairment in schizophrenia patients. Once they are convinced of the benefit of diagnosing it and the potential of treating it, they are likely to adjust their priorities and fit cognitive assessment into the clinical encounter.

In spite of the above reservations, I hope that Richard Keefe's suggestion to include cognitive impairment as a criterion for schizophrenia is accepted. A diagnostic classification that leaves out an aspect which is so prevalent among the affected individuals and so central to their daily life would be deficient.

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Domains of dysfunction in schizophrenia: implications for diagnosis

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Psychiatry suffers from a paucity of molecular and cellular markers for its diseases. We do not have "measures" for diagnosis (like a hematocrit or a blood glucose) and therefore lack biological leads to pathophysiology of illness, critical for modern disease management. While knowledge of basic brain mechanisms is still incomplete, expectations still exist for a molecular and cellular pathophysiology in our diseases. Until we meet success with this goal, we have to be clever and insightful in using existing phenomenology and pharmacology to substantiate accurate diagnoses. From this perspective, the proposal raised by Richard Keefe, to include cognitive dysfunction in the diagnostic criteria for schizophrenia, is supported by our current knowledge and formulation of the illness. In addition to his argument that cognition adds a "point of rarity" for schizophrenia diagnoses, it is also true that amending the diagnosis to include cognitive dysfunction improves its accuracy as a base for proposing pathophysiology and new treatment.

It is useful to consider what we can do to structure our clinical data to advantage progress in the molecular understanding of schizophrenia. Hyman and Fenton suggest that we can use "a clinical target, a well-defined risk state, illness or symptom complex for which treatment is meant… that can be monitored to test whether the drugs are effective" (1). Based on leadership from the National Institute of Mental Health, the field began doing exactly this, looking carefully at schizophrenia phenomenology to find distinctions between symptomatic domains. The analysis of large clinical data sets showed the correlation of groups of related symptom types across clinical course, organized into "domains" of dysfunction, specifically cognition, psychosis, negative symptoms and affect. The independence of these domains with respect to available treatments has become clear, especially for psychosis and cognition. Antipsychotics improve psychosis but do not treat cognitive dysfunction; the pharmacology of cognitive dysfunction is based on animal studies and supports the activity of drugs very different from antipsychotics, such as dopamine agonists, cholinergic drugs (nicotinic and muscarinic), and glutamatergic drugs (2). Thus, distinguishing between the process of psychosis and the development of cognitive dysfunction could bring a new clarity to pathophysiology.

What are the domains of dysfunction in schizophrenia? The most frequently mentioned domains are positive symptoms (hallucinations, delusions and thought disorder), cognitive dysfunction (attention, working memory and episodic memory functions and processing speed), and negative symptoms (paucity of thought, lack of affect). These domains are independent with respect to clinical course and treatment. Whether they are independently associated with genetic or environmental risk factors has not been determined. Whether they are linked or independent with respect to pathophysiology remains a question.

What is their relevance to pathophysiology? Whether these domains are en-

tirely independent disease constructs or are related to each other, their pathophysiologies must be largely separable even if linked. Models of pathophysiology can best advance thinking if they are based on actual symptoms within a diagnosis. Thus, the disease definitions of schizophrenia and the domain constructs need to be related and valid. An attempt to develop a disease construct for "psychosis and cognitive dysfunction" may generate more successful hypotheses than a construct for "schizophrenia" and may lead to pathophysiologic models with greater disease validity.

What is their relevance to treatment? It is widely accepted that treatments for psychosis and cognitive dysfunction will not be the same set of drugs. For psychosis, we have groups of well-validated antipsychotic drugs, the dopamine antagonists (direct and indirect). These drugs do not correct cognitive dysfunction, but effective cognitive enhancers have not yet been discovered. The concept of domain treatment will not only individualize treatment but will serve to optimize symptomatic treatments for each domain. Clinicians will need to distinguish the target symptoms for antipsychotic drugs and for cognition enhancers. In this situation, it would be not only reasonable but necessary that characteristics of cognitive dysfunction be part of the disease definition.

From a practical perspective, how can cognitive dysfunction be assessed? It is important to consider whether and how treating physicians can gather and use cognition information. While at present "cognition dysfunction" comprises only vague characteristics of illness, there is no need for precise neuropsychological measurements. But, once we define the symptom domain and develop cognitive symptoms for treatment, then the situation will change. We will need the methodologies to assess and monitor cognitive symptoms. Therefore, there will be a critical need for practical approaches to cognition assessment, not only for diagnosis, but also for disease characterization and management. We will need cognition algorithms, developed by experts, for use by clinicians in making diagnoses and in measuring treatment outcomes. Since clinicians will be monitoring cognitive change once we have successful treatments, algorithms should be treatment-sensitive.

Based on these considerations, should cognitive dysfunction be included in the diagnosis of schizophrenia? Given that cognitive dysfunction is now a recognized, relevant and nearly ubiquitous aspect of schizophrenia that will undoubtedly be important for disease understanding and for treatment success, the question almost answers itself. Moreover, this opinion reflects advances in our understanding of the illness that clinical assessment and research has brought to modern psychosis diagnosis. Keefe's proposal that cognitive dysfunction be a criterion for schizophrenia is reasonable and should be implemented. It will remain for experts in the area to develop algorithms which are both simple and effective so that clinicians can implement the new perspective.

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The assessment of cognitive impairment would be a relevant addition to the criteria for diagnosing schizophrenia

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The paper by Keefe reviews in a comprehensive and balanced way the findings on cognitive disturbances in schizophrenia. These disturbances are prevalent years before the psychotic breakdown, are only partially associated with acute psychotic symptoms, are more or less stable or can even increase over the longitudinal course of schizophrenia. In cross-sectional assessments, they are closely associated with social functioning and are more pronounced in patients diagnosed with schizophrenia than in those with (non-psychotic) affective disorders. All these are good reasons for Keefe to suggest that cognitive impairment should be included in the diagnostic criteria for schizophrenia. I fully agree with this suggestion.

The inclusion of cognitive impairment would correspond very well to the traditional concept of dementia praecox/schizophrenia as proposed by Kraepelin and Bleuler. Kraepelin's term "dementia praecox" emphasized the importance of cognitive deterioration, although it alluded also to the change of personality in terms of negative symptoms. Similarly, Bleuler regarded cognitive alterations and negative symptoms as core symptoms of schizophrenia, while delusions and hallucinations were considered accessory symptoms. The predominance of positive symptoms in the concept of schizophrenia was established later on, especially with Schneider's concept of first-rank symptoms, and endorsed by our modern diagnostic systems, the DSM-IV and the ICD-10. The interest in the core symptoms of schizophrenia, including cognitive impairment, was revived by the introduction of second-generation antipsychotics, which are believed to have a

somewhat stronger impact than older antipsychotics on both negative symptoms and cognitive disturbances (1). The focus on these core dimensions of schizophrenia could result in the development of drugs mainly targeted at cognitive deficit, but also able to treat positive symptoms. It is also important to stress that, in the context of the neurodevelopmental theory, cognitive disturbances are interpreted as being a vulnerability marker indicative of subtle brain alterations, and that modern neurogenetics applies cognitive impairment as an endophenotype (2-4).

In the old days, the group of cognitive deficits consisted primarily of those disturbances which can be observed directly during psychiatric examination, such as deficits in attention and abstract thinking, thought blocking, incoherence, etc. These symptoms are still included in some schizophrenia rating scales, such as the Positive and Negative Syndrome Scale (PANSS). Nowadays, neurocognitive tests are able to assess cognitive impairment objectively and reliably and to describe the disturbances in verbal fluency, working memory, executive control, visual and verbal memory, and mental speed. There is no doubt that neurocognitive testing would be the proper way to diagnose cognitive deficits in schizophrenia. However, it should be kept in mind that, to my knowledge, thought disorders like thought blocking or incoherence are not covered by these tests.

The question whether neurocognitive testing can be performed in the frame of routine care, as addressed by Keefe, is of course of great importance. Although several West European countries and the United States have a long tradition of psychological test assessments in the routine care of hospitalized patients, there are other regions of the world where this is not affordable. A categorical criterion, which is primarily based on clinical explorations of the patient and his relatives, might therefore be preferable. I think that a test battery specifically developed for the assessment of cognitive disturbances in schizophrenia, like the MATRICS (5), might complicate the test procedure in psychiatric hospitals or outpatient facilities. It seems more pragmatic to apply those neurocognitive test batteries which are used in the routine care of each facility. Of course, when it comes to research, an internationally standardized procedure like the MATRICS would be the best option.

I definitely support Keefe's view that the inclusion of cognitive impairment in the diagnostic criteria for schizophrenia would enrich the diagnostic concept and hopefully contribute towards a better definition of a "point of rarity" between schizophrenia and affective psychosis. If DSM-V and ICD-11 follow a dimensional approach, including negative and cognitive symptoms as separate dimensions beside positive symptoms, it may be possible to achieve both a better differential diagnosis and a more powerful prognostic differentiation.

I believe that such a dimensional approach, as an additional descriptive level to a categorical differentiation between schizophrenia and affective disorders or as a primarily syndromic classification of a broad psychosis category, could represent a fruitful improvement of our current diagnostic systems (6,7).

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The added value of including cognitive impairment in the diagnostic criteria for schizophrenia

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Keefe's article provides convincing arguments in favor of the inclusion of cognitive impairment in the diagnostic criteria for schizophrenia. I would like to briefly discuss those arguments in the light of the criteria for assessing the clinical usefulness of diagnostic tests proposed by Bossuyt et al (1) and Boutros et al (2): a) demonstration by independent, well-conducted studies that a biological variable is deviant in a patient population as compared with healthy controls and shows good test-retest reliability; b) demonstration of the potential clinical usefulness of the test (the target patient population differs from groups of patients with disorders that commonly require differential diagnosis); c) evaluation of the sensitivity, specificity, positive and negative predictive value of the test (at this step the added diagnostic value of the test should be evaluated against the "gold standard"); d) standardization of the test in large multicenter, cross-cultural clinical trials and development of large normative data-

bases that can eventually be used to examine single subject's data.

No doubt that cognitive impairment in schizophrenia meets the first requirement: many independent studies reported deviant neuropsychological performance in groups of patients with schizophrenia as compared with healthy controls. The second requirement is only partially met, as distinct patterns of cognitive impairment have been identified in schizophrenia and mood disorders without psychotic features but, when the latter aspect comes into play, the discrimination becomes subtle and the quantification of the distance from normative data might be crucial. The third requirement is also partially met: cognitive impairment has a negative predictive value, that is missing in the present diagnostic criteria. The fourth step is "in fieri": the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) represents an important advance toward test standardization and creation of normative databases (3). The inclusion of cognitive impairment in the diagnostic criteria could bring the added value of encouraging a more comprehensive approach to the management of the disorder.

In which way should the diagnostic criteria be modified to include cognitive impairment? This issue is actually more difficult to address. Keefe's proposal conveys most of the present knowledge on the issue when recommending this wording: "a level of cognitive functioning suggesting a consistent severe impairment and/or significant decline from premorbid levels considering the patient's educational, familial, and socioeconomic background". It may be useful to better clarify the meaning of the terms "consistent" (involving several cognitive domains or consistently found in different test sessions?) and "severe" (one standard deviation below the norm?). It would be also appropriate to specify that the decline from premorbid levels is not limited to the acute psychotic phase. For the assessment of all the above aspects, formal testing is more reliable than interview based instruments. The reluctance of clinicians often involves both formal testing and interview based instruments. Once an educational effort needs to be done, it is worth to point to the right direction.

In summary, Keefe's arguments supporting the inclusion of cognitive impairment in the diagnostic criteria for schizophrenia are convincing and firmly rooted in research findings. The proposed implementation of the criterion is probably influenced by the awareness that clinicians are neither skilled nor inclined to spend their time in formal testing. However, also considering the efforts of many researchers to provide the field with validated and standardized assessment instruments, a more ambitious goal appears worth to be pursued.

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Inclusion of cognitive impairment in the DSM diagnosis of schizophrenia: if not now, when?

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An increasing bulk of evidence indicates that neurocognitive impairment is one of the core symptoms of schizophrenia (1,2). The question therefore is not whether this should be included as one of the diagnostic criteria for schizophrenia, but when and how this inclusion should occur.

One of the foremost experts in the field, Richard Keefe, proposes that the presence of neurocognitive impairment should be included in the DSM-V diagnostic criteria for schizophrenia. The essence of the suggested criterion is a consistent and severe impairment in cognitive functioning as well as a significant decline from premorbid levels. The acceptability of this criterion would be partly based on its sensitivity and specificity, which Keefe has made a case for through the demonstration of the boundary or "point of rarity" between schizophrenia and other related disorders. Although much more data would be needed to evaluate the validity of this criterion, there are still compelling reasons for it to be included in DSM-V. It would make clinicians more aware of the presence of this component and its impact on the functioning of the patient independent of the psychotic symptoms. It would likely lead to a more comprehensive assessment, management and prognostication. Although cognitive impairment is not a *sine qua non* of schizophrenia, as there may be a subgroup who does not show clinically relevant cognitive deficits (3,4), the structure of DSM could easily accommodate this, since most of the disorders in the manual are defined polythetically (5).

The devil is in the details of what constitutes the core neurocognitive deficits and how they can be assessed. The term "cognitive functioning" is all-encompassing and includes a wide range of information processing, memory, attention, and language functions. Studies based on neuropsychological tests have suggested that patients with schizophre-

nia generally fall into three cognitive subtypes: generalized impairment, executive dysfunction, and memory dysfunction (1,6,7). These domains require neuropsychological testing by trained assessors. Even with a brief battery which could be learnt by clinicians, as suggested by Keefe, transcultural variability in normative data is a relevant issue.

Cognitive impairment is already part of the diagnostic criteria for Alzheimer's dementia, where clinical judgement has been found to be quite accurate when following the DSM-IV criteria (8). However, cognitive symptoms have been explicitly described in relation to functioning, while this connection between cognition and functional outcome is lacking in the criterion proposed by Keefe. There is a large body of research demonstrating a clear association between impaired cognition in schizophrenia and community functioning as well as acquisition of certain skills (9). Although the correlations between performance on individual cognitive domains and functional outcomes are generally moderate, and real-world functional outcomes may be influenced by affective symptoms, motivational and environmental and societal factors (10), it would not be inappropriate to include descriptions of some effects of cognitive impairment on social and vocational functioning, which would facilitate clinical assessment.

The DSM-IV has been criticized for not being researcher-friendly (11,12), and various proposals have been made to rectify this in the DSM-V (13-15). The inclusion of the cognitive impairment criterion would enhance the already considerable ongoing research in this area. The "official" recognition that this is a fundamental and characterizing aspect of schizophrenia would facilitate the approval and labeling process of drug regulatory bodies like the Food and Drug Administration in the US, which in turn would attract more investment from the pharmaceutical industry for research in developing cognition-enhancing drugs (16). For the criterion to be useful to researchers, however, it would have to be more precise and with explicit guidelines for reliable assessment (17).

It is time to include the criterion of cognitive impairment in DSM-V, but it will have to be in such a way as to optimize its clinical and research utility.

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Integrating evidence-based treatments for common mental disorders in routine primary care: feasibility and acceptability of the MANAS intervention in Goa, India

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Common mental disorders, such as depression and anxiety, pose a major public health burden in developing countries. Although these disorders are thought to be best managed in primary care settings, there is a dearth of evidence about how this can be achieved in low resource settings. The MANAS project is an attempt to integrate an evidence based package of treatments into routine public and private primary care settings in Goa, India. Before initiating the trial, we carried out extensive preparatory work, over a period of 15 months, to examine the feasibility and acceptability of the planned intervention. This paper describes the systematic development and evaluation of the intervention through this preparatory phase. The preparatory stage, which was implemented in three phases, utilized quantitative and qualitative methods to inform our understanding of the potential problems and possible solutions in implementing the trial and led to critical modifications of the original intervention plan. Investing in systematic formative work prior to conducting expensive trials of the effectiveness of complex interventions is a useful exercise which potentially improves the likelihood of a positive result of such trials.

Key words: Depression, anxiety, low-income countries, primary care, effectiveness of interventions

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Depressive and anxiety disorders, also referred to as common mental disorders (CMD), are widely prevalent in primary care settings in low- and middle-income countries (LAMIC)(1) and are associated with significant levels of disability, increased health care costs and reduced economic productivity (2-4). Although substantial proportions of primary care attenders in LAMIC suffer from a CMD – estimates vary from 10 to 30% (1,5) – the vast majority of patients do not receive effective treatments (6). This treatment gap persists even as a growing evidence base demonstrates that there are efficacious treatments that are feasible in LAMIC settings (7-10). To address this treatment gap, integration of mental health services into primary care is widely acknowledged as the most feasible strategy (11). While we now have encouraging evidence that specific treatments for CMD work in LAMIC, the challenge is to integrate these in a comprehensive intervention package within routine primary care systems. This is one of the key research priorities for CMD in LAMIC (12).

A recent review of evidence from high-income countries highlighted the components that are necessary for the effective integration of services for depression in primary care settings (13). These were the routine screening of patients, education for primary health care staff, skilled mental health providers delivering a stepped-care intervention and the active collaboration of mental health specialists in the programme.

The adaptation of these principles in LAMIC primary care settings presents several challenges. These include limited skilled mental health resources, vastly different social and cultural contexts and an already constrained primary care system (14-16). Other barriers to possible integration include the low recognition rates of CMD by primary care doctors (17), limited primary health care staff and large numbers of patients, infrequent and/or inadequate use of antidepressants (18) and the frequent use of medications such as vitamin injections which are prescribed for their supposedly "restorative" properties (19). Low adherence to medication regimens further minimizes the gains of treatment. In addition, few patients receive psychosocial treatments, typically because of a scarcity of personnel with the time and skills to deliver these (20).

The MANAS project is an effectiveness trial of a multicomponent, comprehensive intervention to integrate the treatment of CMD in primary care facilities in Goa, a state on the West coast of India which has been the setting for a

number of studies on the epidemiology and treatment of CMD (21-23). The original intervention plan was based on two principles: first, the treatments selected would be based on evidence from published trials in LAMIC and, thus, include psychoeducation (24,25), antidepressants (7,9) and group interpersonal therapy (IPT) (8,10); and, second, the intervention would address the challenges highlighted earlier and be based on the best global evidence available (13). The intervention would involve a reconfiguration of both the human resources and the principles of care delivery in primary care. The personnel would comprise a low cost, skilled mental health care provider working in the clinics (the "health counselor"), who, along with the existing primary care doctor, would detect and provide treatments for CMD with the support and supervision of a visiting psychiatrist. The treatments provided would be matched to the needs of the patient (stepped care) (7), including brief psychoeducation as the first step, with the more intensive treatments (antidepressants and IPT) being available for those with more severe problems (Table 1). We refer to this collaborative, stepped care intervention as the MANAS intervention. As a word, MANAS means "humanity" in the local Konkani language. It is also an acronym for MANAShanty Sudhar shodh ("project to promote mental health").

Our aim is, ultimately, to evaluate the MANAS intervention in a cluster randomized controlled trial in primary care settings in Goa, India. This trial is now in progress. In this paper, we describe the preparatory stage (October 2005 - December 2006), in which the feasibility and acceptability of the intervention was evaluated systematically, in keeping with the current recommendations for the conduct of complex intervention trials (26). The preparatory stage had three distinct phases: a) consultation with stakeholders; b) formative research to evaluate key components of the intervention; and c) piloting of the entire intervention. Each stage is described sequentially, with a focus on the methods and key findings, and questions which arose which were then addressed in the subsequent stage.

CONSULTATION PHASE

Objectives and methods

The objective of this phase was to consult with local, national and international stakeholders from the public, private and academic sectors about the feasibility of the proposed intervention. A total of 14 consultation meetings were held at primary health care centres and conference venues with the local stakeholders. A total of 145 doctors from the Directorate of Health Services and private practitioners participated, in addition to the primary health care staff. During these meetings, a key member of the team described the MANAS intervention. Group exercises were undertaken to get feedback on the relevance and need of the programme in primary care, on the feasibility of implementing the intervention and on the specific problems and solutions that were likely to occur in these settings. A meeting of national and international collaborators involved with the trial was held in early 2006, during which results of the previous consultations were presented and further inputs of this group were considered.

Results

Doctors suggested that the routine screening results for detection of CMD be presented to them in a simple manner that would also be of assistance in providing feedback to patients. Psychoeducation (Step 1) should be brief, emphasize the connection between the stressors and the symptoms, and be delivered in an empathic manner. The health counselor should avoid using terms that could be stigmatizing.

Public sector doctors wanted the antidepressant to be made available free of cost, in keeping with usual care practices and in order to improve adherence rates. The participants suggested that the group psychological intervention be delivered either in primary health care centres or in community locations (e.g., temple courtyards or local schools),

Table 1 The collaborative stepped care intervention framework for the MANAS project

Steps of care	Objective	Responsible health workers	Intervention
Recognition	Sensitive and specific detection of CMD	Health counselor	Use of screening questionnaire
Step 1	Provision of health promotion advice and education about symptoms	Health counselor	Psychoeducation
Step 2	Provision of evidence-based pharmacotherapy or psychotherapy to patients who do not respond to Step 1	Primary health care centre doctor and health counselor	Antidepressant (fluoxetine 20-40 mg/day for at least 6 months) OR interpersonal psychotherapy
Step 3	Provision of both treatments for patients who do not respond to Step 2	Primary health care centre doctor and health counselor	Antidepressant plus interpersonal psychotherapy; intensive adherence management
Step 4	Management of treatment resistant cases or suicidal patients	Psychiatrist (visiting)	Referral (either through phone discussion or face to face evaluation in primary health care centre)

CMD – common mental disorders

for men and women separately and in the evenings to maximize attendance. Furthermore, concerns were expressed that many patients would not find group sessions acceptable or convenient, and that an individual treatment format should also be offered as a choice.

Many of the participants felt that including yoga as one of the group activities would make the intervention more culturally acceptable. It was agreed that a set of yoga techniques, selected on the basis of their efficacy for anxiety and depression, would be utilized in the MANAS intervention. It was proposed that the yoga sessions be available to all primary health care attendees and staff, in addition to the patients receiving the intervention, so as to destigmatize the overall program.

According to the original formulation of the program, doctors would provide patients with a choice of antidepressants or psychological treatments. However, the stakeholders felt that, in the context of the strong medical model in current care, this would lead to most patients receiving antidepressants. It was recommended that the effectiveness and appropriateness of psychological treatments be emphasized in the training of doctors, to make the process of choice more balanced. Furthermore, doctors felt there should be a distinction in guidelines for mildly ill patients from those who are severely ill (based either on screening questionnaire data or clinical assessment), so that the latter can be moved straight to a higher step on their first presentation. Considering the multiple responsibilities of the health counselor, the decision was made to separate the roles of screening and intervention delivery. Thus, two additional full-time staff would be based in facilities, one to screen and, where needed, to register patients (whom we refer to as the "health assistant") and one to be the case manager for the MANAS intervention (the health counselor). The health counselor was seen as the most important human resource of the program, and most of the participants were of the opinion that she should be a woman, be fluent in the local languages, have excellent communication skills and be available for consultations on a regular basis in the clinics. Many also wanted her to be called the "*salagar*" (advisor), to reflect local understandings and improve her acceptability.

FORMATIVE PHASE

Objectives and methods

The objective of the formative phase was to evaluate the feasibility and acceptability of the specific treatments in the intervention.

The formative research was conducted over 16 weeks (April - July 2006) in four primary health care centres and four private general practice facilities. The primary health care centres, which were staffed by 3-5 doctors backed up by nursing and administrative personnel, offered outpatient care 6 days a week, as well as limited inpatient facilities. The private general practice clinics were in urban and rural areas and were run by a single doctor with or without inpatient facilities in single rooms or in small hospitals referred to locally as "nursing homes". None of these facilities had counsellors or health educators and specialty mental health care was accessible only through referrals.

In keeping with the recommendations made during the consultation phase, 10 women (4 health counselors and 6 health assistants) were recruited. The health counselors were trained to deliver the various treatments, including counseling skills, psychoeducation, yoga and IPT; their training was based on a draft manual developed for the intervention. The health assistants were trained in the use of the screening instrument chosen for the trial. The final training exercise for the doctors was conducted either individually or in small groups. This focused on the recognition and management of CMD, with a particular emphasis on the rational use of antidepressants and avoidance of non-evidence based medications. A set of materials were developed for patients and program staff, including a "patient card" for the reporting of the screening results to the doctor, handouts for various symptom management strategies and a doctor's guide on the use of antidepressants. The health counselor and health assistant were then placed in facilities where they implemented the specific treatments.

Two types of data were collected for the assessment of the formative phase:

Process indicators. These were the total number of attendees in each facility; the number who were excluded from undergoing screening on the basis of *a priori* exclusion criteria (<18 years old, inability to speak any of the local languages, in need of urgent medical care, attending the clinic within 2 weeks of the initial screening and therefore not eligible for screening at this contact, refusal to answer); the number who screened as having possible CMD; the number who met the health counselor after consulting the doctor during their initial visit; and the number who returned for follow-up sessions. These data were collected on a daily basis by the health counselor and collated weekly; analysis was carried out using the SPSS14 package.

Qualitative data. In-depth, semi-structured interviews with key stakeholders (doctors, facility staff, health counselors and patients) were conducted to document their perspectives about the feasibility, utility and acceptability of various aspects of the intervention. Since we wanted to elicit specific information from each of the groups, different interviews were developed for each group. For example, the interviews for patients focused on their recollection of the process of the intervention and their opinion about the utility of the treatments; the interviews for primary care physicians elicited their perceptions of the feasibility of the intervention and the individual treatments as well as their role in the overall process. The thematic method of analysis of qualitative data was used to generate results.

Results

A total of 7473 patients attended the primary care facilities during the formative phase (Table 2). Of those who were screened, 899 (31.6%) were positive for CMD. Of these cases, 70.6% were women; the average age was 41 years (SD 13.5). Among them, 53% actually received the first session of psychoeducation and only 24.3% of those who had received the initial session returned for further follow-up appointments. IPT was offered (all opted for the individual format) to 16 patients, 11 of whom (68%) attended at least four sessions and only 3 (19%) completed six or more sessions.

A total of 89 interviews were completed with doctors (n=10), patients (n=50), staff in the facilities (n=17) and the intervention team (n=12). Clinic and programme staff spoke of problems in providing counselors with work space that offered an acceptable level of privacy, especially in the smaller general practice clinics. Facility staff and the counselors consistently suggested that a systematic mapping of the physical infrastructure and the personnel in the facility be conducted prior to implementing the intervention. This would orient counselors to the usual care processes in their clinics, and help them identify any potential difficulties in positioning the intervention. Doctors and staff in the facilities also mentioned the need for counselors to be visible members of the facility. Several strategies to achieve this goal were suggested, including meetings between the counselors and the doctors every day before and after the outpatient clinic, regular meetings with other facility staff, and counselors' attendance at the scheduled monthly review meetings with the field staff of the primary health care centres. There was near unanimity in stakeholder groups that women with excellent communication skills were the ideal choice for being effective health counselors.

A majority of patients reported screening to be a useful process, as they were asked about emotional problems, which were not otherwise usually assessed. Most patients felt that the duration of the screening was acceptable, and the clinic staff did not feel that the new procedure adversely impacted on the usual care processes. The 30 minute psychoeducation session was described as useful by most patients, with the majority able to recall the contents of the session. Most endorsed the role of stress in contributing to their health problems, and were practicing the suggested techniques to improve their symptoms. In particular, the breathing exercises, and advice about sleep and diet, were felt to be the most useful components of the psychoeducation session; this was also endorsed by the health counselors. The efforts to deliver IPT met with limited success, as users cited a variety of problems in returning for treatment on a weekly basis, in particular the loss of wages and the cost of repeated travel to the clinic. Another important barrier, specific to the group format, was concerns about confidentiality, given the personal nature of the issues being discussed and that other members of the groups who lived in the same community might gossip about their problems to others.

In conclusion, the formative research suggested that, with the exception of the group IPT component, specific treatments of the MANAS intervention were feasible and acceptable to patients and providers. We were reassured that the locally recruited and trained health counselors (who had no prior mental health experience) could provide the intervention consistently. We agreed that facilities that lacked a private space for the health counselor office could not participate in the program. A "running-in period" before starting service delivery was accepted as an important exercise for the team to become familiar with the physical layout of the clinic, the staff and usual procedures. Though patients felt that the intervention was acceptable, the poor follow-up rates indicated that non-adherence would be a major obstacle to the successful implementation of the intervention. To generate an appropriate and effective adherence management strategy, it was felt that an in depth understanding of the reasons for non-adherence from the service user perspective was essential. Another concern was the large number of patients who did not meet the health counselor after being screened and seen by the doctor, and were lost to the program. Greater attention to minimize this attrition by initiating changes to the care pathway in the clinic became an immediate priority.

PILOTING PHASE

Objectives and methods

The objectives of the pilot phase were to implement and evaluate the intervention, and to understand the reasons for

Table 2 Salient process indicator data in the formative and piloting phases of the MANAS intervention

	Total attenders	Total screened	Reasons for exclusion	Total cases identified	% receiving psycho-education	% returned for follow-up
Formative phase	7473	2846 (38.0%)	530 (41.0%) <18 years 165 (12.8%) acutely ill 214 (17.4%) attending specialist unit	899 (31.6%)	53.0%	24.3%
Pilot phase	7194	2530 (35.1%)	1711 (38.7%) <18 years 497 (11.2%) acutely ill 1167 (26.4%) repeat attenders in <2 weeks	854 (33.7%)	65.8%	43.8%

non-adherence while implementing efforts to improve follow-up rates.

The intervention was piloted in four primary health care centres between August and November 2006. In this phase, the MANAS intervention, as originally proposed, was considerably modified in the following ways: a structured adherence management protocol was developed; the role of the health counselors was broadened so that they would also provide advice for practical social difficulties (e.g., by keeping a referral register of community agencies for social problems); the focus of IPT was switched from group to individual formats; a structured protocol for the supervision of the health counselor by the visiting psychiatrist (clinical specialist) was produced. Finally, a list of process indicators that would enable the clinical specialist to effectively support and monitor the progress of the intervention was developed (Table 3).

Quantitative and qualitative data were collected during this phase by using the above-mentioned process indicators and by administering semi-structured interviews to patients who provided consent to describe their experiences of the intervention and reasons for adherence or non-adherence. Purposive, random sampling generated two groups of participants who were interviewed in their homes: 50 who were adherent and 50 who were not (attended two or less sessions and not following-up). A guide took each participant through the process of the MANAS intervention and explored his/her reasons for adherence or non-adherence. Feedback was also sought on the participants' views about the utility of the adherence management strategies. The qualitative data were compiled and analysed by using thematic analysis techniques.

Results

A total of 7194 patients attended the primary health care centres during the piloting phase and, of these, 854 (33.7%) were identified as possible cases. Of the patients identified by screening, 68.3% were women, and the average age was 40 years (SD 12.8). The adherence management procedures improved both the rates of patients receiving the first psychoeducation session and those attending follow-up for further consultation (Table 2). When reminder letters and telephone calls were feasible, the response was also encouraging and suggested that these would be important adherence management aids during the main trial.

Our attempts to provide IPT in a group format were again not successful. Problems in finding mutually convenient times and inadequate local transportation facilities made it impossible to form ongoing groups of a minimum of 3-4 patients. However, while the health counselors were, with supervision, able to confidently deliver IPT in an individual format, adherence remained a major challenge. Out of 12 patients who were offered IPT, only 7 (58%) attended the first session, of whom only 2 completed all of the sessions.

Health counselors conducted a total of 7 yoga courses (5 daily sessions each) in the selected primary health care centres: four of them were for the staff of the centres, while three were conducted for patients and members of the local community. All yoga courses were well attended and most participants continued for the full 5 days of the course.

Data on the use of antidepressant medication (fluoxetine) were collated across the formative and the pilot phases. Of 1753 patients who had screened positive, 598 (34.1%) were prescribed fluoxetine. Of those who received the medication, only 148 (24.7%) returned for a repeat supply. This is possibly an underestimate, because some patients prescribed antidepressants in the later part of the phase are likely renew their medication supply after the end of the collation of process indicators.

Of the 100 patients selected for the study of reasons for adherence, 77 could be interviewed. The most frequent reasons for not being interviewed were that the user was not at home (61%) and the evaluation team did not have the correct address (22%).

The results of this study are reported in Tables 4 and 5. The most frequently cited reason for not returning to meet the health counselor was economic: patients were daily wage earners and could not come to the clinic during the working week. Other reasons for non-adherence included child care obligations and annoyance with waiting for long periods to see the doctor and health counselor. Feeling better after receiving and practicing treatments like the breathing exercise was a reason for adherence. The importance of proactively reminding patients to return for follow-up emerged as a key factor influencing adherence. In contrast to the patients who were adherent with treatment (three quarters of whom reported the reminder as a reason for adherence), the majority of non-adherent patients (61%) reported that they had not been sent any reminders. Patients who were adherent reported that one of the most important reasons for coming back was that their problems were understood by the intervention team, who talked to them in a sympathetic manner within a confidential relationship. Adherent patients also

Table 3 Process indicators to monitor progress of MANAS intervention

- The number/proportion of patients screened as having CMD who received the first psychoeducation session
- The number/proportion of patients with moderate/severe CMD (based on screening questionnaire score) who were started on step 2 treatments (antidepressant/interpersonal psychotherapy) on the initial visit
- The number/proportion of patients in the program who attended scheduled follow-up appointments
- The number/proportion of patients receiving interpersonal psychotherapy
- The proportion of patients started on antidepressant who completed 3 months of treatment
- The proportion of patients started on interpersonal psychotherapy who completed 6 sessions
- The number/proportion of patients who have been discharged from the program

CMD – common mental disorder

Table 4 Commonly cited reasons for adherence with the MANAS intervention (n=41)

- Felt problems were understood by doctor and health counselor	38 (92%)
- Belief in the beneficial effects of treatment	37 (90%)
- Confidence in the ability of doctor and health counselor to handle problems	37 (90%)
- Felt better with treatment	36 (87%)
- Given an active role and hence a sense of control in treatment	33 (80%)
- Treated with empathy and respected by the team	32 (78%)
- Treatment for these problems was being provided in the centre	31 (75%)
- Flexible follow-up appointment given	30 (73%)
- Reminders sent for appointment (postcard/phone)	30 (73%)
- Treatment was provided free of charge	26 (63%)
- Family was supportive about practicing techniques like breathing exercise at home	24 (58%)
- Ease of transport facilities	23 (56%)
- Family encouraged continuation of treatment	22 (53%)
- Family believed that subject has an illness that needs regular consultation at health facilities	14 (34%)
- Short waiting period to meet the doctor and health counselor	13 (31%)

Table 5 Commonly cited reasons for non-adherence with the MANAS intervention (n=36)

- Engaged in work – cannot find time to get to treatment	18 (50%)
- Have become better and saw no need to follow-up	7 (19%)
- Caring for children or other family members	7 (19%)
- Long wait to meet the doctor and health counselor	6 (16%)
- Side effect of medication	3 (8.3%)
- Difficult transport facilities	3 (8.3%)
- Change in health status, i.e. developed other illness	3 (8.3%)
- Distance of home from clinic	2 (5.5%)
- Expense of transportation	2 (5.5%)
- Feeling worse since last consultation and did not feel advice was useful	2 (5.5%)
- Family emergency	2 (5.5%)

reported being supported by the social network of their immediate family, friends and other relatives.

Respondents in both the adherent and non-adherent groups had adequate recall of the process of the program, and there were few differences in the way they perceived the acceptability of the interventions. For example, most respondents identified the screening process as being useful in helping them gain an understanding of their problems, especially endorsing the concept of "tension". The majority of patients remembered the content of the initial psychoeducation session with the health counselor, and reported that advice on the breathing exercise, improving the quality of sleep and diet problems was the most useful. Most adherent patients appreciated that they had an active role to play in getting better, which reinforced their sense of mastery and control over their symptoms.

In conclusion, the principal outcome of the piloting phase was the confirmation of the feasibility of the MANAS intervention, in general, and of the adherence management and supervision protocols, in particular. However, a number of modifications were still needed: a) the inclusion of an adherence management protocol in the initial assessment of the patient, exploring possible risk factors for non-adherence and guiding the development of a careful plan to improve adherence at every step of the process of care delivery; b) replacing group IPT with individual IPT; c) confirming the use of yoga, in a course of 5 sessions delivered over consecutive weekdays, as a component of the intervention (since it was a culturally acceptable mental health promotion activity, yoga could also improve the overall acceptability of the intervention); d) the use of structured sentinel indicators to enable supervision and monitoring of the program by the visiting psychiatrist.

DISCUSSION

To the best of our knowledge, this is the first systematic effort in a low-income country to develop a complex intervention for integrating the care of CMD into routine primary care. These studies were carried out prior to testing the effectiveness of the MANAS intervention in a cluster randomized trial. We used a three-phase method for the development of the intervention. This method provided a systematic framework, while at the same time being sufficiently flexible to ensure that outputs from each stage raised questions and informed the design of the subsequent stage. We believe that such preparation is critical in ensuring the feasibility and acceptability of complex interventions, and serves to identify a number of challenges which need to be addressed before conducting an effectiveness trial.

Each of the three phases was a rich learning experience and resulted in incremental improvements in the development of the final intervention. We have been able to demonstrate the need for such an intervention, by confirming that about 12% of all primary care attendees are suffering from a CMD. Although the final intervention protocol continues to use the same specific treatments that we had originally envisaged, there have been a number of key modifications to improve their feasibility and acceptability. Eight examples are considered in this discussion. First, we had initially conceptualized IPT as a group intervention with 8-12 sessions, based on the evidence available from the trial in Uganda (8). However, we discovered that the group format and number of sessions were likely to be impractical in the social context of primary care in Goa; thus, we have had to reformat the IPT to be delivered in an individual format over 6 to 8 sessions. Second, adherence management moved from being a peripheral component of the intervention to becoming a central feature, running across the intervention from the first psychoeducation session onwards, with a proactive set of strategies. Third, we had originally anticipated that the health counselor would carry out both screening and delivery of the intervention. This proved to be unfeasible and we added an additional, low-cost, human resource (the health assistant) to administer the screening instrument. Fourth, the scope of the health counselors' role expanded to include a range of additional activities, such as managing adherence and being a link between the health centre and existing resources in the community. Fifth, we had anticipated no se-

lection criterion for facilities, apart from consent of the facility. However, we accepted that the lack of a minimum private space for the health counselor was a non-negotiable criterion for a facility to be eligible. Sixth, the important role of yoga was affirmed as a means to both promote mental health and possibly destigmatize the MANAS intervention. Seventh, we learnt that the intervention should have a running-in phase, during which the team employs a structured mapping process to familiarize itself with the primary health care centre and, thus, to identify and address potential physical and logistic barriers. Finally, the process indicators allowed us to set realistic and appropriate targets for the delivery and monitoring of the intervention.

The preparatory phase also provided critical feedback regarding the content and structure of the training for the team members, as well as the content and format of the materials used for the intervention. We have not described our findings in detail in this paper due to space considerations, but these are available from the authors.

We wish to re-emphasize the importance of a preparatory phase as a crucial step before conducting clinical trials of complex interventions in mental health. In our experience, the MANAS intervention has been improved significantly, at least in terms of its feasibility and acceptability, as a consequence of this work. We hope that these modifications will help enhance the overall effectiveness of the intervention, currently being conducted in its first phase in 12 primary health care centres in Goa.

In conclusion, complex interventions for CMD are best delivered by teams who are adequately skilled, motivated and have in place structured supervision and strong leadership to improve their practice. This involves a clear delineation of the roles of each member of the team and mechanisms to manage and resolve conflicts. The preparatory phase has given us the opportunity to develop a framework that will streamline the safety, quality and comprehensiveness of the subsequent program.

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Suicidal process, suicidal communication and psychosocial situation of young suicide attempters in a rural Vietnamese community

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The study aimed to explore the suicidal process, suicidal communication and psychosocial situation of young suicide attempters in a rural community in Hanoi, Vietnam. Semi-structured interviews were conducted, in a community setting, with 19 suicide attempters aged 15-24 who had been consecutively hospitalized in an intensive care unit. In 12 of 19 cases, the first pressing, distinct and constant suicidal thoughts appeared less than one day before the suicide attempt in question. However, distress and mild, fleeting suicidal thoughts had been present up to six months before the suicide attempt in 16 cases. Five respondents had a suicide plan one to three days before attempting suicide. Altogether, 13 engaged in some form of suicidal communication before their attempt. This communication was, however, difficult for outsiders to interpret. Twelve of the respondents were victims of regular physical abuse and 16 had suffered psychological violence for at least one year before attempting suicide. Eighteen of the respondents used pesticides or raticides in their suicide attempts. None sought advice or consultation in the community despite long-standing psychosocial problems. The strategy of reducing the availability of suicide means (e.g., pesticides or raticides) in Asian countries should be complemented with a long-term suicide-preventive strategy that targets school dropouts and domestic violence, and promotes coping abilities and communication about psychological and social problems as well as recognition of signs of distress and suicidal communication.

Key words: Suicide attempters, suicidal communication, psychosocial situation, preventive strategies

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Over the last 45 years, mortality due to suicide has increased in some developed and developing countries, among both adults and young people (1-2). Depending on age, sex and location, suicide attempts are 10-40 times more frequent than completed suicides (3-5). The results of SUPRE-MISS (the World Health Organization's Multisite Intervention Study on Suicidal Behaviours, within the Suicide PREvention initiative) show that suicide attempts, plans and ideation varied by a factor of 10-14 among the study sites in the ten countries concerned, in five continents (5). The incidence ratios of suicide attempts to suicide plans and thoughts varied substantially. The authors concluded that the idea of the suicidal process as evolving continuously from thoughts to plans and attempts needs further investigation, and that the process appears to depend on the cultural setting (6).

A study from China (6) found that younger individuals are more likely to attempt low or intermediate-planned acts than high-planned acts. The attempts were classified as "low-planned" when the time lag between the first reported suicidal thought and the suicide attempt itself was less than two hours. Those who attempted low-planned acts were found to be more likely to have experienced greater acute stress than those whose attempts were characterized as "high-planned" (6). The majority of low-planned suicides in the study were carried out with pesticides, which were readily available at home.

The results from the SUPRE-MISS study showed that 71.6% of female and 61.5% of male attempters in China, compared with 33.8% of male and 23.8% of female attempters in India, used pesticides as a means of attempting suicide (7). Studies from China and India conclude that restriction of access to toxic means of suicide, safer storage and a reduction of the toxicity of agricultural chemicals and rat poisons are advisable. An evidence-based suicide-preventive strategy focusing on restriction of lethal means of suicide is widely advocated (8,9). Other suicide-preventive strategies include improved recognition of suicidal communication (10-13) and better risk recognition of depression and substance abuse, especially in schools (14) and by primary care physicians (15).

Several investigations in Western countries show that 48-84% of people who committed suicide repeatedly communicated their suicidal intentions to their significant others and to more than one person. Significant others' responses to the suicidal communications of distressed, suicidal persons and lack of support have an impact on the course of the suicidal process (13). Significant others often fail to recognize suicidal communication, owing to their lack of knowledge, but also because their own ambivalent attitudes and behaviour towards self-destructive persons come to the fore when they are confronted with suicidal communication.

Suicidal communication can be divided into direct and indirect verbal communication, on the one hand, and direct and indirect non-verbal communication on the other. "Direct verbal suicidal communication" refers to clearly expressed suicidal intentions. "Indirect verbal suicidal communication"

means the expression, in various ways, of the feeling that one's situation is hopeless, that life has no meaning, that there is no solution to one's current problems and that it would be better to disappear or die. In "direct non-verbal communication", a suicidal person undertakes various kinds of preparation for the suicide attempt, such as collecting drug prescriptions, buying pesticides or raticides, or writing a farewell letter. "Indirect non-verbal suicidal communication" refers to withdrawal, deliberate self-isolation, weakening or rupturing ties with family and friends and/or taking concrete steps to put personal affairs in order before committing suicide.

The present study was based on a sample of young suicide attempters in a rural community in Hanoi, Vietnam. The aim of the study was to explore the suicidal process (from the onset of suicidal ideation to the appearance of suicide plans and attempted suicide), suicidal communication and the psychosocial situation of suicide attempters. The theoretical background of the study was the stress-vulnerability model and the notion of the developing suicidal process (16,17).

METHODS

Procedures

All suicide attempters who were hospitalized from August 2001 to August 2003 in the Intensive Care Unit at the Socson District Hospital in Hanoi were studied. All 29 suicide attempters from rural areas aged 15-24 years were selected for in-depth interviews. Four respondents had moved from the catchment area at the time of the study, three gave incorrect addresses and three patients refused to participate, which resulted in a total of 19 interviews. Interviews were performed using a uniform procedure and method. The time interval between the suicide attempt and the interview was 5-6 months (range 1-11 months).

The interviews lasted up to two hours and were performed by one of the authors (HT). The location was chosen by the participants. In 14 cases it was the participant's home, in three the community health centre and in two a rice field. Basic sociodemographic data were collected and semi-structured interviews then enabled the participants to describe the course of events freely. In each case, however, structured questions were posed covering the following areas: I. Family relations and psychosocial situation as risk or protective factors; II. Presence of suicidal communication before attempted suicide; and III. Development of the suicidal process from suicidal thoughts to suicide plans and suicide attempts. The detailed questions asked during the interview are presented in Table 1.

The in-depth interview records were translated into English and then interpreted by five persons (MG, AN, HT, CW, and DW) independently. After careful revision of the interview records, coding was used, based on the theoretical concept of the developing suicidal process and on the types of suicidal communication used. A peer-review group of qualitative researchers from the Swedish National and Stockholm County Centre for Suicide Research and Prevention of Mental Ill-Health (NASP) discussed both the

Table 1 Structured questions posed in the interview

Area I. Questions concerning family relationships and psychosocial situation

Theme 1. Motives for suicide attempt
- Describe the motives that led you to attempt suicide.

Theme 2. Ability to seek help
- Did you try to get help and advice, and to communicate your needs, if and when you had difficulties in your everyday life?

Theme 3. Mental health, alcohol problems, attempted suicide or suicide among family members
- Is there anyone in your family with a mental health problem?
- Is there anyone in your family with an alcohol problem?
- Has anyone in your family made a suicide attempt?
- Has anyone in your family committed suicide?

Theme 4. Violence
- Have you ever suffered physical abuse from your family or a partner?
- Have you ever suffered psychological abuse from your family or a partner?

Theme 5. Support from family and partners
- Describe your family situation.
- Describe your relationships with your family members.
- Have you ever been in need of financial support from your family or a partner?
- Have you ever been in need of psychosocial support from your family or a partner?
- Have you ever received any financial support from your family or a partner?
- Have you ever received any psychosocial support from your family or a partner?

Area II. Questions related to various types of suicidal communication

- Did you tell your family members, friends and/or neighbours explicitly that you had the intention of taking your life? *[direct verbal communication]*
- Did you tell your family members, friends and/or neighbours implicitly that you thought life was not worth living, or that you wanted to disappear from this life, or take a break from this life, that you saw death as a solution, etc? *[indirect verbal communication]*
- Did you prepare for the suicide attempt in any way (e.g. by saving pills or buying pesticides or raticides, or writing a farewell letter)? *[direct non-verbal communication]*
- Did you do anything like paying bills, saying goodbye, writing your will, disrupting ties with your family, deliberately self-isolating yourself or withdrawing once you had decided to take your own life? *[indirect non-verbal communication]*

Area III. Questions concerning the suicidal process

Theme 1. Previous suicide attempts and suicidal thoughts
- Had you ever attempted suicide before?
- When did you first think about suicide?
- When did you first experience mild suicidal thoughts, fleeting and sporadic suicidal thoughts, pressing and distinct suicidal thoughts, and constant suicidal thoughts?

Theme 2. Suicide plan and probability of detection after suicide attempt
- Did you have a plan before attempting suicide?
- What was your plan?
- How long before the attempt did you make the plan?
- Did you do anything to prevent someone from finding you?
- Was anyone near you at the time of the suicide attempt?

Theme 3. Method
- What method did you use to attempt suicide?
- Why?
- How did you get hold of what you needed? From neighbours, at home, purchased?

Theme 4. Retrospective feelings after the suicide attempts
- How did you feel after the suicide attempt(s)?

coding scheme and coding decisions. Analysis was based both on the three selected themes listed above and on narrative descriptions of the cases. Results for each theme were identified in the interviews and afterwards pooled.

Subjects

Ten females and nine males participated in the interviews. The mean age of the subjects was 19.5 years (range 15-24 years). Five of the 19 subjects were married. Fifteen were primary or secondary school dropouts. The parents of 12 respondents had primary education, while seven respondents' parents had attended secondary school. Most of the participants lacked hobbies, with the exception of one male who was interested in football. None of the subjects had previously attempted suicide. Eighteen of the subjects were given the diagnosis of X68 (intentional self-harm by exposure to pesticide or raticide), according to ICD-10, while one subject received the diagnosis of X83 (intentional self-harm by other specific means). None were given psychiatric diagnoses by doctors during their stay in hospital after their suicide attempt. Their hospital treatment lasted from one to three days.

RESULTS

Area I. Family relationships and psychosocial situation as risk or protective factors

Theme 1. Motives for suicide attempt

Personal conflict was the main motive of attempted suicide for 18 suicide attempters. Seven committed a suicidal act after being scolded by a parent, five after quarrelling with partners and two after quarrelling with other family members. In three cases, the act took place after a parent had interfered in the subject's love life; in one after a parent refused to give the subject money to buy a birthday present for a friend; and in one because the subject felt sad.

"*... I was very upset and depressed, and I did not want to suffer from my mother's blame any more. I thought that death could free me from my current terrible life ...*" (Participant 4, male).
"*…He still blamed me when he sobered up. I ran to my parents' house and told them what had happened. My parents also beat me and chased me back. I did not have any friends to confide in. I thought of death as a solution…*" (Participant 17, female).

Theme 2. Ability to seek help

None of the suicide attempters sought advice, consultation or communicated with parents, relatives or community services concerning the difficulties in their lives during the year before their attempted suicide.

Theme 3. Mental health and alcohol problems among family members

Four of the participants had fathers (2) or husbands (2) who were alcohol abusers. One of them had an elder brother who had abused drugs. None of them had anyone in the family with mental health problems or who had attempted or committed suicide.

Theme 4. Violence

Ten of the young suicide attempters were regularly beaten by their parents. It happened "*all the time*" and "*without reason*". Two of the four young married female suicide attempters regularly suffered from domestic violence.

Sixteen of the suicide attempters were psychologically abused by their families for at least one year before attempting suicide, incurring regular scolding, blame, and criticism, or being reproached in ways that made them feel guilty and sad.

Theme 5. Support from family and partners

Fourteen participants wanted financial support from their parents and four received it. Sixteen reported that they had asked their parents and family for psychological and moral support, but none of them received it.

"*... I sometimes felt my life was meaningless, and I wanted to put an end to my life. I was the only son in my family, but most of my family members have hardly spoken to me. An only son is said to be treated beautifully, but it seemed to be the opposite in my case. Almost every day, I was blamed for various things during mealtimes. I was even treated worse than a dog ...*" (Participant 4, male).
"*... Every day, my husband gambled and his behaviour affected our family finances. I tried to tell him, but he did not change. On that day, my husband continued gambling. I felt angry. We had an argument, I felt that life was not worth living and I went out to buy raticide…*" (Participant 15, female).
"*... I had to pay a tuition fee of 20,000 Vietnam Dong (that's about 1.5 US dollars). My father refused to give it to me. I didn't think it was that much money. At the time, my father drank a lot and scolded me all the time. I felt sad, so I attempted suicide...*" (Participant 5, male).

Area II. Suicidal communication

Three of the 19 respondents used direct verbal suicidal

communication. Sixteen of the 19 respondents felt deep frustration with their life situations for at least six months before they attempted suicide, and ten of them for at least one year, but they were unable to express in words to their families not only their need for help, but also their fleeting, vague suicidal thoughts.

Seven of the 19 respondents communicated with their friends or peers about their distress and their wish to disappear from life. However, they were afraid of self-exposure and negative repercussions. They also thought that it is "sick" to harbour suicidal thoughts and they felt that it was easier to acknowledge or to talk about feelings of unhappiness, despair and distress. There was a marked discrepancy between what those young people expressed verbally and the desperation they felt. They were ashamed and they felt that they should cope on their own without intervention from outside. They wanted to give the impression of being strong. Feelings of being strong alternated with feelings of being useless and worthless. Their feelings of anxiety and anguish were not expressed either.

Ten youngsters expressed their distress in a non-verbal way by deviant behaviour and weakening or rupturing ties with their families. They also had time to buy raticide in a shop. Two of the 19 respondents wrote farewell letters before attempting suicide.

Area III. Suicidal process

Theme 1. Previous suicide attempts and suicidal thoughts

For 12 suicide attempters, the first suicidal thoughts became overwhelming, very pressing and constant less than one day before the suicide attempt in question. In five cases, the suicidal thoughts became overwhelming one to three days before the suicide attempt. One male had had fairly pressing, but sporadic suicidal thoughts for approximately a year before the attempt.

Al least six months before they attempted suicide, 16 of the 19 respondents were *"very sad"*, *"wanted to cry"*, felt "unpleasant", "self-pitying" and thought that *"life was meaningless"* and not worth living. They wanted to disappear or take a break from life. Sometimes they thought that death might be a solution to their problems. They acknowledged vague and fleeting suicidal thoughts, which could disappear quickly and recur equally fast in response to new or renewed strains. Ten of the respondents had felt deeply distressed for at least one year before their suicide attempt. Only two believed that those vague and fleeting suicidal thoughts were serious or could lead to a suicidal act. Almost all of them thought that their suicide attempt was due to chance circumstances. The information concerning the suicidal process and the presence of suicidal thoughts was unclear for one participant. All the young persons studied hoped that their difficulties would pass without any active steps being taken by themselves or others, and that their lives would be better in the future.

Theme 2. Suicide plan and probability of detection after suicide attempt

Five respondents had a suicide plan for one to three days before attempting suicide.

"…I had planned suicide two days before I attempted it. That morning I bought six or seven ampoules of raticide. After finishing work on the field and in the house, I took the raticide at around 5 pm, because my husband was often drunk and frequently beat me…" (Participant 17, female).

All the young interviewees thought it highly unlikely that their suicide attempt might be interrupted or that external intervention could save them. On the other hand, 14 subjects had someone nearby or present when they displayed their suicidal behaviour.

"…During dinner my mother like always repeatedly blamed various things on me. Moreover, my older sister came home and backed my mother up in the way she was speaking to me. I became very upset because I thought I was right, yet I was seriously blamed by both my mother and sister. I was tired after a long day's work, and very irritable. I did not have any hope for a change in my life. I stopped eating, left the living room and went to my bedroom. This was a small room next to the living room, separated from it by a curtain. I poured a packet of pesticide into my mouth without hesitation …" (Participant 4, male).

Theme 3. Method

Pesticides were used by nine subjects, raticide was also used by nine, and one male used allergy medication in his suicide attempt. According to the young suicide attempters interviewed, raticides are cheap and pesticides easily available for purchase in rural areas.

"…because raticide was cheap and easy to buy. First, we wanted to use an electric wire [for hanging] but this way [raticide] was quicker…" (Participant 7, male)

Theme 4. Retrospective feelings after the suicide attempt

Eight of the subjects felt regret, another eight were ashamed, two had feelings of failure and shame, and one was unclear about his feelings.

"... I felt tired, and regretted my actions. I realised that my parents were right and I had failed..." (Participant 6, male).

"... I was very upset and depressed and I did not want to suffer from my mother's blame any more. I thought that

death could free me from my current terrible life. Unfortunately, my action was discovered and I felt like a failure. I was sad that I could not kill myself. Rumours about my act will spread widely, and I will suffer from it for the rest of my life." (Participant 4, male).

DISCUSSION

Methodology

The interviews were performed after treatment, outside hospital settings, confidentially and in an empathic atmosphere. These conditions helped respondents to freely express their experiences, which also included positive and negative aspects of their stay in the ward. However, the respondents may not have described their experiences in full, for two reasons. First, some of the subjects were interviewed 10-11 months after their attempt and may therefore have forgotten some details about past events. Second, the participants may not have wished to be reminded of the negative circumstances that led to their suicide attempts, and may therefore have evaded answering questions that were emotionally challenging. The dropout rate (approximately 30%, i.e. 10 of the 29 consecutively selected patients) limits generalization of the results of this study. Suicide attempters who were not hospitalized were not included in the study.

Suicidal communication and length of suicidal process

Suicidal communication is a manifestation of personal style, reflecting a person's capacity to ask for help. For suicide-preventive purposes, it may be important to uncover various manifestations of suicidal communication, as well as the subject's despair and motives for attempting suicide. In the present study, seven of the 19 respondents used indirect verbal forms of suicidal communication and three engaged in direct verbal suicidal communication.

Ten of the 19 patients felt they were in desperate straits and experienced profound and prolonged distress for at least one year before their suicide attempt. Sixteen of the 19 had experienced an intense and constant sadness, as well as fleeting, vague suicidal thoughts, and felt that "life is meaningless", for one week to six months prior to their suicide attempt. However, they were unable to communicate constructively with their parents or other family members about their feelings. Inability to seek advice and communicate in a dialogue with others about their distress and a need for psychological or financial support were obvious in almost all the persons studied. The fact that vague and fleeting suicidal thoughts, which are dependent on stressful life situations, are not taken seriously is also seen in patients from Western cultures (18,19).

Although 12 of the 19 youngsters showed a short time lag (less than one day) and five of the 19 had a time lag of between one to three days between their first distinct, pressing suicidal thought and their suicide attempt, they had experienced vague and fluctuating suicidal thoughts in the preceding months and 13 of them had used some form of suicidal communication. However, indirect communication can be difficult for outsiders to interpret, and direct suicidal communication was utilised by only three people.

In this investigation, only very distinct, constant and pressing thoughts centred on suicide shortly before the suicide attempt were perceived by respondents as suicidal thoughts. Studying the presence of suicidal thoughts and of suicidal communication is difficult from a methodological point of view, since it requires a quantitative interview methodology. Experiences from this study show that further development of the concepts and measurements used, as well as interpretation, is necessary.

Five of the 19 young people had some kind of suicide plan one to three days before the suicide attempt. Results from Western studies also show that young people have a short suicidal process (20, 21). The short decision time was used by young suicide attempters in this investigation for buying raticides or pesticides. If they had been taught to communicate, or if their distress had previously been understood by significant others, they might possibly have been able to speak to someone instead of buying poison.

It was apparent from the narrative analysis that the young people in our study displayed their distress in several ways, often by deviant behaviour, not only to their families but also to the immediate community. The majority of youngsters felt a lack of acceptance in the community, and this feeling exacerbated their deviant behaviour and led to isolation. Absence of constructive communication and dialogue is characteristic of suicide attempters in the Western countries as well (13).

A study of adult suicide attempters in Sweden (13) has shown that almost total silence was not an unusual response to suicidal persons' communication. Anxiety, anguish and tensions grew in silence; problems became more insoluble and overwhelming; and in some cases there were aggressive undertones in significant others' treatment of the distressed suicidal person. From other Western studies, it is known that family members can show indifference, ambivalence and, in some cases, anger and hostility – even explicit death wishes – towards a suicidal person (22-25). This absence of good communication and dialogue seems not to be characteristic of the young rural Vietnamese families studied here alone.

In a Chinese study (6) the association between impulsive, low-planned suicidal actions and acute life events was described. Our study results confirm the important role played by these acute and prolonged psychosocial stressors in the suicidal process.

Given the high proportion of low-planned suicides that involve pesticides stored in the home, Phillips et al (26) recommend restricting the accessibility of these drugs as an effective suicide-preventive strategy. This is important, but re-

stricting the means of committing suicide may only postpone suicidal acts. On the basis of the interviews in the present study, teaching young people and their parents to use communication skills and coping abilities, instead of resorting to violence and punishment when problems arise in everyday life, appears to be an equally important strategy.

The low educational level of the suicide attempters' parents may be a limitation on their ability to understand these young people's communication of distress. However, the same problems may exist in suicidal families where the parents' educational level is high (20, 21). The barriers characteristic of Vietnamese culture, in which disclosure of emotional problems is unusual, are of limited explanatory value, since lack of communication between parents and suicidal young people is also observed in Western studies (13,20,21).

Perception of support from the family

The young persons in the present study felt, deeply and bitterly, that they did not receive practical, financial and psychological support when they felt distressed. Moreover, 15 of the 19 young people were primary or secondary school dropouts. Reactions from the school, society and the family were lacking.

The Programme on Global Child Mental Health (www.globalchildmentalhealth.com) recently launched by the WPA, in cooperation with the World Health Organization and the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), makes school dropouts the focus of interventions aimed at preventing mental problems and suicide. Dropping out of school is one of the most significant indicators of mental distress and mental problems, of which suicide attempts and suicide are the ultimate consequence.

Suicide prevention

Is suicide prevention through detection of suicidal communication and distress possible? It is difficult to judge how much this kind of intervention could prevent suicide attempts among Vietnamese youngsters. However, it seems meaningful to supplement restriction of highly toxic and lethal means of suicide with some kind of psychosocial strategy. Psychosocial strategies that focus on young people at risk, such as school dropouts, and on teaching families how to communicate about problems and distress, can be tested. Teaching young people where to find other people for a dialogue if the family fails to give them support is another strategy.

Based on the stress-vulnerability model, suicidal behaviour occurs when there is imbalance between risk factors and protective factors. In our study, personal conflicts and lack of support were found to be the main reason for suicide attempts. Suicide attempts usually occurred after physical or psychological abuse such as blame or scolding by the respondents' parents or husbands. This kind of phenomenon is highlighted by World Health Organization's strategies of how to prevent domestic violence and avoid battering of children and partners (27).

Psychological environmental stressors as risk factors for attempted suicide

Attempted suicide and suicide are complex behaviours that do not result from a single disease or a single social or psychological problem. There are usually several interacting factors, such as psychiatric disorders, physical illnesses, personality disorders and stress factors, that may result in suicidal behaviour at times of brief or prolonged distress. In this study, no research diagnoses were made concerning psychiatric disorders. Nor were there, in the hospital records, any notes on psychiatric or personality disorders. It is unknown whether these young people had any kind of depression, post-traumatic stress disorder or personality disorder. Only their method of attempting suicide, impulsively using pesticides and raticides, was specified. In some suicidal adults and many young suicidal people, impulsivity is a salient personality characteristic. Their underlying genetic vulnerability may be expressed in a situation of stress (28,29). In a recent study (30), both healthy and suicidal persons characterised by an "angry hostility" personality type, that is often linked with impulsivity, showed modifications of the genetic system involved in the regulation of the hypothalamus-pituitary-adrenal axis.

The role of protective factors – such as problem-solving capacity, asking for help and good relationships with the family and other close associates – in reducing stress seems to be important. Poor relationships and inadequate problem-solving strategies can be expressed in not asking for help and, as this study has shown, lead to attempted suicide in times of distress. The role of "psychological environmental stressors" in suicide risk has been relatively little explored for the purpose of suicide-preventive strategies. We would like to encourage more qualitative studies focusing on the suicidal process and suicidal communication, and on long-term and short-term stressors in suicidal behaviour.

Conclusions

Psychosocial interventions in the form of programmes targeting school dropouts, domestic violence, communication and coping abilities in distress should complement the well-known suicide-preventive strategy of decreasing the availability of lethal means of suicide and attempted suicide, such as pesticides and raticides.

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Community-based mental health care in Africa: mental health workers' views

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The World Health Organization (WHO) has for long proposed the development of community-based mental health services worldwide. However, the progress toward community mental health care in most African countries is still hampered by a lack of resources, with specialist psychiatric care essentially based in large, centrally located mental hospitals. It is again time to reconsider the direction of mental health care in Africa. Based on a small inquiry to a number of experienced mental health professionals in sub-Saharan Africa, we discuss what a community concept of mental health care might mean in Africa. There is a general agreement that mental health services should be integrated in primary health care. A critical issue for success of this model is perceived to be provision of appropriate supervision and continuing education for primary care workers. The importance of collaboration between modern medicine and traditional healers is stressed and the paper ends in a plea for WHO to take the initiative and develop mental health services according to the special needs and the sociocultural conditions prevailing in sub-Saharan Africa.

Key words: Africa, community mental health care, primary care, continuing education

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In Western countries, community-based mental health services are now becoming the preferred model for delivery of psychiatric care, in contrast to the more traditional mental hospital-based services. The World Health Organization (WHO) is a proponent of such an approach, not only in the high- and middle-income countries of the West, but also in low-income developing countries (1). In the Western setting, the different elements of a community-based service are well-recognized and include closing down or down-sizing mental hospitals, the establishment of psychiatric units in general hospitals and the formation of community-based mental health teams. The latter are composed of psychiatrists, nurses, social workers, psychologists, occupational therapists and other mental health professionals, and provide outpatient and outreach services aiming to support patients in their homes wherever possible. Primary health care works in synergy with the specialized community-based service, with the expectation that the bulk of mental disorders will be managed in this setting by health workers who have received basic mental health training. The system often includes collaboration between social services in the local community, as well as the formation of close links with families, user organisations, charities and telephone information and support lines.

This model is not, however, directly applicable to low-income countries in Africa, where there is a great scarcity of trained mental health professionals and virtually no social service, and where families, traditional healers and religious leaders often play the dominant role in dealing with mental disorders. In many countries the number of mental health professionals is very low. In Ethiopia, for example, there are only 18 psychiatrists for 77 million people, and there is no clinical psychologist, no trained social worker and only one 360-bedded mental hospital located in the capital, Addis Ababa (2). Likewise, to date, all psychiatrists are working in Addis Ababa, although psychiatric nurses provide hospital-based outpatient clinics in the regions (3). The situation is similar in other African countries, where the majority of mental health specialists work in the capital cities, leading to neglect of the rural areas (4). Many psychiatric hours are devoted to private practice, because of the poor remuneration within the government health system, further eroding the service available to the majority of the population.

The WHO has proposed the development of community mental health services through integration of mental health into the existing primary health care system and mobilization of community resources. The structure of the primary health care system in sub-Saharan Africa is reasonably well-established, although with variable coverage and quality of service. The model for primary health care is usually based on two or three levels. Closest to the community is the health post, where one or two health workers with very limited training provide basic medical and preventive care for a population of 1000-5000 people. At the next level are health centres, where registered nurses and sometimes doctors are working with a catchment area of 20,000-100,000 population. Above that there are district hospitals and regional hospitals, where sometimes there might be a psychiatrist or other specialized mental health worker, but most often not (4).

The mainstay of care for mentally ill persons in traditional African societies is not, however, accessed through primary health care at present. In Ethiopia, for example, only 33.4% of persons with persistent major depressive disorder had contacted governmental health services in the preceding three months (5). Families and the folk sector thus provide the lion's share of care. Compared to the

Western world, African society is much more tightly knit, with both stronger family coercion and greater social support. There is almost always an extended family to rely upon, and even severely ill persons are usually living with their family, although a minority of mentally ill persons may choose to move away from their families, often ending up as vagrants. Only in more extreme cases of violence or extremely deviant behaviour, or when the family's resources are stretched to breaking point, will mentally ill persons be excluded from their families, although they may be chained up or neglected. Overall, however, it is families, and to a lesser extent communities, who form the basis for mental health care in traditional societies.

Innovative strategies for delivering community-based mental health care in Africa have come and largely gone, with few initiatives sticking or proving possible to roll out on a broad basis. Pioneers of African psychiatry took promising initiatives to collaborate with traditional healers and to adapt services to the African socio-economic setting. The model village of Aro developed by Lambo in Nigeria (1954) is one example. Other examples are those of Henri Collomb in Senegal and Margaret Field in Ghana, who also developed collaboration with traditional healers, and of Tigani El Mahi and Taha Baasher in Sudan, who established working relationships with Muslim leaders to facilitate identification, referral and de-stigmatization of persons with mental illness.

WHAT DO AFRICAN MENTAL HEALTH PROFESSIONALS THINK ABOUT COMMUNITY-BASED MENTAL HEALTH CARE?

Three decades on from the WHO imperative to develop community-based mental health services in Africa, we conducted a small survey to explore how do mental health practitioners on the ground see the situation. What is the prevailing conceptualization of community mental health care, African style? A questionnaire was developed with questions on the basic elements required for a community-based mental health service approach for Africa, as well as on protective and negative factors in the traditional African society and how to support the positive aspects and counteract the negative ones. The questionnaire was sent out by e-mail to mental health workers in sub-Saharan Africa. Out of the 20 respondents, 15 were psychiatrists, of whom four were professors of psychiatry.

The survey emphasized the immense variation between African countries, as well as the differing needs of rural and urban settings. Linked to this, several respondents stressed the importance of not just diluting Western models, but instead developing culturally-sensitive approaches and models that can be adapted to the particular situation. Many respondents endorsed principles of care provision such as accessibility, comprehensibility and equity, which echo those guiding community mental health services in Western settings (6). The lack of human resources and the difficulty retaining staff, especially in rural areas, was an important obstacle identified by the majority. Likewise, the necessity of finding ways to collaborate with traditional healers and spiritual leaders in order to facilitate detection, referral and rehabilitation of persons with mental disorders was mentioned by almost everybody. The community was also identified as important, providing a base of local expertise upon which mental health care might be built. Targeting the community for sensitization regarding mental disorders and anti-stigma campaigns was seen by most respondents as vital. Providing support to patients and their families was less often suggested.

Very few respondents spoke of the value of national mental health policies and only one person mentioned mental health promotion and mental illness prevention programmes. The broader context of mental health care was alluded to by several people, particularly the impact of poverty on mental health and provision of services. However, nothing was said about the impact of wars, forced displacement, societal transition and exposure to violence. Working with non-health agencies, such as educational services and the justice system, was not mentioned as an integral part of community-based mental health care.

There was notable uniformity of responses to the question on resources required for the development of a community mental health model. Almost everybody thought that there should be some kind of mental health community worker in the primary health care system, located at the village level in rural areas. Mental health skills should be taught to primary care workers, who would need to be supported by some kind of specialist psychiatric back-up. The concept of a mental health extension worker, or some kind of "link worker", who would work close to the community, was developed in several of the responses. The importance of such a worker liaising with traditional healers and spiritual leaders was repeatedly emphasized. The main tasks for this person were seen as providing support to families and helping to maintain patients in their homes. He/she was also expected to be able to detect relapse and refer to the next level of the primary health care system when appropriate. At the health centre level, some respondents felt that more specialized, mental health expertise should be available: for example, community health workers with special skills in mental health.

Regarding the training for these mental health workers, most recommended development of standardized training packages, complemented by on-the-job training. The necessity for ongoing monitoring with specialist back-up was stressed. Regular refresher courses were thought to be important, preferably short and frequent courses rather than long ones with extended intervals in between them.

The absolute necessity of a reliable supply of essential medications, seen to be a chronic problem in most African countries, was a prominent comment. The need for transport facilities for outreach and attending to the logistical

aspects of providing care was particularly stressed by those respondents who might be expected to be closest to the coal-face of mental health care provision, the clinical officers and nurses.

Concerning factors which protect against mental disorder, almost everybody mentioned the extended family and associated social support as being a positive and protective feature of life in traditional African societies. The sense of belonging to the community and the presence of connections with other members of the community, ancestors and the land, as well as collective responses to suffering, were features seen as advantageous to mental health. The valuable role of sociocultural beliefs in giving meaning to the experience of mental disorder and facilitating healing was also mentioned. A number of respondents emphasized that communities should be encouraged to value and appreciate what they have and avoid uncritical acceptance of Western ideas. Economic support of patients and their families, together with provision of effective modern psychiatric care, was also seen as an important strategy for supporting the beneficial fabric of traditional life.

Perceived disadvantages of traditional African societies reported by respondents included the presence of high expressed emotion within families, a lack of individuality in psychological functioning, a lesser focus on individualized human rights and the associated tendency towards overriding patient autonomy. An unrealistic expectation of the Western medical model was another issue raised: for example, patients expecting fast and complete cures. Some directly harmful aspects were mentioned, including chaining, beating, fumigation and other violating traditional practices. The cultural use of psychoactive substances such as khat, cannabis and alcohol was also mentioned by respondents as a potential threat to mental health. Some respondents highlighted the role of childrearing practices that might be harmful.

It was suggested that community primary health care workers should be properly informed about good and bad aspects of traditional therapies for mental disorder, and use this knowledge to sensitize community members and traditional healers to the dangers and to the existence of effective alternatives. By increasing involvement of the patient, family and community in mental health care, it was thought that safe and effective practices could be disseminated. Equipping a few key influential community members with knowledge regarding mental health issues was proposed as an effective strategy for countering stigmatizing attitudes and harmful practices.

DISCUSSION

Although the number of responses was limited, we consider the above views to have useful bearing on the question of how to develop community-based mental health care in sub-Saharan Africa. The respondents included a number of leading mental health professionals in their countries and persons with direct experience in the provision of care.

The key WHO proposal that mental health services should be integrated into primary health care (7,8) was supported by all respondents. In most African countries this basic infrastructure of primary health care does exist and studies have demonstrated that those who are already working in these settings can be equipped with basic mental health skills. In our survey, however, primary health care workers devoted to mental health issues were also thought to be required for effective provision of community care. The reasons underlying this suggestion deserve further exploration, as they may reflect dissatisfaction with the quality and effectiveness of mental health care that generic primary health care workers are realistically able to provide. Such real-life evaluations of mental health care provided within primary health care in rural sub-Saharan settings are essential to direct policy in this area.

A critical issue to be addressed is how to provide primary health care workers, generic or specialized, with appropriate supervision and continuing education. Our survey indicated failings in current arrangements. Poor support in the field, together with inadequate remuneration, are likely to fuel the high turnover of staff which undermines every effort to expand provision of mental health care.

Another area highlighted by our survey is the importance of the relationship between community mental health care workers and traditional healers. It is well-recognized that a wide diversity of healers deal with mental health issues in traditional African societies: religious healers, herbalists, those practicing sorcery and witchcraft, as well as spiritual healers based on other traditional belief systems. The need to find ways to collaborate with all these different groups was emphasized already at the First Pan African Psychiatric Conference in Abeokuta, Nigeria, in 1961 (9), but remains a pressing issue according to our respondents. We consider the prominence given to this issue by our respondents to be an important change from earlier days when modern medicine tended to have a negative and distancing attitude towards traditional healers. Dissemination of successful strategies for collaboration and further scientific evaluation of potential models would be timely in this climate of receptiveness.

The particular needs of urban and rural populations were seen as a high priority to be addressed. The majority of people in sub-Saharan Africa are still living in rural areas, where there is a lack of specialist back-up, grave problems retaining trained health workers and difficulties with transportation. In urban areas the challenges are different: over-crowding, abuse of alcohol and other substances, commercial sex working, child labour, homelessness, mentally ill migrants and many other problems associated with the rapidly growing cities.

All this taken together tells us that it is time for some kind of pan-African initiative to develop mental health services according to the special needs and the social and

cultural conditions in sub-Saharan Africa. Efforts to date have been laudable, but limited in their impact at the grass-roots level. The WHO has taken the initiative up to now and is probably the best-placed organization to restart the movement towards a truly community-based mental health system for the people of sub-Saharan Africa. We hope the opinions in this paper will spark the debate.

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Side effects of atypical antipsychotics: a brief overview

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This paper reviews the available evidence concerning the side effects of atypical antipsychotics, including weight gain, type II diabetes mellitus, hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract. Some recommendations about how to prevent and manage these side effects are also provided. It is concluded that atypical antipsychotics do not represent a homogeneous class, and that differences in side effects should be taken into account by clinicians when choosing an antipsychotic for an individual patient.

Key words: Schizophrenia, atypical antipsychotics, side effects, treatment guidelines, individual treatment

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Patients with schizophrenia suffer from increased rates of multiple medical problems, due to their lifestyle (high smoking prevalence, high-fat diet), inherent neglect of personal care, and barriers to treatment of physical illness (1). A further important contributor to adverse health outcomes is the side effect profile of antipsychotic medications. Since the introduction of the second generation or atypical antipsychotics (AAP), these agents have been widely prescribed for the management of patients with schizophrenia, bipolar disorders, other psychotic disorders or conditions with severe behavioral disturbance. The increasing use of AAP is in part due to their lower propensity to induce extrapyramidal symptoms and tardive dyskinesia compared to typical antipsychotics.

Now, more than 15 years after the first atypical antipsychotic entered the market, psychiatrists have gradually come to realize that while extrapyramidal symptoms and tardive dyskinesia occur less frequently with atypical agents, these medications may present a different set of adverse effects. The quality of available evidence for the association of specific antipsychotics with particular side effects varies considerably. In this article, we review the recent findings concerning weight gain, diabetes mellitus (DM), hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract in patients receiving AAP.

WEIGHT GAIN

Forty to sixty-two percent of people with schizophrenia are overweight or obese. Obesity increases these patients' risk for cardiovascular morbidity and mortality. In addition, excessive weight and obesity can have important effects on an individual's adjustment in the community, adherence to prescribed medication, ability to participate in rehabilitation efforts, and self-image (2).

Treatment with first- and second-generation antipsychotics can contribute to weight gain (3-5). A meta-analysis by Allison and Casey (4) provided an estimate of the mean weight gain in patients receiving standard doses of antipsychotics over a 10-week period: the mean increases were 4.45 kg with clozapine, 4.15 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone. Data on quetiapine have been variable, but it seems that the weight gain liability on this drug may be similar to that of risperidone (6). Weight gain with olanzapine at the commonly used dose of 15mg/day may exceed 10 kg during the first year of treatment (7). On the other hand, weight gain seems to be dose-dependent: Rondanelli et al (8) reported no change in weight in elderly patients who received 1.4 mg/day risperidone or 4.4 mg/day olanzapine or 75 mg/day quetiapine over a 12-month period.

Marder et al (9) recommended that the patient's body mass index (BMI) should be recorded before medication initiation or change and at every visit for the first 6 months. The patient should be weighed (and the BMI recorded) at least quarterly when he stabilizes, and more often if he is overweight. BMI monitoring should be supplemented with the measurement of the patient's waist circumference. A gain of one BMI unit in a normal-weight or overweight patient should lead the clinician to consider an intervention. Intervention may include nutritional counseling (for both the patient and caregiver or food preparer), initiation of a personal exercise program, use of medications that promote weight loss, and/or a change of the antipsychotic medication to another one associated with less weight gain (10,11).

DIABETES MELLITUS

The prevalence of type-2 DM in people with schizophrenia is more than twice higher than in the general population (12). In the past decade there have been numerous case reports, retrospective studies, and epidemiological investigations suggesting that certain AAP may be associated with a greater risk of DM than others. Most of these studies indi-

cate that drugs associated with greater weight gain (e.g., clozapine, olanzapine) are associated with increased risk of DM in comparison to no treatment or a drug producing less weight gain (2,13-15). However, the studies suffer from a number of limitations (most importantly, the reliance on insensitive, unreliable, surrogate markers for diabetes).

Evidence from case reports suggests that new onset type-2 DM and diabetic ketoacidosis occur more frequently with clozapine and olanzapine treatment, with relatively fewer case reports on quetiapine and risperidone (2). In a recent study, it has been reported that 6.9% of patients receiving AAP developed new-onset type-2 DM over a one-year period, and that the risk was higher with olanzapine exposure, while quetiapine and risperidone showed no effect relative to haloperidol (16).

The underlying mechanisms of antipsychotic-induced disturbances of glucose metabolism are unknown. The studies are often confounded by concomitant weight gain and dyslipidemia, which are known diabetic risk factors. Increased abdominal obesity, especially visceral obesity, can increase insulin resistance and contribute to hyperglycemia and diabetes both in healthy subjects and patients with schizophrenia.

As diabetes occurrence is not always associated with weight gain, monitoring weight alone may be insufficient to screen for DM risk. The methods that can be used to assess the effects of medications on glucose and insulin metabolism include (ranked least to most sensitive/reliable): random glucose, glycated haemoglobin (HbA_{1C}), fasting plasma glucose, homeostasis model assessment insulin resistance (HOMA-IR), post-prandial glucose, the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (IVGTT), and the hyperinsulinaemic-euglycaemic clamp. In a recent animal study, it has been reported that olanzapine and clozapine acutely impaired insulin sensitivity whereas ziprasidone and risperidone had no effect (17). Similarly, higher fasting insulin and insulin resistance index levels were reported in first episode patients with schizophrenia who were treated with clozapine and olanzapine compared to risperidone and sulpiride (18).

Consensus guidelines have been published which elaborate on the differences in risk between agents and provide specific monitoring recommendations (9,19,20). However, a recent study showed that the rate of screening for metabolic side effects of atypical antipsychotics is still low (21). Psychiatrists had the lowest rate of screening, particularly in non-schizophrenic patients and those who take lower doses of atypicals.

HYPERLIPIDEMIA

Serum lipid levels may be influenced by multiple factors, including genetics, diet, weight gain, and exogenous agents like alcohol and medications. It seems that there is an association between use of dibenzodiazepine-derived atypical antipsychotics (i.e., clozapine, olanzapine, quetiapine) and higher serum trigliceride levels (22). Both risperidone and ziprasidone are non-dibenzodiazepine AAP, and appear to have minimal effects on serum lipids (22,23).

In a recent study, it was found that clozapine and olanzapine, but not risperidone, were associated with increase in cholesterol and triglyceride levels at the end of an 8-week treatment in patients with first-episode schizophrenia (18). Similar changes due to olanzapine or clozapine, but not amisulpride or ziprasidone, were reported as early as in the fourth week of treatment (24). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), olanzapine was associated with greater and significant adverse effects on lipids, while ziprasidone was the only antipsychotic associated with improvement in these metabolic variables (25).

PROLONGATION OF QTc INTERVAL

Prolongation of the QTc interval of the electrocardiogram (ECG) may be associated with the development of torsade de pointes, a ventricular arrhythmia that can cause syncope and may progress to ventricular fibrillation and sudden death (26). The average QTc interval in healthy adults is approximately 400 msec. A QTc interval of 500 msec or greater is considered to be a substantial risk factor for torsade de pointes. In the CATIE study (25), there were no different effects of olanzapine, risperidone, quetiapine and ziprasidone on QTc interval.

A recent focus on the QTc interval and antipsychotics emerged during trials of two AAP, sertindole and ziprasidone. Sertindole in the amount usually administered in a clinical dose was found to increase the QTc interval by 22 msec, and the increase was dose dependent. There was evidence of increased risk of arrhythmias and unexpected deaths with this drug (26). On the other hand, Wilton et al (27) investigated mortality rates and cardiac dysrythmias in prescription-event monitoring studies of sertindole and two other drugs (risperidone and olanzapine) for comparative purposes. No statistically significant difference was found in mortality rates. Six cases of QTc prolongation were identified in the sertindole group, giving a risk rate of 1.3%, which was similar to that reported in clinical trials with this antipsychotic, and higher than in patients treated with olanzapine and risperidone.

In initial trials, ziprasidone was found to increase the QTc interval by 6-10 ms (27). The US Food and Drug Administration (FDA) was concerned that the prolongation might be considerably higher at ziprasidone's maximal plasma concentration or when ziprasidone was administered with a drug that inhibited its metabolism. This concern led to a study that was carried out by Pfizer at the request of FDA. When each agent was administered in conjunction with a drug that inhibited its metabolism, the results for the mean increase in the QTc interval were as follows: ziprasidone 20.3 ms, risperidone 11.6 ms, olanzapine 6.8 ms, que-

tiapine 14.5 ms, thioridazine 35.6 ms, and haloperidol 4.7 ms. The intervals were not substantially affected by the inhibitor. As suggested in a recent paper (9), in the absence of increased risk factors for QTc interval prolongation or cardiac arrhythmias, ziprasidone can be prescribed without ECG monitoring. However, patients who are to be treated with this drug should receive a baseline ECG before treatment is initiated if any of the following cardiac risk factors are present: known heart disease, a personal history of syncope, a family history of sudden death at under age 40 years (especially if both parents had sudden death), or congenital long QTc syndrome. A subsequent ECG is indicated if the patient presents with symptoms associated with a prolonged QTc interval (e.g., syncope).

MYOCARDITIS

Case reports suggest that clozapine is associated with an increased risk of myocarditis (28,29). Less than one hundred cases have been reported up to now. Eighty percent of cases occurred within 6 weeks of the patient's starting clozapine, and the mortality rate approached 40%. Myocarditis should be suspected in clozapine-treated patients who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or ECG findings such as ST abnormalities and T wave inversions.

As recent evidence suggests that clozapine is associated with a low (0.015% to 0.188%) risk of potentially fatal myocarditis or cardiomyopathy (30), we do not recommend routine monitoring for myocarditis. However, we recommend that clinicians who prescribe clozapine be alert for the symptoms of myocarditis in patients who receive this medication. If myocarditis is identified, clozapine should be stopped and the patient should be urgently evaluated by a primary health care provider.

SEXUAL SIDE EFFECTS

Human sexual function is complex and is affected in many ways by schizophrenia, antipsychotic drugs, comorbid mental disorders such as depression, DM, substance use and smoking, as well as by social isolation, disturbances in interpersonal relations and partner problems. It has been reported that patients with schizophrenia are more commonly affected by sexual dysfunction than those with affective disorders, and that untreated schizophrenia patients have fewer dysfunctions compared to those on antipsychotic medication (31). Antipsychotic-induced sexual dysfunction is related to the effects of the drugs on alpha-1 and alpha-2 adrenergic, H1 histamine and dopaminergic receptors, in particular to the blockade of D2 receptors in pituitary lactotroph cells, which leads to an excess of prolactin secretion (32,33).

Prolactin elevation is less of a concern with AAP. The exception is risperidone, which results in a prolactin increase similar to that associated with first-generation antipsychotics. A meta-analysis by Kleinberg et al (34) found that prolactin levels in patients who were taking 2-16 mg/day of risperidone were similar to those in patients taking 20 mg/day of haloperidol, while those of patients taking 1-16 mg/day of risperidone were significantly higher than those of patients receiving 10 mg/day of haloperidol. Studies of other AAP have found that these agents may result in transient elevations in prolactin levels, which tend to return to the normal range within a few days (35-38).

When hyperprolactinemia occurs during treatment and is associated with menstrual or sexual dysfunction, consideration should be given to changing the patient's medication to a prolactin-sparing agent.

EXTRAPYRAMIDAL SIDE EFFECTS

Besides the subjective feeling of discomfort, extrapyramidal side effects of antipsychotics in general can add to the stigma associated with schizophrenia. Some patients can have preexisting motor abnormalities, before the initiation of any antipsychotic medications. However, the overwhelming majority of cases of extrapyramidal symptoms appear to be due in large part to exposure to antipsychotic medication.

Meta-analyses indicate that, when AAP are used at recommended doses, they are associated with significantly lower rates of extrapyramidal side effects compared with (generally high-potency) conventional antipsychotics (39). Some AAP (e.g., risperidone and olanzapine) have a dose-response relationship for extrapyramidal side effects, while with others (e.g., clozapine, quetiapine) this relationship is not apparent.

On the basis of available data, tardive dyskinesia appears to occur significantly less frequently with clozapine, risperidone, olanzapine and quetiapine than with typical antipsychotics (40). Fewer data are available for ziprasidone and aripiprazole, but early evidence suggests a low risk of tardive dyskinesia with these drugs as well.

We recommend that the patients at high risk for extrapyramidal symptoms (i.e., elderly patients and those who have experienced dystonic reactions, clinically significant parkinsonism, and/or akathisia) who are taking AAP be examined every 6 months.

CATARACT

Because patients with schizophrenia often have risk factors for lens opacities, such as DM, hypertension and poor nutrition, clinicians should inquire about visual changes and ensure that guidelines for visual monitoring are followed. Certain AAP may be associated with an increased risk of ocular lens opacities. An epidemiologic study that used the UK General Practice Research Database did not find an

overall increase in the risk for cataracts among patients treated with antipsychotics (41).

Focal triangular cataracts were found in beagle dogs that received quetiapine for 6 or 12 months. The dogs received four times the maximum human dose of the drug on a milligram-per-kilogram basis. This prompted concern despite there being no known causal link between quetiapine and lens opacities in humans (42). Cataracts were not found in other species, including monkeys. Nevertheless, quetiapine's manufacturer issued formal recommendations for ophthalmological follow-up examinations with the use of this drug. Infrequent occurrences of cataract development have been documented in people taking olanzapine but, again, without an established causative association. A similar situation is seen with ziprasidone. There were no significant differences among the patient groups in the incidence of new cataracts in the CATIE study (25).

Periodic ocular examinations of the lens are suggested for patients prescribed long-term treatment with phenothiazines or quetiapine. However, after studying 34 cases of lens opacities in 620,000 patient exposures to quetiapine in the U.S., Fraunfelder (43) concluded that cataractogenesis secondary to quetiapine is "unlikely" by World Health Organization's guidelines, and that it is unnecessary to require biannual ophthalmic examinations.

CONCLUSIONS

AAP have helped to improve the lives of many patients with schizophrenia by alleviating positive and negative symptoms and bringing some improvement in cognitive function. Accordingly, evidence-based international schizophrenia treatment guidelines recommend these drugs as first-line treatment (44). However, these medications do not represent a homogeneous class, given their differences in effect size regarding both alleviation of clinical symptoms (45) and their potential for inducing side effects such as new-onset DM, weight gain, hyperlipidemia, or sexual and cardiac dysfunction.

Clinicians have to take into account these differences when choosing an antipsychotic for an individual patient and when screening and monitoring for physical problems. It will be a task for further guideline revision to develop explicit algorithms for differential drug indications depending on the individual symptom profile and risk status concerning potential side effects. We believe that the full spectrum of marketed antipsychotics (including the typical drugs) should be kept available. "The right drug for the right patient" (46) is a claim still valid today.

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The 14th World Congress of Psychiatry (Prague, September 20-25, 2008)

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The World Congress of Psychiatry in Prague, with the motto "Science and humanism: for a person-oriented psychiatry", is an opportunity for psychiatrists of various countries, affiliations and ways of life to meet in that beautiful city in the middle of Europe and discuss the challenges psychiatry is expected to address.

There will be Plenary and Special Lectures, delivered by distinguished specialists in the field, such as Felice Lieh-Mak, Juan José Lopez-Ibor, Mario Maj, Juan Mezzich, Ahmed Okasha, Norman Sartorius and Costas Stefanis. Also, the presentation of the mayor of the city of Prague, Pavel Bém, a psychiatrist specialized in addictology, will bring some more views and experiences.

Controversial and globally important issues will be the content of Special Symposia, the chairpersons of which were invited by the WPA Executive Committee. Topics like "Psychiatric services: meeting professionals' demands or patients' needs" (G. Lucatelli) or "Issues of concern in the rehabilitation of severely traumatized" (M. Kastrup) will be of great interest.

The most frequent format will be Regular Symposia, which will deal with issues of interest for the worldwide psychiatric community, problems that may be usefully discussed at a broad forum like the World Congress of Psychiatry. Naturally, all the WPA Scientific Sections have been invited to present the development in their field of inquiry and interest at Section Symposia. In addition to that, the Organizing and Scientific Committees decided to extend invitation to major international or regional organizations in psychiatry, neurology, primary care, psychopharmacology, biological psychiatry, social psychiatry and mental health.

The participants in the Congress will have an opportunity to hear news on the latest developments in psychopharmacology (S. Kasper), reviews of the present state of classification efforts (G. Christodoulou, J. Mezzich, C. Mundt, B. Ustun), and a discussion of the problems of violence and its control in psychiatry (J. Alboreda-Florez, Z. Rihmer). They will attend lectures and discussions on adequate services in various settings (Y. Chen, W. Rutz, N. Shinfuku), and on provision of services for minorities and special groups (M. Amering, J. Copeland, P. Ruiz). Further contributions will deal with the complex relationship between an individual and his environment (J. Aarli, R. Cloninger, K.W.M. Fulford, A. Jablensky).

Posters and oral communications at the Congress will provide for the mainstream of the information flow necessary to make all the contemporary hot issues of psychiatry a topic of global effort for professional understanding and consensus.

The participants in the Congress will also be informed of the latest results in research in biological psychiatry, psychiatric epidemiology and other areas in New Research Sessions. In order to ensure the access to the latest results, the deadline for submissions of new research will be later than the deadlines for all other formats (February 29, 2008).

Last, but not least, there will be an opportunity to discuss practical issues of psychiatric care at Workshops and Master Clinical Case Conferences. Also, Video and Film Sessions will help to expose and clarify practical problems, and to understand the ways to deal with the stigma towards psychiatric patients and psychiatry.

The Organizing Committee is also preparing a unique cultural and social program divided in special days, which should enable foreign participants to be acquainted with some interesting events from the local history.

Wolfgang Amadeus Mozart composed the opera Don Giovanni for "the people of Prague who understand me" and completed it during his stay in the Czech capital. The world premiere of this opera was conducted by Mozart himself in the Estates Theatre of Prague in 1787. We have already made a reservation for two nights, September 21 and 22, and the participants in the Congress will be able to attend this opera in the original Estates Theatre.

Franz Kafka lived and wrote in Prague at the beginning of the 20th century. His grave can be found in the New Jewish Cemetery in Zizkov, one of Prague's quarters. During the Congress, a thematic trip will be organized to Kafka's museum and other relevant places in Prague.

Modern Czech psychiatry developed under the influence of German psychiatry. One of the oldest German psychiatric departments was set up in Prague at Charles University in 1886. The most important representative of German psychiatry in Prague was Arnold Pick (1851-1924). He served as the first head of that Department for the incredible length of 35 years. At the same time when Alois Alzheimer in Munich studied presenile dementia, Pick described in Prague his fronto-temporal dementia (Pick's disease) in 1892. During the Congress, there will be an opportunity to visit the Department, which houses modernized patient wards, day care as well as rehabilitation centres and modern biochemical laboratories. It will also be possible to admire the Department's guest book, dating back to 1834.

It is not commonly known that Sigmund Freud was born on the territory of the present-day Czech Republic. It was on May 6, 1856 in Pfiíbor, a small city in Moravia. The house of his birth, where he spent the first three years of his life, has been recently reconstructed and at present houses a museum with an exhibition that follows Freud's whole life. During the Congress, it will be possible to visit this house.

For further information about the Congress, please visit the website www.wpa-prague2008.cz.

The Congress in Prague aspires to help psychiatry in confirming its position of respected medical discipline with many special insights and skills to offer to medicine in general. Come and take part in the World Congress of Psychiatry in Prague!

The update of the WPA Educational Programme on the Management of Depressive Disorders

Norman Sartorius
Geneva, Switzerland

With the approval of the Executive Committee, the WPA Secretary for Education, A. Tasman, has recently established a Task Force that will review and update the WPA Educational Programme on Depressive Disorders, issued in 1996. The 1996 version of the programme, consisting of four volumes of text with several hundred slides, has been widely used in training psychiatrists and health personnel in other branches of medicine. It has been translated into a number of languages and used as a basis for the production of local training programmes.

Several important developments made it necessary to update this programme. First, it was necessary to clarify the issues of diagnosis and classification of depressive disorders. Recent epidemiological studies, including the World Mental Health Surveys (1), continued to show considerable differences in the prevalence of depressive disorders in different countries. It is likely that most of these differences are due to methodological problems and the imperfections of the diagnostic systems (including differences in delineation of the disorder) currently used in research and practice of psychiatry. On the whole, epidemiological studies indicate that the prevalence of depression is high and increasing; at the same time, there are numerous reports – some produced by groups such as the scientologists and some by other organizations and scientists – stating that the prevalence of depressive disorders is actually stable and that the higher figures are the result of a collusion between the pharmaceutical industry and the medical profession. The need for a clear and authoritative statement about the diagnosis of depressive disorders – for use in practice, teaching and research – has therefore grown in importance and had to be clearly stated in the WPA programme.

Another reason for the updating of the programme was that, in the period 1996-2006, there were several important additions to knowledge, which had to be reflected in the programme. These were in particular findings about the comorbidity of depression and physical illness, a new understanding of the ethiopathogenesis of depression, the confirmation of the contribution of depression to the global burden of illness, new findings about the high prevalence of depressive disorders in disaster stricken populations and new experiences and evidence about depression in the elderly.

Depressive disorders in children have also in recent years become a focus of attention of psychiatrists and of the general public and the media. The recognition of the risk of suicide in young age, the recognition of the continuity of childhood and adulthood depressive disorders as well as the role of depressive disorders in the causation of physical illness have also been listed as reasons for an updating of the programme.

The new version of the programme will consist of five chapters (in brackets are the names of the members of the Task Force with primary responsibility for the text): 1. Overview and fundamental aspects (M. Maj, O. Gureje); 2. Depressive disorders and physical illness (M. Riba); 3. Depressive disorders in older persons (E. Chiu, H. Chiu); 4. Methods of education about depression (N. Sartorius, D. Goldberg, L. Gask); 5. Depressive disorders in special situations and population groups (M. Maj, O. Gureje, N. Sartorius). Responsible for the overall coordination and review will be N. Sartorius, while A. Tasman will have responsibility for the supervision and linkage to the WPA Executive Committee. Each of the chapters will be accompanied by slides and recommendations for further reading.

The Task Force which is developing the programme includes: N. Sartorius (Co-chairman), A. Tasman (Co-chairman), M. Benyakar, E. Chiu, H. Chiu, S. Douki, L. Gask, D. Goldberg, O. Gureje, S.V. Ivanov, S. Kanba, M. Kastrup, M. Maj, M. Riba, S. Tyano and D. Wasserman. Substantial contributions to the texts have also been received from: M. Bradley, S. Chaturvedi, F. Cournos, F. Creed, R. Fahrer, L. Grassi, C. Lyketsos, S. Marcus, K. McKinnon, S.R. Vagnhammar and L. Wulsin. Senior Advisers to the project are: J.J. Lopez-Ibor, F. Lieh Mak, E. Paykel and C. Stefanis.

The WPA will make the programme available free of charge in electronic form on its website www.wpanet.org. In addition, it is expected that a printed version will be issued in 2008.

Reference

1. Kessler RC, Angermeyer M, Anthony JC et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 2007;6:168-76.

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