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Further information on the WPA can be found on the website www.wpanet.org.

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World Psychiatry

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1. Bathe KJ, Wilson EL. Solution methods for eigenvalue problems in structural mechanics. Int J Num Math Engng 1973;6:213-26.
2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijs de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). Stress analysis. London: Wiley, 1965:145-97.

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EDITORIAL

Is it possible to explain complex mental disorders at the biological level?

Mario Maj

President, World Psychiatric Association

The Forum which appears in this issue of *World Psychiatry* and the one we published in the previous issue (1-7) aim to help practising clinicians to orient themselves in the huge mass of data which have accumulated in the past decades concerning the pathophysiology of two major mental disorders, schizophrenia and depression.

It is a fact that the gap between the restricted circle of researchers working in this area and the large population of clinicians dealing with patients worldwide has been constantly increasing over the years. The average psychiatrist does not follow the progress of biological research with the same attention and confidence as the average clinician in the other branches of medicine. He either does not believe at all in that research, or does not expect that research to produce in the near future anything which may be of practical utility for his daily practice. Furthermore, he does not perceive the gradual accumulation of "evidence" as an indication of a continuing increase of "knowledge", but rather as a sign of uncertainty and confusion.

Is there anything, in the mass of biological data on schizophrenia and depression, which promises to become in the foreseeable future of any usefulness for everyday clinical practice? This is the question that the two Forums were expected to address, and the reader will see that the views expressed by the participants are quite different. They can be schematically reconducted to two main positions.

The first position is that we are on the wrong track. This may be because the current characterization of the phenotypes (schizophrenia and depression) is inadequate, or because these conditions are very heterogeneous and largely overlap with each other, or because the biological level at which our current research efforts are being displayed (e.g., neuronal circuits, neurotransmitters) is very far from the one at which a convincing explanation of the disorders is likely to be found; or because brain dysfunctions can only account for a vulnerability to something which emerges at the interface between the brain and the world of interpersonal relationships, so that many different brain dysfunctions can be found in patients with schizophrenia or with depression, but the essence of these disorders cannot be delineated at the biological level.

The second position is that we are on the right track, but we are dealing with conditions that are very complex, much more than those which are the subject of investigation of the other branches of medicine. The functions which are perturbed in schizophrenia and in depression are the most complex of human beings. Most of them involve an interaction between such a composite organ as the brain and the even more composite world of interpersonal relationships in which all of us are immersed. It is not surprising that research is progressing so slowly and that many alternative avenues are being pursued. Our current technology and modeling may not be adequate to address that complexity, and the future may bring out very important advances in this respect. Furthermore, we cannot expect a single model to explain all the constituents of the complex picture of schizophrenia or depression: "decomposing" these disorders in their various elements may be very helpful. On the other hand, the many models which are currently proposed should not be regarded as mutually exclusive: they may address different levels of the complexity and may turn out to be consistent with each other.

Time will tell whether it is possible to explain complex mental disorders at the biological level, or whether biological dysfunctions can only account for various pathways of vulnerability to those disorders, whose identity emerges at a higher level. Meanwhile, we hope these Forums will offer to our readers a clear and accessible picture of the ongoing research and of the hypotheses which are currently put forward.

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WPA guidance on mental health and mental health care in migrants

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The purpose of this guidance is to review currently available evidence on mental health problems in migrants and to present advice to clinicians and policy makers on how to provide migrants with appropriate and accessible mental health services. The three phases of the process of migration and the relevant implications for mental health are outlined, as well as the specific problems of groups such as women, children and adolescents, the elderly, refugees and asylum seekers, and lesbian, gay, bisexual and transgender individuals. The concepts of cultural bereavement, cultural identity and cultural congruity are discussed. The epidemiology of mental disorders in migrants is described. A series of recommendations to policy makers, service providers and clinicians aimed to improve mental health care in migrants are provided, covering the special needs of migrants concerning pharmacotherapies and psychotherapies.

Key words: Migrants, mental health, cultural bereavement, cultural identity, cultural congruity, schizophrenia, common mental disorders, suicide, pharmacotherapies, psychotherapies, mental health services

(World Psychiatry 2011;10:2-10)

The WPA is committed to promote equity in the access to mental health services for persons of different age, gender, race/ethnicity, religion and socioeconomic status. As part of this commitment, the Association decided to devote one of the guidances to be developed within its Action Plan 2008-2011 (1,2) to mental health and mental health care in migrants. A Task Force was appointed for this purpose, which produced the present document.

Mental health practitioners work in an increasingly multicultural world, shaped by the migrations of people of many different cultural, racial and ethnic backgrounds. People migrate for many reasons: political, socioeconomic and educational. The diversity of cultures, ethnicity, races and reasons for migration can make understanding experiences of illness challenging in migrants whose background differs significantly from the clinician.

Culture has an important role in the presentation of distress and illness, and cultural differences impact upon the diagnosis and treatment of migrant populations in part due to linguistic, religious and social variation from the clinician providing care. Additionally, it appears that the incidence and prevalence of mental disorders varies among people of different cultural backgrounds, due to an interplay of biological, psychological and social factors. The provision of health care is necessarily influenced by the demands of people of many different cultures, and it is important that cultural differences be appreciated and understood to arrive at a correct diagnostic impression and treatment plan.

MIGRATION AND MENTAL HEALTH IN MIGRANTS

Migration is defined as the process of going from one country, region or place of residence to settle in another. The duration of this new settlement varies, but for the purposes of this report the focus is on individuals who relocate either semi-permanently or permanently to another country. Migrants may move *en masse* or singly. For example, people who migrate for economic or educational reasons may move singly and at a later date be joined by their families, whereas people who migrate due to political reasons may move *en masse* but with or without their families (3). A significant proportion of people who migrate will become an ethnic minority in the new country.

The process of migration has been described as occurring in broadly three stages. The first stage is pre-migration, involving the decision and preparation to move. The second stage, migration, is the physical relocation of individuals from one location to another. The third stage, post-migration, is defined as the "absorption of the immigrant within the social and cultural framework of the new society". Social and cultural rules and new roles may be learnt at this stage (4,5). The initial stage of migration may have comparatively lower rates of mental illness and health problems than the latter stages, due to the younger age at that stage, and the problems with acculturation and the potential discrepancy between attainment of goals and actual achievement in the latter stages (6). It is worth noting that the stages are often not discrete and merge into one another.

During the stages of migration, there may be factors that

predispose individuals to mental disorders. Pre-migration factors include the personality structure of an individual, forced migration, and persecution, among others. Migration factors include cultural bereavement. Culture shock, a discrepancy between expectations and achievement, and acceptance by the new nation are potential post-migration factors (7,8). Table 1 provides a guide to the assessment of the above factors in migrants.

Table 1 Items to be covered in history taking with migrants

Pre-migration
Reasons (e.g., student, economic, political)
Preparation
Group or singly
Degree of control over migration
Migration
How long ago?
Why?
Age on arrival?
Possible return or permanent?
Asylum status?
Previous experiences
Post-migration
Aspiration/achievement
Acculturation and adjustment
Attitudes towards new culture
Attitudes of the new culture
Support networks available/accessible
Interviewer
Own values, prejudices
Being aware of strengths of one's own culture and its weaknesses

Special groups

Some groups have additional factors that need to be taken into account in assessment and management.

Women

Women may be the primary migrant or they may follow the primary migrant. Their experiences of migration and response to the stress will be different from those of men. Furthermore, changes in gender role after migration and gender role expectations will influence the way women respond to the stress of migration and post-migration adjustment. Increasing changes in demographics towards more women migrating and working full time mean that stress on women is increasing further.

Children and adolescents

Children and adolescents may have different reasons to migrate and may accompany the family or migrate by themselves, especially as refugees or asylum seekers. Separation from one or both parents, as part of or as a sequel of migration, may create problems in attachment and subsequent development. Seasonal regular migration of parents or serial migration of family members and other patterns of migration will create additional stress. Children may have difficulty in adjusting both at home and in school, and older children may end up looking after the younger ones.

Elderly

The reasons for migration of older adults may differ in comparison with younger ones. Elderly people may have migrated at an earlier stage of their career and life and may already feel settled down in the new country, or may migrate at an older age to the new country in order to join their family. Multiple jeopardy of ageing migrants related to racism, ageism, gender, poor access to services may all act as barriers to help seeking and health (9). Dementia, depression and anxiety among the elderly may vary according to the migrant status, but help seeking may vary as well (9,10).

Refugees and asylum seekers

According to the Geneva Convention, a refugee is someone who has a "well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality and is unable or owing to such fear is unwilling to avail himself of the protection of that country". An asylum seeker is someone who has left his/her country of origin, has applied to be recognized as a refugee and is awaiting a decision from the new government.

Refugees are perhaps the most vulnerable of all migrant groups to mental and physical ill health. Lack of preparation, attitudes of the new country, poor living conditions, poor or lack of employment and variable social support all add to this vulnerability. Rates of mental disorders may be high in some refugee groups: those of common mental disorders are twice as high in refugee populations in comparison with economic migrants (11).

The risk of post-traumatic stress disorder and common mental disorders increases with the length of stay in detention (12,13) and is also related to unemployment, lack of family support and the complicated asylum process (11). Asylum seekers are less likely to engage with mental health services (14,15). Pathologization and medicalization of common experiences must be avoided.

Lesbian, gay, bisexual and transgender individuals

Lesbian, gay, bisexual and transgender individuals (LGBT) may wish to escape if their country of origin holds these behaviours to be illegal. They may have problems

coming out to themselves and to others, adding to internalized stress. They may choose to escape but the laws in the new countries may not allow this or prevalent public attitudes to LGBT may colour the societal responses. For transgender individuals, it may be a search for surgical/medical interventions which drives them. Attitudes of the family, the ego-dystonia in the individual and homophobia in the new society will affect settling down.

Cultural bereavement

The loss of one's social structure and culture can cause a grief reaction (16). Migration involves the loss of the familiar, including language (especially colloquial and dialect), attitudes, values, social structures and support networks. Grieving for this loss can be viewed as a healthy reaction and a natural consequence of migration; however, if the symptoms cause significant distress or impairment and last for a significant period of time, psychiatric intervention may be warranted. Eisenbruch (17) has defined cultural bereavement as an experience resulting from loss of social structures, cultural values and self-identity. The person lives in the past, is visited by supernatural forces from the past while asleep or awake, and experiences feelings of guilt. Images of the past (including traumatic images) intrude into his/her life, and he/she is struck by anxieties, morbid thoughts, and anger. The symptoms of cultural bereavement may be misdiagnosed due to problems with language and culture, and the use of Western diagnostic criteria in non-Western people.

Cultural identity

Psychosocial changes experienced by immigrants include acculturation, a process that may be voluntary or forced, which results in the assimilation of cultural values, customs, beliefs and language of the majority community (18). Changes in attitudes, family values, generational status and social affiliations can occur in both the majority and minority cultures as the two interact; however, typically one culture tends to dominate (19).

Cultural changes in identity can be stressful and result in problems with self-esteem and mental health. Contact between the immigrant, or minority, community with the dominant, or new community may lead to assimilation, rejection, integration or deculturation (4). Rejection, in which the individual or minority group withdraws from the majority group, can lead to apartheid or segregation in extreme cases. Deculturation, in which the individual or minority group experiences a loss of cultural identity, alienation and acculturative stress, can lead to ethnocide (4). Post-migration stresses include culture shock and conflict, both of which may lead to a sense of cultural confusion, feelings of alienation and isolation, and depression (7). New societies' attitudes, including racism, compounded by stresses of potential unemployment, a discrepancy between achievement and expectations, financial hardships, legal concerns, poor housing and a general lack of opportunities for advancement within the host society, can lead to mental health problems in vulnerable individuals.

Acculturation may enable culturally bereaved individuals to gain a semblance of equilibrium. Migrants who experience the loss of their culture and guilt over leaving their homeland may find that, as acculturation proceeds, a sense of belonging in the new country occurs. The majority culture may seem less threatening and more inviting as the individual becomes more linguistically and socially proficient in this new culture. Social support can ensue in the forms of friendships, employment opportunities, and medical care. Integration and assimilation can help reduce feelings of loss and grief as the migrant starts to incorporate aspects of the majority culture.

In acculturation, the interaction of the migrant's culture with the majority culture of the new country is a dynamic and reciprocal process that can result in changes in the broader cultural group, enhancing the ability of people of the dominant culture to better appreciate and understand aspects of the immigrant's culture and recognize some of the needs of those who have migrated.

Cultural congruity

Ethnic density, i.e. the size of a particular ethnic group in proportion to the total population in a specified area, may be a factor that influences the rates of mental disorders in ethnic minorities. Additionally, a sense of alienation may occur if the cultural and social characteristics of an individual differ from those of the surrounding population, whereas a sense of belonging tends to occur if the individual and surrounding population have similar cultural and social characteristics.

An increase in ethnic density may improve the social support and the adjustment of some individuals who have migrated, yet increase distress in others, in particular if there exists a cultural conflict between the individual and his/her culture of origin (8). This may account for some of the conflicting results from studies of the relationship between ethnic density and the incidence of mental illness in ethnic minority groups. For example, an inverse correlation between the incidence of schizophrenia in non-White ethnic minorities in London and the proportion of those minorities in the local population was found; it was hypothesized that increased exposure to or a lack of protection from stress may increase the rate of schizophrenia in non-White ethnic minorities (20); however, a previous study failed to support the ethnic density hypothesis for the increased incidence of schizophrenia in immigrant groups (21).

It is important to consider the nature of the society an individual has migrated from and to, and the social char-

acteristics of the individual who has migrated, in determining how well a person will adjust during the migration process. Sociocentric or collectivist societies stress cohesiveness, strong ties between individuals, group solidarity, emotional inter-dependence, traditionalism and a collective identity. Egocentric or individualistic societies stress independence, loose ties between individuals, emotional independence, liberalism, self-sufficiency, individual initiative, and autonomy. Bhugra (22) has hypothesized that individuals who migrate from predominately sociocentric, or collectivist, societies into a society that is predominately egocentric, or individualistic, are likely to have problems adjusting to the new culture, especially if the individuals are sociocentric in their own belief system. A consequent lack of an adequate social support system, a disparity between expectations and achievements and a low self-esteem may result from this dissonance in culture between the individual and the surrounding population.

An increase in ethnic density may help decrease the distress of the individual in this situation, especially by providing a social support system. For example, a person who migrates to the United States, a predominately egocentric society, from Vietnam, a predominately sociocentric society, may feel isolated and alienated, especially if the individual is sociocentric in outlook. Feelings of isolation and alienation may be decreased, and social support improved, if other people from Vietnam, with sociocentric views, surround this person in the area of resettlement; however, the sociocentric individual may remain on the periphery of the new country's society since linguistic and social fluency of the dominant culture may not be attained.

Cultural bereavement may also be minimized if the immigrant is able to maintain ties to the culture of origin, either through increased ethnic density, improved social support or maintenance of religious beliefs and practise. Individuals who migrate from a predominately sociocentric culture into a society that is predominately egocentric in nature may experience little in the way of problems, and a relatively easy transition to the new culture, if they are mostly egocentric, or individualistic, in their outlook. In this case, an increase in ethnic density may be disadvantageous and exacerbate or cause cultural conflict and mental distress.

EPIDEMIOLOGY OF MENTAL DISORDERS IN MIGRANTS

Schizophrenia

Ödegaard (23) first reported that the rates of schizophrenia among Norwegians who had migrated to the USA were higher when compared with Norwegians in Norway. He noted that the peak of admission rates occurred 10-12 years after migration and saw this as a result of migration.

Subsequently, several studies have shown that migrants, especially African-Caribbeans in the UK and in the Netherlands, have rates of schizophrenia between 2.3 and 16 times those of local White populations (24,25). A threefold risk for schizophrenia in migrants has been reported in a recent systematic review (26).

Cochrane and Bal (27) demonstrated that admission rates of patients with schizophrenia were elevated among the Irish, Pakistani, Caribbean and Indian born migrants. They put forward (28) various hypotheses to explain these differentials, which are considered briefly below.

The first hypothesis was that sending countries have high rates of schizophrenia. However, four studies from the Caribbean (29-32) reported no increase. Rates of schizophrenia in the UK have been shown to be higher among the younger (second) generation African-Caribbeans, indicating that genetic factors may not play a role and other social and environmental factors may be important (33,34).

A second hypothesis was that schizophrenia predisposes to migration. The individual with schizophrenia feels restless and this contributes to potential movement across boundaries. However, not only are there few data to support this, but, if that were the case, rates would be high in every migrant group, which is not what is reported.

A third hypothesis was that migration produces stress. Migration and related losses are significant life events and may contribute to the genesis of schizophrenia. However, as Ödegaard (23) demonstrated, the peak of the rates is 10-12 years post migration. Separation from parents has been shown to be more common in African-Caribbeans in comparison with South Asians and also in comparison with community controls (35), which may suggest that insecure attachment patterns may contribute to a disjointed sense of the self, thereby affecting cultural identity.

A fourth hypothesis was that a misdiagnosis of schizophrenia was involved, due to a lack of awareness of migrants' culture and norms (36,37). Bhugra et al (38) showed that, in their Trinidad sample, delusions of persecution were rare, but visual hallucinations commoner than the London group. Stompe et al (39) also noted cultural differences in symptoms.

Ethnic density has been shown to be an important factor in understanding the elevated rates of schizophrenia in some migrant groups (20,40). Bhugra (22) postulated that cultural congruity, when people with similar cultural values live close to one another, may be more important in this respect. Further work is urgently needed to map cultural congruity and ethnic density with epidemiological data.

Parker and Kleiner (41) hypothesized that a discrepancy between achievement and expectation may have contributed to high rates of psychoses in their sample. This has been replicated in London, especially for discrepancy between aspirations and achievements in housing (42,43), which may affect an individual's self-esteem. Why this lack of self-esteem should lead to schizophrenia and not depression needs to be explored further. Racial harassment

is not uncommon and may further contribute to low self-esteem (44). Veling et al (45) found perceived discrimination to match the rates of psychosis in migrants.

Common mental disorders

There have been a number of population studies in the UK which have looked at the rates of common mental disorders in migrants. The findings have not been entirely consistent. It is not surprising that immediately after migration individuals may be optimistic and hopeful, and thus show low levels of depression and anxiety, which may change as they start to settle down, feel let down by the new culture and perhaps their own culture and start to ruminate over losses they have faced, thereby leading to depression. Some studies show that the rates of common mental disorders among migrants are higher than among the members of the new culture, but others show either no difference or lower rates (46-48).

The EMPIRIC study in the UK reported that Pakistani women were 1.37 times more likely and Bangladeshi women were 0.65 times less likely to have common mental disorders (48). From the same data set, Weich et al (47) noted that older women of Indian and Pakistani origin (aged 55-74) had higher rates of common mental disorders. This may reflect the period since migration and deserves to be studied further. One possibility is that the migrant feels trapped and develops a sense of defeat which may lead to depression. Gilbert and Allan (49) associated entrapment in an area with learned helplessness. Nazroo (46) reported that those who migrated before the age of 11 or who were born in Britain were much more likely (2.5 times for the Caribbean and Indian group, and 1.5 times in the Bangladeshi and Pakistani samples) to receive a diagnosis of an anxiety disorder. Those who were fluent in English were especially more likely to be diagnosed with an anxiety disorder.

Post-traumatic stress disorder

Political refugees or those escaping war or natural disasters will respond differently to trauma (50). Jenkins (51) noted that Salvadoran refugee women in North America explained their suffering as "nervios" – a cultural category including dysphoria, aches and pains and subjective bouts of feeling intense heat which are a culturally created normative response to abnormal stressors. Similar experiences have been described among Tibetan (52) and Khmer refugees (53).

Suicide and attempted suicide

The rates of attempted and completed suicide have been shown to be elevated in the South Asian female diaspora around the globe (54). The rates are raised among younger women aged 18-25, but not among adolescents (55,56). This increase around the age 18 suggests that, when women start to individuate and find their way in the world, an element of culture conflict with their parents or family members may play a role. Comparing cultural identity between the adolescents and their parents, it was found that adolescents who took overdoses held less traditional views compared with their parents. McKenzie et al (57) noted that rates of suicide were higher than expected among older Asian females.

Rates of suicide among British, New Zealander and Irish migrants to Australia were higher compared with the rates in their countries of origin (58). Low rates among South Europeans were explained as a result of pre-migration health checks. Morrell et al (59) also reported from Australia that rates among North Europeans were higher, while Middle Eastern women showed very low rates. Socio-economic status for men (60), cultural transitions and tensions for women (61) and quality of life and emotional functioning (62) are some of the factors influencing rates of suicide.

MENTAL HEALTH CARE IN MIGRANTS

Table 2 lists a series of recommendations to policy makers, service providers and clinicians aimed to improve mental health care in migrants. Some more specific issues are highlighted in the following sections.

Physical health

The physical health of migrants needs to be explored in every assessment for a number of reasons. Mental disorders may be hiding underlying infectious diseases, which may influence their presentation. Physical conditions may be affected by psychiatric conditions. Individuals from traditional countries may not believe in mind-body dualism and may present with somatic symptoms which may become medically unexplained, therefore leading to unnecessary, often obtrusive, investigations adding to stress. The clinician must carry out a full physical examination and necessary investigations as indicated, providing a clear explanation for what is done.

Pharmacological treatments

Due to different pharmacokinetics and pharmacodynamics of psychotropic drugs, a number of ethnic groups show an increased vulnerability to side effects. With a fixed dose regimen of haloperidol, Asians experienced significantly more extrapyramidal side effects than Whites

Table 2 Recommendations to improve mental health care in migrants

Policy makers
- Clear policies taking into account human rights of migrants, refugees and asylum seekers should be developed.
- Adequate resources should be made available according to the needs.
- Adequate resources for training, including cultural competency training, should be available.
- Different parts of the government (e.g., health, education, justice, home, external affairs) should be involved.
- Changes in admission criteria should be discussed with stakeholders, rather than being imposed arbitrarily.
- Public education and public mental health messages for refugees, asylum seekers and migrants should be carried out.

Service providers
- Separate or joined up services should be made available, but it is essential that there are no barriers to help seeking.
- Services should be culturally sensitive, geographically accessible and emotionally appropriate.
- Cultural competence training must be provided and mandatory measures to achieve this should be considered.
- Other models, such as culture broker or cultural liaison, should be employed where indicated.
- Regular research into epidemiological factors, along with qualitative approaches, should be carried out in order to assess and monitor pathology.
- Regular audits into treatment accessibility, acceptability and usage must be conducted.

Clinicians
- Clinicians must have access to resources informing them of specific cultural issues.
- Cultural awareness and competence training must be mandated and regular updates must form a part of this.
- Clinicians must provide culturally appropriate services related to language and other needs of migrants, refugees and asylum seekers. Children, the elderly and other special groups must have their needs met.
- Clinicians may wish to discuss and develop specific services, either condition based (e.g., trauma) or gender based.
- Wherever possible, mental health issues of migrants, refugees and asylum seekers should be part of the curriculum and training of clinicians.
- Cultural training is everyone's business and must be a part of training other health professionals, including primary care professionals.

(63). Hispanics are reported to require half the dose of a tricyclic antidepressant to achieve therapeutic benefit and are more sensitive to side effects (64). African Americans are said to be at greater risk of developing lithium toxicity, because the lithium-sodium counter-transport pathway, a genetically determined mechanism that exchanges intracellular lithium for extracellular sodium, is less effective (65). Thus, clinicians must look out for differences in migrants and ensure that patients are started at low doses and then are gradually built up.

Different cultures have different attitudes and expectations of medication. Individuals may see herbal medication as more natural and acceptable. Those ethnic groups with a strong tradition of herbal remedies may hold beliefs antithetical to the advanced practice of psychopharmacology. The patients may engage in home preparation of the herbs, dosages are fixed, rapid relief is anticipated, side effects minimal, and switching to a new regimen is straightforward (66). If a medication fails to meet these ideals, it will be discontinued and the corresponding illness model disparaged.

Cultural attitudes also affect the interpretation of side effects, which may fit into the explanatory models held by the patient. For instance, the side effect profile of lithium is thought to be universal, but certain effects convey a culturally salient meaning (67). Chinese patients on long-term lithium are unperturbed by polydipsia and polyuria, because these are compatible with the perception that excess removal of toxins from the body is good, but do not welcome fatigue, as it may signify loss of vital energy (67).

Adherence is greatly influenced by the quality of the doctor-patient relationship. The view of the physician as an expert in collaboratively managing chronic conditions, currently favoured by professional bodies and patient groups in the West, might not conform to the "good" doctor in other cultures, where a more authoritative/directive style is preferred. When the patient's and the doctor's cultural groups have been in conflict, this may be played out in the consultation room, leading to a cultural transference and counter-transference which will affect adherence (68). Indeed, the reduced compliance with psychiatric treatment found in African Americans is said to be a result of this factor (69).

Cultural dietary practices will also directly impact upon the pharmacokinetics of a drug. CYP3A4 is inhibited by grapefruit juice and CYP1A2 by caffeine, and the latter is induced by cruciferous vegetables (cabbage, broccoli and brussels sprouts) and smoking. The induction of CYP1A2 by polycyclic aromatic hydrocarbons (PAH) found in cigarette smoke leads to a fall in plasma levels of antidepressants and antipsychotics (70). Smoking is affected by religious values, thus rates vary significantly across ethnic groups. Grilling meat over a dry heat also produces PAH, so CYP1A2 induction will occur in places where this is common, such as Turkey and many Asian countries.

Use of complementary medicines, often not declared to the doctor, either because it is seen as insignificant or because it is felt that doctors will not understand it, may cause pharmacological interactions. St. John's Wort and liquorice (commonly used in traditional Chinese medicine) increase the plasma levels of active metabolites of tricyclics, and may produce serious side effects (71). Other traditional medicines may contain large quantities of heavy metals – such as gold, silver, tin, copper, barium, lead, mercury, zinc, antimony and iron – that can cause toxicity. Associated prescriptions of changes in diet and fluid intake will influence absorption and action of medicines. Religious rituals such as fasting totally or partially can similarly alter the efficacy and tolerability of a prescribed drug.

Doctors must explore attitudes about the medication, expectations of its actions, religious beliefs, diet and use of tobacco and alcohol. It is always worth starting at a low dose, gradually building it up, monitoring side effects and

keeping the patient and his/her carers as informed as possible.

Psychotherapies

Migrants face particular challenges when seeking assistance from psychotherapy services, not least their belief that such services may not apply to them, or be useful for them.

An accurate understanding of a person's cultural background is an essential prerequisite to effecting a helpful therapeutic relationship. For psychological treatments to work, especially in interpretive psychotherapy, the underlying philosophical basis of the approach must be acceptable to the patient. The therapist must allow the therapeutic technique to be modulated by the belief systems of the patients (and their families or carers who may have significant effect on the patient) rather than the other way around. Perhaps the most useful approach may be to tailor the therapy with the most relevant components of Western psychotherapy and the patient's own belief systems to effect the most useful therapeutic encounter.

Migrants may bring with them to the clinic their experience of racism, trauma, war, economic hardship, or enforced relocation. This must be listened to and taken seriously. Rathod et al (72) refer to work done with African-Caribbean patients in which it was necessary to allow the discussion of issues of slavery, racism, and discrimination raised during cognitive behavioural therapy to allow progress to occur.

Inevitably, the degree of acculturation of a patient will make a difference in them accepting therapy. It is possible that especially older Asian patients may see the professionals as authority figures, and expect a directive therapeutic encounter where they are told rather than collaborated with. A didactic style in the early stages may helping engaging the patient. The therapist must be aware of the cognitive styles within the patients' primary culture. Concepts of shame may be stronger in some cultures compared with notions of guilt, thus tailoring of therapy is important.

It can be argued that in sociocentric cultures it should be possible to use group psychotherapy, but this may also raise issues of confidentiality and cultural values adding to stigma. Different levels of linguistic competency and acculturation will add to difficulties. An ethnically diverse group may produce some splitting according to ethnic and racial factions with racial stereotypes playing a role. Members may feel that they are "representing" their culture, which may produce additional stress. Whether a multicultural group is more therapeutic compared with a homogeneous monocultural group depends upon the context and the purpose of the group.

Despite these potential difficulties, evidence suggests that group psychotherapy can be effective in assisting migrants with mental distress. Jenkins (51) states that "interracial and/or interethnic group therapy can be effective if the minority members satisfy themselves that the therapist is sensitive to their socio-cultural and personal situation". Hence, in a group setting with an ethnically diverse population, the responsibility lies with the therapist in ensuring that the difficulties do not inhibit the success of group therapy.

Like other patients, migrants approaching psychotherapy for the first time may carry a mental picture of their therapist and what to expect from him/her. This fantasy will be culturally moulded, influencing expectations and rapport. Patients from a traditional background in Eastern culture may perceive the role of the therapist to be analogous to the role of the *guru* or "spiritual teacher", who divines and explains in a directive manner. Similarly, in traditional African culture – specifically in some parts of Nigeria – Bhugra and Tantam (73) state that "the belief prevails that the most powerful healers know what the person's problem is before the person says anything. Taking a history is, according to this view, a symptom of therapeutic weakness".

The therapist's experience in general, and in working with ethnic minorities in particular, will affect therapeutic engagement. The therapist, by virtue of his/her position, may identify with the new culture to a greater extent than his/her patients, thus contributing to patients' alienation.

In couple therapy, mixed-race or intercultural couples will face specific issues of their own, especially related to acceptance by their family or kinship, which may cause additional stress. This may be used as an advantage in that in some cases they are together despite family opposition, which is an indication of the relationship's robustness. Gender role expectations in the new culture may change and cause stress. Obviously, therapists must explore whether the couple is experiencing distress due to cultural difference between the two partners or any other factors.

Refugees and asylum seekers may see the therapist as an authority figure who in their view can enable them to stay in the country, and help them receive social support and other non-medical outcomes. Thus, the therapist should make the purpose of the therapeutic encounter clear and also set realistic expectations about achievements and outcomes. Therapy may be terminated with little warning if the patient's asylum application is unsuccessful and he/she is deported. In initial stages, the therapist may simply provide a listening ear, allowing the patient to vent his/her feelings. Some such patients, after experiencing sexual or physical violence, may be very wary of authority figures. The therapist and the patient should agree on the priorities and the expected outcomes of therapy fairly earlier in their encounter so that no misapprehension remains. It is entirely possible to engage patients who have different beliefs and explanatory models as long as these views are not denigrated.

CONCLUSIONS

Migration in itself can be a stressful experience. However, not all migrants will experience or respond to the stress in the same way. Individual responses will be influenced by a number of personal, social and cultural factors. Some of these factors can be alleviated by social support networks and cultural congruity. There is considerable evidence to suggest that some migrant groups are more at risk of developing mental disorders. Clinicians, policy makers and service providers need to be aware of specific needs that migrants may have and how these needs are met. Migrants can and do contribute positively to the new cultures and it is imperative that their mental health needs be identified in a culturally appropriate way and services delivered accordingly.

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Adjustment disorders: the state of the art

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Adjustment disorders are common, yet under-researched mental disorders. The present classifications fail to provide specific diagnostic criteria and relegate them to sub-syndromal status. They also fail to provide guidance on distinguishing them from normal adaptive reactions to stress or from recognized mental disorders such as depressive episode or post-traumatic stress disorder. These gaps run the risk of pathologizing normal emotional reactions to stressful events on the one hand and on the other of overdiagnosing depressive disorder with the consequent unnecessary prescription of antidepressant treatments. Few of the structured interview schedules used in epidemiological studies incorporate adjustment disorders. They are generally regarded as mild, notwithstanding their prominence as a diagnosis in those dying by suicide and their poor prognosis when diagnosed in adolescents. There are very few intervention studies.

Key words: Adjustment disorders, sub-threshold diagnosis, suicide, normal adaptive stress reactions, depressive disorder, classification

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The diagnostic category of adjustment disorder was introduced in the DSM-III-R (1). Prior to that, it was called transient situational disturbance. The DSM-IV (2) and ICD-10 (3) descriptions of adjustment disorder are broadly similar. The main features are the following: a) the symptoms arise in response to a stressful event; b) the onset of symptoms is within 3 months (DSM-IV) or 1 month (ICD-10) of exposure to the stressor; c) the symptoms must be clinically significant, in that they are distressing and in excess of what would be expected by exposure to the stressor and/or there is significant impairment in social or occupational functioning (the latter is mandatory in ICD-10); d) the symptoms are not due to another axis I disorder (or bereavement in DSM-IV); e) the symptoms resolve within 6 months once the stressor or its consequences are removed. Adjustment disorders are divided into subgroups based on the dominant symptoms of anxiety, depression or behaviour.

Since its introduction, the category of adjustment disorder has been the subject of criticism on three fronts. The first was that it constituted an attempt to medicalize problems of living and did not conform to the criteria for traditional disorders such as having a specific symptom profile (4). The second was that it was a "wastebasket diagnosis" which was assigned to those who failed to meet the criteria for other disorders (5). The third was on its diagnostic instability (6) and that its main utility was to serve as a "justification" for diagnosis-based reimbursement operating in the healthcare system of the US. Despite this, the category has been retained in the further classifications, in large measure due to its clinical utility.

PREVALENCE OF ADJUSTMENT DISORDER IN VARIOUS CLINICAL SETTINGS

Adjustment disorder continues to be diagnosed in a range of clinical settings. Consultation-liaison psychiatry is the context in which the diagnosis is most likely to be made. Around 12% of referrals are so diagnosed in university hospitals in the US (7), a figure that resembles that in European hospitals (8). Nevertheless, the frequency with which adjustment disorder is now diagnosed seems to be declining, in parallel with an increase in the diagnosis of major depression (9), possibly due to the availability of psychotropic drugs, especially selective serotonin reuptake inhibitors (SSRIs), that are safer in those who are medically ill than the older agents. So, changes in the prevalence of adjustment disorders may reflect a change in the "culture of prescribing", stimulating changes in the "culture of diagnosis" (10).

Adjustment disorder has been reported to be almost three times as common as major depression (13.7 vs. 5.1%) in acutely ill medical in-patients (11) and to be diagnosed in up to one third of cancer patients experiencing a recurrence (12). In obstetric/gynaecology consultation-liaison (13), adjustment disorders predominated over other mood disorders. Among those assessed in an emergency department following self harm, a diagnosis of adjustment disorder was made in 31.8% of those interviewed, while a diagnosis of major depression was made in 19.5% of cases (14).

None of the major epidemiological studies carried out in the community, such as the Epidemiological Catchment Area Study (15), the National Comorbidity Survey Replication (16) or the National Psychiatric Morbidity Surveys (17) included adjustment disorder among the conditions examined. An exception was the Outcome of Depression International Network (ODIN) study (18), which found a prevalence of only 1% for adjustment disorder in five European countries. A possible reason for this was that mild depression was included in the depressive episode category, inflating that category at the expense of adjustment disorder. By contrast, a study of elderly people from the general population (19) found the prevalence of adjustment disorder to be 2.3%, similar to that of major depression.

Adjustment disorder is reported to be very common in primary care, but relevant epidemiological studies in this setting are rare and report rates of the disorder range from 1 to 18% (20,21) among consulters with mental health problems.

Concerning psychiatric settings, a study of intake diagnoses into outpatient clinics (22), combining clinical evalua-

tion and the use of the Structured Clinical Interview for DSM-IV (SCID, 23), found that adjustment disorder was the most common clinical diagnosis, made in 36% of patients, whereas the diagnosis was made in about 11% of cases using SCID. Among psychiatric inpatients, 9% of consecutive admissions to an acute public sector unit were diagnosed with adjustment disorder (24).

Quantifying the prevalence of adjustment disorder in child and adolescent populations is difficult, due to changes in the diagnostic criteria over time (25). In the younger age groups, unlike adults, adjustment disorder carries with it significant morbidity and a poor outcome, frequently developing into major psychiatric illness (25,26). A general population study in Puerto Rico (27) found a rate of 4.2% among 14-16 year old people, while the total psychiatric morbidity was 17.8%. A similar rate was found in children aged 8-9 in Finland (28). Among outpatients, figures of 5.9-7% have been reported (29,30). In child liaison psychiatry, over one third of those with recent onset diabetes were so diagnosed (31), making it the most common psychiatric disorder to follow this well defined stressor.

PROBLEMS WITH THE CURRENT CLASSIFICATION OF ADJUSTMENT DISORDER

The current diagnosis of adjustment disorder assumes that there is a stressor which acts as a trigger and that the condition is self-limiting. So, adjustment disorder is closer to the definition of a discrete disorder as proposed by Kendell (32) than most other disorders in psychiatry, since its etiology and course are encapsulated within the diagnosis, while the definition of many other mental disorders is cross-sectional and based on symptoms alone. Yet, the current classifications impose a hierarchical model that assumes equivalence in how adjustment disorder and other diagnoses are construed.

As currently classified, adjustment disorder is a sub-threshold diagnosis, that is trumped once the symptom threshold for another diagnosis is met. There is an inherent belief that a sub-threshold condition is less severe than a full-blown disorder such as major depression, the diagnosis by which adjustment disorder is most often superseded. Yet, the evidence for this is lacking, and there is empirical data (33) that, when measures of symptom severity or social functioning are examined, there is no difference between those with mood disorders and adjustment disorder.

Furthermore, up to 25% of adolescents with a diagnosis of adjustment disorder engage in suicidal behaviour (34), while among adults with this disorder the figure is 60% (35). Adjustment disorder is the diagnosis in up to one third of young people who die by suicide (36), while among all suicide deaths in the developing world it is the most common diagnosis (37). These data show that, far from being a mild condition, adjustment disorder has a significant impact on behaviour.

On the other hand, the current classifications fail to distinguish between adaptive and maladaptive reactions to stress. The DSM-IV tries to address this problem by stating that a diagnosis of adjustment disorder is only made when the distress is of clinical significance (38). There are two components to this: the distress must be in excess of what would normally be expected and/or there is an impairment in social or occupational function. In relation to the first of these, one of the most insightful critics of the DSM-IV, J. Wakefield (39), points out that it would allow the top third in the normal distribution of mood reactivity to be classified as disordered, and that it does not take into account the contextual factors that might cause this excess in distress. For example, the loss of a job for one person might be manageable while for another it could heap poverty on a family resulting in distress that might not be inappropriate under the circumstances.

Cultural differences in the expression of emotion also need to be considered. In liaison psychiatry, where the diagnosis of adjustment disorder is most frequently made, a knowledge of "normal" coping with illness in that specific culture is essential and the diagnostic process will be guided by the extent to which an individual's symptoms are in excess of this. Some might argue that the fact of visiting a doctor indicates abnormal distress, yet the tendency to consult is also determined by factors additional to illness, including cultural and personal attitudes to symptoms. So, the mere fact of a consultation should not of itself be taken as a proxy measure of excessive distress. Neither should the decision to refer to psychiatric services, since this too is governed by factors that are not always related to symptom severity (e.g., a wish "to do something" under pressure from a patient in the face of continuing distress).

Because adjustment disorder is a diagnosis made in the context of a stressor, there is a danger that any distress following such an event might be labelled as a disorder (40). Clinical judgement, therefore, plays a large part in making the diagnosis of adjustment disorder in the current criterion vacuum and future classifications should accord weight to culture, context and personal circumstances in differentiating normal from pathological distress.

The second criterion, requiring impairment in functioning, is arguably a more robust indicator of disorder, since it is this which leads to treatment seeking. For example, the inability to work is potentially a significant indicator of impairment. However, there may be situations where functioning is reduced in the presence of non-pathological reactions. For instance, if the circumstances are especially traumatic, such as the loss of a child, the period of impaired function may be longer than anticipated in those with non-pathological responses.

The evaluation of functioning in children places special demands on the assessor, since it has to be set against the demands of the developmental stage, and the degree of dependency and autonomy in key relationships. The presence of pre-existing impairment and extant vulnerabilities, such as learning disability and developmental disorders, must also be considered when making the evaluation.

The ICD-10, contrary to the DSM-IV, requires the pres-

ence of both excessive symptoms and functional impairment for the diagnosis of adjustment disorder, thus narrowing the application of this category.

Because of the hierarchical nature of ICD-10 and DSM-IV, adjustment disorder cannot be diagnosed once the criteria for another condition are met. The condition that most frequently trumps adjustment disorder is major depression/depressive episode. This is evident from studies that compare the clinical with the research approach. For example, in a study of those presenting because of self-harm, a clinical diagnosis of adjustment disorder was made in 31.8% and one of major depression in 19.5% of cases, but using SCID the proportions changed to 7.8% and 36.4% respectively (14).

However, there is a point of departure between the two conditions when other variables are considered. Suicidal behaviour occurs earlier in the course of adjustment disorder as compared to major depression (41) and the interval from suicidal communication to completion of suicide is shorter (42). The socio-demographic profile and childhood risk variables differ between the two groups (41). Among adolescents dying by suicide, there is much less evidence of prior emotional or behavioural problems (42). In addition, the readmission rates for those with adjustment disorder are significantly lower than for those with major depression, generalized anxiety or dysthymia (43) and hospitalization is also shorter (6). This highlights the need for the clearer operationalization of adjustment disorder in future classifications.

A further but lesser area of potential overlap is with post-traumatic stress disorder (PTSD). The conflation is not so much related to the symptoms of these disorders but to the stressors themselves. There has been an expansion in the stressors that are deemed to trigger PTSD, from those that are potentially life threatening, as originally described, to events that are less traumatic, such as financial problems or watching distressing images on television – a phenomenon called "criterion creep" (44). In clinical practice, a diagnosis of PTSD is often made reflexively (45) once such an event is identified, although adjustment disorder might be a more appropriate diagnosis.

Overall, it is clear from the data available that adjustment disorder is sufficiently severe and distinct from other disorders, especially major depression, to warrant upgrading from its sub-syndromal status to that of a full-blown and independent mental disorder. Criteria for the DSM-IV revision have already been suggested (46).

STRUCTURED INTERVIEWS, SCREENING INSTRUMENTS AND ADJUSTMENT DISORDER

The Clinical Interview Schedule (CIS, 47) and the Composite International Diagnostic Interview (CIDI, 48) do not incorporate adjustment disorder at all. The Schedules for Clinical Assessment in Neuropsychiatry (SCAN, 49) do include adjustment disorder, but only at the end of the interview, in section 13, which deals with "inferences and attributions". This comes after the criteria for all other disorders have been completed, and there are no specific questions with regard to adjustment disorder to assist the interviewer, relying instead on clinical judgement.

The SCID (23) also includes a section dealing with adjustment disorder, but the instructions to interviewers specify that this diagnosis is not made if the criteria for any other mental disorder are met, with the *de facto* effect of relegating it to a sub-syndromal status. In light of the very low threshold for diagnosing major depression, even in studies using SCID and purporting to be inclusive of adjustment disorder, major depression will often supersede adjustment disorder, irrespective of the context in which the symptoms have arisen.

The Mini International Neuropsychiatric Interview (MINI, 50) also incorporates a section on adjustment disorder but, as in SCID, that disorder is trumped when any other diagnosis is made.

So, while structured interviews have greatly facilitated epidemiological research in psychiatry, the possibility that they are overly rigid, having been designed for use by lay interviewers, cannot be excluded. This is especially pertinent for a diagnosis such as adjustment disorder, which relies heavily on clinical judgement, context and presumptive longitudinal course rather than symptoms alone. As a result of the problems with the current crop of structured diagnostic instruments, attempts have been made to identify suitable screening instruments for adjustment disorder.

Because there is symptom overlap with major depression, there is a possibility that instruments which screen for depression might identify people with adjustment disorder. A number of scales have been used for this purpose, including the Zung Depression Scale (51), which has been shown to be an adequate screen for adjustment disorder and major depression combined (52), but when compared to SCID has inadequate sensitivity and specificity (53). A study of health care workers with "reactive depression", an old-fashioned diagnosis but one which encapsulates the concept of adjustment disorder most closely, found little correlation with the Zung scale score (54).

Efforts to develop a screening instrument using a coping measure have also been unsuccessful (55). The Hospital Anxiety and Depression Scale (HADS, 56) has been used for screening purposes in cancer patients, but it does not distinguish between major depression and adjustment disorder (57). Similar problems arose when the 1-Question Interview and the Impact Thermometer (58) were tested for their ability to screen for adjustment disorder.

The Inventory of Depressive Symptomatology (59) might have a role in distinguishing adjustment disorder from major depression and has been used in one study reporting that non-environmentally induced disorder had more melancholic symptoms and a different quality to the mood changes compared to environmentally triggered disorder (59). Further investigation of this is clearly required.

MAKING THE DIAGNOSIS OF ADJUSTMENT DISORDER IN CLINICAL PRACTICE

The stressor

Adjustment disorder cannot be diagnosed in the absence of a stressor. The event must be external and occur in close time proximity to the onset of symptoms. The longer the time period between the triggering event and the onset of symptoms, the less likely is the diagnosis to be adjustment disorder. For this reason, a period between the event and symptom onset of 3 months in DSM-IV and 1 month in ICD-10 is required. Caution must be exercised when this gap is relatively long, for two reasons: firstly, those who are depressed often attach significance to particular events, that in themselves were neutral in effect at the time, in an "effort at meaning"; secondly, recall bias may lead to an unreliable date of the event. The 3 month upper limit may prove to be excessively long and it is difficult to ascertain the empirical data on which this is based.

Concerning the type of event, there is little to assist the clinician in distinguishing adjustment disorder from major depression. While 100% of those with a diagnosis of adjustment disorder have recent life events, 83% of those with major depression also report such events, with more related to marital problems and fewer to occupational or family stressors in the adjustment disorder group (60). Such differences, while statistically significant, are unlikely to be clinically meaningful in an individual patient, since they are not exclusive as precipitants to either major depression or adjustment disorder. And the events can range in severity from those that are generally regarded as mild, such as a row with a boyfriend, to those that are more serious. This will be mediated by individual vulnerability.

Vulnerability

In the preamble to the section on adjustment disorder, the ICD-10 states that "individual vulnerability and risk plays a greater role than in other disorders" such as PTSD or acute stress reactions. However, it is unclear on what evidence this is based. By contrast, the DSM-IV is silent on this issue. The possibility that a diathesis-stress model operates is worthy of consideration and personality is arguably the most obvious predisposing factor. There have been few studies directly comparing adjustment disorder against other disorders to allow definitive claims about the role of personality, and caution is advisable in the current state of knowledge. The relevant studies can be classified in two broad groups: those directly examining adjustment disorder and those examining diagnoses akin to adjustment disorder.

The prevalence of personality disorder among those with adjustment disorder in comparison to those with other depressive disorders seems to be not different (20), although studies are few and numbers small. Among personality dimensions, neuroticism emerged as a factor predisposing to adjustment disorder in a military sample (61). Attachment style has also been examined, and maternal overprotection was found to be a risk factor for later adjustment disorder (62,63), while paternal abuse was associated with the severity of the disorder (63).

Studies using terminologies that imply a diagnosis of adjustment disorder, such as "reactive", "non-endogenous" or "situational" depression, are also of interest, although there is a caveat that these conditions may not be identical to adjustment disorder due to differences in the definitions in the earlier classifications. One such study (64) found that the strongest relationship was between premorbid neuroticism and a non-endogenous symptom pattern and evidence of "oral dependent" personality. The findings in relation to neuroticism and a non-endogenous pattern of symptoms were replicated by others (65) in studies of subjects and their relatives (66).

Symptoms

The absence of clear symptomatological criteria for adjustment disorder in either DSM-IV or ICD-10 means that greater weight is attached to clinical judgement than in most other current conditions. Symptoms of low mood, sadness, worry, anxiety, insomnia, poor concentration, having their onset following a recent stressful event are likely indicators of a diagnosis of adjustment disorder, although it must be borne in mind that major depression can also present similarly. Mood disturbance is often more noticeable when the person is cognitively engaged with the event, such as when speaking about it, while at other times mood is normal and reactive. The removal of the person from the stressful situation is associated with a general improvement in symptoms. In the case of those who develop adjustment disorder in response to serious illness, changes in mood are related to changes in the illness itself.

The more typically "melancholic" the symptoms are – e.g., diurnal change, early morning wakening, loss of mood reactivity – the less likely is the diagnosis of adjustment disorder. A family history of depression might also suggest a depressive episode.

Due to the low symptom threshold for diagnosing major depression, it is easy to make a diagnosis of this condition rather than adjustment disorder. While the National Institute for Clinical Excellence (NICE) guidelines on depression recommend a period of "watchful waiting" (67), so as to allow for the possibility of spontaneous resolution, under pressure from the patient and his/her family, or the doctor's own desire "to do something", a diagnosis of major depression (or generalized anxiety) may be made and antidepressants prescribed.

Difficulties also arise when the stressor, and hence the symptoms, is persistent and has little likelihood of resolving. Antidepressants may be prescribed on pragmatic grounds, as there is no way of establishing if the symptoms are likely to spontaneously remit or if they are now independent of the

initial trigger and constitute major depression. The absence of a response to antidepressants should raise the possibility that this is an adjustment disorder, so that psychological therapies are offered rather than engaging in protracted trails of multiple medications.

A further consideration is that what appears to be a single stressor (e.g., a diagnosis of a serious physical illness) may be associated with ongoing symptoms as different facets of the diagnosis impinge upon the patient (e.g., the initiation of painful treatments, treatment failures, etc.). Failure to appreciate that rolling stressors prolong symptoms might lead to an erroneous diagnosis of major depression. The role of the consequences of the initial stressor in prolonging symptoms is recognized in the DSM-IV definition of adjustment disorder.

Based on the predominant symptoms, several subtypes of adjustment disorder are recognised by DSM-IV and ICD-10 (Table 1).

The subtypes are broadly similar in the two classifications but, apart from adjustment disorder with depressed mood, they have received little attention. The depressed subtype is the most common in adults, while the subtypes with predominant disturbance of conduct or of conduct and emotions are more commonly diagnosed among children and adolescents.

Differential diagnosis

The distinction between adjustment disorder and a normal stress response is based on the severity of symptoms and their duration; the impact on functioning taking into account the nature of the stressor; the personal and interpersonal context in which it has occurred; cultural norms with regard to such responses.

PTSD and acute stress disorder require the presence of a stressor of a magnitude that would be traumatic for almost everybody and the symptom constellation is also specific, although both of these have recently been challenged (40). Moreover, not everybody exposed to such traumatic events responds by developing PTSD and the possibility that other disorders can follow instead needs to be considered. For those not meeting the PTSD diagnostic criteria, but with significant symptoms and/or functional impairment, adjustment disorder should be considered a possible alternative.

What may appear to be an adjustment disorder, because of the sub-threshold level of the symptoms or the lack of functional impairment, might be an axis I disorder in evolution that only emerges as a recognizable syndrome after a period of watchful waiting. Thus, the revision of an index diagnosis of adjustment disorder may be necessary at times, especially if there are persisting symptoms in spite of termination of the stressor.

Comorbidity

Few studies have examined the disorders that are comorbid with adjustment disorder, an exercise that is hampered by the fact that the criteria for this disorder preclude axis I comorbidity. Yet, a recent study (19) found that almost half of patients exhibited comorbidity with major depression or PTSD. Surprisingly, complicated grief and adjustment disorder were not significantly comorbid.

The relationship between substance abuse and adjustment disorder is also deserving of mention, since it may explain the seeming instability of the adjustment disorder diagnosis. Firstly, substances may be misused for relief of symptoms such as anxiety and depression, which are prominent in adjustment disorder. Substances such as alcohol are themselves depressogenic and may present with mood changes leading to misdiagnosis. This may explain why in one study (6) several patients with an admission diagnosis of adjustment disorder were relabelled on discharge as having a primary diagnosis of substance misuse.

MANAGEMENT OF ADJUSTMENT DISORDER

The evidence base for the treatment of adjustment disorder is limited, due to the paucity of studies. A further problem is that these are self-remitting conditions, so that trials of interventions may fail to identify any benefits due to spontaneous resolution.

In general, brief therapies are regarded as being the most appropriate, with the exception that, when stressors are ongoing, prolonged supportive measures may be necessary. However, there is a caveat for children and adolescents diagnosed with adjustment disorder, since there is evidence (26) that a majority of adolescents eventually develop major mental disorders.

Table 1 Subtypes of adjustment disorder in DSM-IV and ICD-10

DSM-IV	ICD-10
With depressed mood (309.0)	With brief depressive reaction (F43.20)
With anxiety (309.24)	With prolonged depressive reaction (F43.21)
With depression and anxiety (309.28)	With mixed anxiety and depressive reaction (F43.22)
With disturbance of conduct (309. 3)	With predominant disturbance of other emotions (F43.23)
With disturbance of emotion and conduct (309.4)	With predominant disturbance of conduct (F43.24)
Non-specified (309.9)	With mixed disturbance of emotions and conduct (F43.25)
	With other specified predominant symptoms (F43.26)

Practical measures may be useful to assist the person in managing the stressful situation. A person being bullied at work might decide to invoke an internal redress system or may seek the support of the trade union. A person in an abusive relationship might seek a barring order. A vulnerable person taking on too much work may benefit from simple, directive advice. Harnessing family members' input, involving supportive agencies such as social services or encouraging involvement in a support or self-help group may alleviate distress.

Psychological therapies, delivered individually or in groups, span the range including supportive, psychoeducational, cognitive and psychodynamic approaches. Relaxation techniques can reduce symptoms of anxiety. Facilitating the verbalization of fears and emotions and exploring the meaning that the stressor has for the individual might also ameliorate symptoms. In persons who engage in deliberate self-harm, assistance in finding alternative responses that do not involve self-destruction may be of benefit and to date dialectical behaviour therapy (DBT) has the best evidence base (68). Ego enhancing therapy was found to be useful during periods of transition in older patients (69). "Mirror therapy", a therapy including psychocorporeal, cognitive, and neurolinguistic components, was effective in patients with adjustment disorder secondary to myocardial infarction (70). Cognitive therapy was helpful when administered to patients with adjustment disorder who experienced work-related stress (71) and among army conscripts with adjustment disorder (72). In a study of terminally cancer patients (73), similar improvements were found in those with adjustment disorder and other psychiatric diagnoses.

Some of these psychological interventions have been tested in specific medically ill groups, such as those with cancer, heart disease or HIV. While improvements in coping have been demonstrated, it is unclear if subjects had adjustment disorder, some were open pilot studies (e.g., 74) and survival and quality of life rather than symptoms were the outcome measures in others (e.g., 75).

The basic pharmacological management of adjustment disorder consists of symptomatic treatment of insomnia, anxiety and panic attacks. The use of benzodiazepines to relieve these is common (76). While antidepressants are advocated by some (77), especially if there has been no benefit from psychotherapy, there is little solid evidence to support their use. Nevertheless, those with sedative properties targeting sleep and anxiety may have a role when benzodiazepines are contraindicated (78), such as in those with a history of substance dependence.

There are few trials specifically directed to the pharmacological treatment of adjustment disorder and these are mainly on subjects with the anxiety subtype (79-85). A study (79) comparing a benzodiazepine with a non-benzodiazepine found that the anxiolytic effects of each were similar, although more responded to the non-benzodiazepine. Two randomized placebo-controlled trials examined herbal remedies, including extracts from kava-kava (80) and valerian plus other extracts (81), and demonstrated a positive effect on symptoms. A study found that tianeptine, alprazolam and mianserine were equally effective (82), while a pilot study of cancer patients with anxious and depressed mood found trazodone superior to a benzodiazepine (83). One study in primary care (84) examined the response of patients with major depression and with adjustment disorder to antidepressants, using reported changes in functional disability based on case note information. Overall, the adjustment disorder group was twice as likely to respond to antidepressants. However, as this was a retrospective case note study, the relevance of the findings is questionable. One study compared pharmacological and psychological interventions in subjects with adjustment disorder randomly assigned to supportive psychotherapy, an antidepressant, a benzodiazepine or placebo, and found that all improved significantly (85). Overall, these studies lend little support for the superiority of antidepressants, and arguably for any specific treatment, in the management of adjustment disorder, but further studies are clearly required.

CONCLUSIONS

Adjustment disorders are common mental disorders, especially in consultation-liaison psychiatry. Their prevalence seems to be higher in children and adolescents, in whom they are associated with significant morbidity and a poorer outcome than in adults. Suicidal behaviour is common in both adolescents and adults with these disorders, and adjustment disorder is the diagnosis in up to one third of young people who die by suicide.

There are major problems with the diagnostic criteria for adjustment disorder in both ICD-10 and DSM-IV. The most prominent of these is the status as sub-syndromal conditions. This has resulted in their being the subject of little research. Furthermore, current classifications fail to provide guidance on distinguishing these disorders from normal adaptive reactions to stress, and encourage the diagnosis of major depression in people with self-limiting reactions to stressors.

Treatments for adjustment disorders are underinvestigated, although brief psychological interventions are likely to be the preferred option.

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Do we have any solid evidence of clinical utility about the pathophysiology of schizophrenia?

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A diagnosis of schizophrenia, as in most of psychiatric practice, is made largely by eliciting symptoms with reference to subjective, albeit operationalized, criteria. This diagnosis then provides some rationale for management. Objective diagnostic and therapeutic tests are much more desirable, provided they are reliably measured and interpreted. Definite advances have been made in our understanding of schizophrenia in recent decades, but there has been little consideration of how this information could be used in clinical practice. We review here the potential utility of the strongest and best replicated risk factors for and manifestations of schizophrenia within clinical, epidemiological, cognitive, blood biomarker and neuroimaging domains. We place particular emphasis on the sensitivity, specificity and predictive power of pathophysiological indices for making a diagnosis, establishing an early diagnosis or predicting treatment response in schizophrenia. We conclude that a number of measures currently available have the potential to increase the rigour of clinical assessments in schizophrenia. We propose that the time has come to more fully evaluate these and other well replicated abnormalities as objective potential diagnostic and prognostic guides, and to steer future clinical, therapeutic and nosological research in this direction.

Key words: Schizophrenia, etiology, pathophysiology, diagnosis, early diagnosis, treatment response, predictive power, likelihood ratio

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In everyday psychiatric practice, diagnoses are made by noting the constellation of a patient's symptoms, with little contribution from observable signs and virtually none from investigations. This places psychiatry in an unusual, but not unique, position compared to other medical disciplines (1,2). Diagnostic accuracy, prognostication, management plans, and treatment evaluation are dependent on relatively subjective clinician assessments, and thereby prey to undue cultural influences and value judgements (3,4). There is a pressing need for objective tests to improve the classification of psychiatric disorders, to stratify patients into more homogeneous groups, and to plan their treatment accordingly. The current research focus on genetic, protein-based and imaging-linked "biomarkers" could help move from syndromal diagnoses to an etiological and/or pathophysiological classification, as well as aiding research into the identification of therapeutic targets.

In the 100 years or so since schizophrenia was first described (5) and named (6), the diagnostic criteria may have been refined, but the process in everyday practice has remained essentially the same. Psychiatrists rely on the patient's description of symptoms, mental state examinations and behavioural observations, in line with the categories listed in the DSM-IV and the ICD-10. In both manuals, the presence of one of Schneider's first rank symptoms (FRS) is usually sufficient to make a diagnosis of schizophrenia. These diagnostic criteria have facilitated research into the causes of schizophrenia, and definite advances in our understanding of its origins and development have been realized. Several risk factors for the subsequent development of schizophrenia are established beyond reasonable doubt (7,8), and an impressive array of genetic, anatomical, functional, neurophysiological and neuropsychological findings regarding the pathophysiology of schizophrenia are now well replicated (9,10). The key clinical question is, however, whether we have learned anything about the nature of schizophrenia that could be useful in the management of our patients.

In this review, we address this question in terms of making a diagnosis or an early diagnosis and in predicting therapeutic response. We do this by identifying the most robust findings and discussing their potential applications in clinical practice, in the realms of clinical features, historical information, cognitive testing, serum biomarkers, structural and functional imaging, and electrophysiological indices.

METHODS OF THE REVIEW

As we are interested here in clinical utility over and above statistical significance, we concentrate on studies which provide data in terms of the sensitivity and specificity of the variables as a diagnostic aid, the predictive power of a test result and/or the likelihood that a test result in an individual patient is indicative of schizophrenia. It is worth noting that sensitivity and specificity are generally constant properties of a test, which are useful in service planning but not in dealing with individual patients. The positive predictive value (PPV) or negative predictive value (NPV) of a test result gives the risk level for a particular patient, which is useful clinically, but PPVs and NPVs are prevalence-dependent measures, and performance can therefore vary markedly in different settings (11). Likelihood ratios are a means of using sensitivity and specificity data to calculate the implications of test results in a particular patient (12-14). As a rough rule of thumb, likelihood ratios of a positive test result (LR+) of more than 5, and preferably more than 10, increase the risk of disorder by about 30% or 45%, respectively. The latter would, for example, indicate a clear change from a pre-test probability of say 50% (maximal

uncertainty) to a post-test probability of 95% (highly likely). This might at first appear to be an alien practice, but it is for example what underpins the use of the CAGE questionnaire in identifying alcohol problems and the Mini Mental State Examination in diagnosing dementia (15,16).

The type of study we need for a diagnostic test is a cross-sectional one comparing a representative population of patients and non-cases (controls for diagnosis, other diagnoses for differential diagnosis) who have been evaluated with the gold standard and blindly assessed with the test. For early diagnosis and treatment response tests, we need a longitudinal and preferably prospective study of a cohort of patients evaluated before or after the onset of their condition and followed up until outcome is clear, with preferably less than 20% loss to follow-up.

In this review, we sought to identify replicated evidence from systematic reviews for the diagnosis, early diagnosis and treatment response of schizophrenia, in terms of the reliability of the examination, the size of the difference between schizophrenia and controls, and the ability to discriminate versus bipolar disorder. In each of our specified domains, we particularly sought reviews with some consideration of measurement reliability, heterogeneity and publication bias. We favoured reviews reporting an effect size such as Cohen's d of 1 or more, as this roughly and generally corresponds to a 70% non-overlap of data distributions and an odds ratio (OR) of approximately 5 (17).

DIAGNOSIS

In everyday medical practice, history-taking identifies diagnostic "hypotheses". Evidence for and against these is sought on physical examination and (ideally) confirmatory diagnostic testing. In psychiatry, a similar initial approach is followed by the mental state examination, which includes more explicit evaluation of appearance, behaviour and speech than in the rest of medicine, but also several questions that are just further history gathering and some cognitive testing often of dubious validity. We psychiatrists are curiously averse to physically examining our patients and surprisingly willing to accept "CNS grossly normal" in medical records when this probably means that no neurological exam has been attempted. We might consider possible "organic" explanations for "secondary schizophrenia" and contemplate referral for brain imaging in unusual cases, but that is about as far as investigation is usually taken.

To provide some clinical background, and as a comparator for laboratory tests, we first consider the evidence base for key aspects of the clinical examination in making a diagnosis of schizophrenia.

Clinical history and examination

Psychotic symptoms

Although counter-intuitive, and despite the potential tautology, particular psychotic symptom types are not in themselves strong associates of schizophrenia. Bizarre delusions, for example, are less reliably elicited (mean kappa across studies 0.5 or "moderate") than delusions in general (0.7 or "substantial agreement") (18), and have a low specificity, despite a PPV as high as 0.82 in 214 consecutive admissions (19). Similarly, Schneider's FRS have been oversold as pathognomic, as they are both too rare to be a generally useful diagnostic aid, especially if strictly defined, and too common in other psychotic disorders (20). Peralta and Cuesta (21) recruited 660 inpatients with "the full spectrum" of psychotic disorders and found that any individual FRS usually had a LR+ of 1-2 for schizophrenia, depending on the particular symptom and the diagnostic criteria examined, and no FRS had a LR+ more than 4.

Risk factors as diagnostic aids

There is clear evidence that several variables increase the risk for schizophrenia to a statistically significant degree (7,8,22). Table 1 lists some of these. Indeed, many of these risk factors, and especially family and developmental history, are sometimes used as supportive evidence to make a diagnosis of schizophrenia, but in an informal and variable way. These factors rarely elevate the risk by more than 5x relative to the baseline population risk of approximately 1%. Even elevating that risk to approximately 10% in the presence of a positive family history in a first-degree relative (10) is clearly not very helpful, and reliably eliciting the information might require structured assessments (23).

Where the presence of such risk factors might be helpful is in differential diagnosis, perhaps particularly in hospital settings where psychosis is much more prevalent, as the major psychoses may breed partially true (24), and urban birth and developmental disruption may be more potent risks for schizophrenia than bipolar disorder (22).

On the other hand, although the risk of schizophrenia is clearly elevated by experiencing obstetric complications (OCs), the additional risk from any one complication is much smaller, and OCs probably increase the odds of a range of adverse neurodevelopmental outcomes (25,26). If one was to make clinical use of the association between immigration and schizophrenia, despite the heterogeneity (27), one might quickly run into allegations of racism. Regular cannabis use is a risk factor for schizophrenia (28,29), but it is sometimes argued,

Table 1 Best replicated historical risk factors for schizophrenia (adapted from 7,22)

Variable	Level of risk	Key supporting reference
Family history	RR up to 50	Gottesman (10)
Immigrant status	OR = 5	Cantor-Graae and Selten (27)
Childhood social difficulties	OR up to 5	Tarbox and Pogue-Geile (110)
Obstetric complications	OR = 2-3	Cannon et al (26)
Cannabis use	OR = 2-3	Moore et al (29)

RR – risk ratio; OR – odds ratio

without much evidence, that this may not be a causal relationship, i.e. that people with pre-schizophrenia take up cannabis use perhaps in a bid to self-medicate (30). Nevertheless, it is clear from randomized controlled trials that cannabinoids prescribed, for example, as anti-emetics for people with cancer increase the risk of hallucinations about six-fold and delusions more than eight-fold (31). Cannabis may therefore only induce psychotic symptoms, and some additional factor or at least chronic, frequent use may be required before schizophrenia develops. Thus, the standard clinical practice of making a diagnosis of drug or cannabis induced psychosis in regular drug users, and watchful waiting to see if schizophrenia develops, is probably rational. We are not aware, however, of any studies examining this practice, or indeed the relative merits of subjective versus objective assessments of cannabis use in so doing.

It should hopefully be clear that we do use risk factors in making a diagnosis of schizophrenia, but as currently implemented this is haphazard.

Physical signs

Despite our reluctance to examine our patients physically, it is clear that there are some physical signs which are risk factors for schizophrenia and of potential pathophysiological significance. Minor physical "anomalies" like abnormal head circumference, hypertelorism, and non-right handedness are, however, too non-specific and only raise the risk of schizophrenia slightly (32,33), while dermatoglyphic patterns are difficult to discern (34). Neurological "soft" signs (NSS) are more promising, as it has been reported that 50-60% of patients with schizophrenia have observable deficits in sensory integration and motor coordination, as compared to about 5% of normal controls (35). In a thorough recent systematic review and meta-analysis, Chan et al (36) found an overall effect size of 1.08, corresponding to a 73% separation (17) between the populations, although this effect size is probably inflated by the difficulties in blinding such assessments to patient and control status. There was, however, largely unexplained statistical heterogeneity, and evidence of publication bias, potentially attributable to difficulties in reliably eliciting these appropriately named phenomena.

Rigorous evaluation of NSS may be particularly difficult in patients with the most acute psychoses. Further, while it is clear that these signs are not simply attributable to antipsychotic treatment, it is unclear to what extent they reflect the nature of the underlying pathophysiological processes of schizophrenia, as disease specificity has only been studied rarely (35). Given, however, that certain NSS may be more genetically mediated (37), and that NSS have been proposed as clinical and functional outcome predictors (35), the area does look promising for further clinically oriented research (see Table 2). There may be value in considering the reliability and diagnostic specificity of individual signs within the major domains of NSS and their likely anatomical underpinnings – motor dexterity (cerebellum), primitive reflexes (frontal lobe), motor sequencing (prefrontal cortex, PFC), and sensory integration (parietal lobe) – in more detail than just a global NSS score.

Cognitive testing

Examining cognitive status in everyday psychiatric practice is usually done with a few quick tests of largely unproven reliability and validity. Evaluating cognitive performance rigorously is not routine outside a research setting, but patients with schizophrenia certainly have a range of intellectual impairments (38), most of which are evident at first episode (39). Meta-analyses have identified large (d>1) deficits in general intelligence (38-40), processing speed (41), various aspects of memory (38,39,42,43), verbal fluency (44), social cognition (45) and theory of mind (46). It remains difficult, however, to establish whether there are specific deficits over and above general performance decrements. There is also marked heterogeneity between studies, potentially attributable to the effects of mental state on performance and cooperation, the fact that many patients can approach normal performances at times, as well as variation in the populations studied and in how assessments are conducted and scored.

From a pathophysiological point of view, there is also the problem that many of these cognitive deficits appear to be largely present prior to the onset of psychosis, with some further deterioration, in some cases at least, after onset; all probably confounded by other risk

Table 2 Large consistent effects from meta-analyses of studies of physical and cognitive examinations of patients with schizophrenia versus controls

	Effect size vs. controls	Different from relatives	Evident at first episode	Specificity vs. bipolar disorder	Other issues
NSS	1.08, but with heterogeneity (Chan et al, 36)	Yes	Yes	Requires more study	Blinding reliability and practicality issues; specific domains and items may have stronger diagnostic properties
IQ	1.10, but with heterogeneity (Heinrichs and Zakzanis, 38)	Yes	Yes, at least in part, but some possible progression	Premorbid IQ deficits may differentiate	Various methods

NSS – neurological "soft" signs

factors, treatment effects and other aspects of the disorder (40,47). Very few studies in this vast literature have considered the potential diagnostic utility of deficits, although there are replicated demonstrations that about 80% of patients score below normal memory thresholds (48,49).

From a clinical perspective, most task deficits also appear to be evident in patients with bipolar disorder and psychotic depression, albeit to a slightly lesser extent (50-52). General intellectual impairments are, however, more commonly found in schizophrenia than bipolar disorder, especially before diagnosis (38,51). It may be that IQ level, and perhaps especially pre- to post-morbid deterioration, would provide useful information in making diagnoses (53,54), or perhaps in identifying a subgroup at risk of poor prognosis and/or in need of aggressive treatment. Given the heterogeneity in IQ assessments in schizophrenia, it may also make sense to evaluate discrete aspects such as processing speed or verbal fluency, perhaps as part of brief assessments with well-evaluated psychometric properties, such as the Brief Assessment of Cognition in Schizophrenia (55).

Blood tests for "biomarkers"

Genomics

It is well known that schizophrenia has a large heritable component. Genetic factors and gene-environment interactions contribute up to 80% of the liability to the illness (10,56). As the clinical phenotype is complex, and the pathophysiology is likely to be polygenic, the genes involved have been hard to find. In recent years, a number of convergent findings in linkage (57), association and animal studies have consistently implicated several genes, for which the most consistent evidence is arguably for the "Icelandic haplotype" in the neuregulin-1 gene (58), although the overall OR of about 2 and continuing uncertainty about which particular genotype is implicated mean that this remains of purely research interest. The recent complete mapping of the human genome has enabled several genome wide association studies in schizophrenia, which have been meta-analysed to reveal multiple small effects across the genome, with the strongest overall effect (OR ~ 1.09) being in the ZNF804A gene encoding a putative zinc finger protein (59).

Rare variants conferring risk for schizophrenia have also been identified. Perhaps the most striking example is the DISC1 (Disrupted in Schizophrenia 1) gene, identified in a large Scottish family in which a chromosomal translocation is associated with a high frequency of schizophrenia (60), although this translocation is possibly unique to this family and raises the risk for bipolar disorder and depression as well. Smaller chromosomal abnormalities, known as copy number variants (CNVs), are also more common in patients with schizophrenia than controls. One relatively common example is the 22q11 deletion known to occur in velo-cardio-facial syndrome, which is associated with a greatly increased risk (RR ~ 30x). Notably, this genomic region includes the catechol-O-methyltransferase (COMT) gene, involved in dopamine metabolism, which may also be a risk gene for schizophrenia, perhaps especially in multiply affected families. Initial genome-wide studies of CNVs provide replicated associations of schizophrenia with rare 1q21.1, 15q11.2 and 15q13.3 deletions. Collectively, several rare CNVs may elevate risk for schizophrenia, perhaps especially the more developmental forms of the disorder, but large CNVs do not appear to be implicated in bipolar disorder. Including 22q11.2 deletions, CNVs appear to account for up to 2% of schizophrenia (61). It would however be premature to routinely screen patients for CNVs, both because causality has yet to be established and the information gained might not influence management.

Proteomics

Quantitative and qualitative protein patterns in cerebrospinal fluid (CSF) and serum have potential as diagnostic and prognostic biomarkers in schizophrenia and other psychiatric disorders (62-64). There has been much interest in serum brain-derived neurotrophic factor (BDNF) levels in patients with schizophrenia, as BDNF has roles in neuronal proliferation, differentiation and dopamine neurotransmission, but extremely mixed results have been reported compared with controls. Inconclusive results have also been reported for serum levels of epidermal growth factor. There are more consistent results from several studies supporting an association between schizophrenia and S100B, a calcium-binding protein produced primarily by astrocytes, where increased concentrations likely result from astrocyte destruction. Most studies report increases in serum and CSF S100B concentrations in schizophrenia (65-68).

The potential importance of immunity in the pathogenesis of schizophrenia is supported by findings of altered serum concentration of several proinflammatory cytokines. Potvin et al (69) examined data from 62 studies, involving a total of 2298 schizophrenia patients and 1858 healthy volunteers, and found consistent increases in interleukin 6 (Il-6), soluble IL-2 receptor, and IL-1 receptor antagonist, and a decreased in vitro IL-2 in schizophrenia. Il-6 is, however, also reduced in depression, and stress and weight gain are potential confounders (70). This highlights the care required in interpreting these studies, particularly given the infamous "pink spot" in the urine of patients with schizophrenia in the 1960s and the consistently reduced levels of platelet monoamine oxidase (MAO) in the 1980s, which were eventually related to smoking status (71).

Brain imaging investigations

There is overwhelming evidence for a variety of consistent abnormalities of brain structure and function and electrophysiology in patients with schizophrenia compared to healthy controls (72,73) (see Table 3 for examples). There are similar concerns as with the cognition studies about when these abnormalities develop. The imaging literature

Table 3 Large consistent effect sizes from meta-analyses of brain imaging studies in patients versus controls

	Effect size vs. controls	Different from relatives	Evident at first episode	Specificity vs. affective disorder	Other issues
sMRI regional brain volumes	Up to 0.86, some with heterogeneity (Wright et al, 76)	Yes, at least hippocampus and ventricles	Yes, at least hippocampus and ventricles	Amygdala volume may discriminate but may depend on age and treatment	Pattern recognition methods may be more powerful
Hypofrontality	0.64 at rest; 1.13 when active (Zakzanis and Heinrichs, 85)	Yes	Yes	DLPFC activity possibly	Performance level needs to be allowed for
Mismatch negativity	0.99 (Umbricht and Krljes, 98)	Possible	Possible, but some possible progression	Possible	-

sMRI – structural magnetic resonance imaging; DLPFC – dorsolateral prefrontal cortex

shows, however, less evidence of heterogeneity across studies and somewhat greater evidence for specificity versus bipolar disorder.

Structural brain imaging

Structural magnetic resonance imaging (sMRI) is relatively straightforward, cheap and available, and shows perhaps the greatest current promise as an objective diagnostic test for schizophrenia. The effect sizes are small, but the measures are inherently quantitative. Perhaps the greatest single demonstration of the power of this approach is from the landmark finding that monozygotic twins with and without schizophrenia could be discriminated by simply eyeballing their sMRI scans, and in particular the ventricles and medial temporal lobes, in 80% or more of the 15 pairs (74). Of course, twins are in short supply in clinical practice. More realistic is to use the evidence from what is now a large sMRI literature in schizophrenia, that there are consistent if relatively small reductions in whole brain, PFC and temporal lobe volumes (d = 0.2-0.4), and consistently reduced amygdala volumes (d ~ 0.7) in schizophrenia (75-77). Moreover, the sMRI changes in schizophrenia are less marked in relatives and others at high risk, show evidence of changes around the time of onset and are largely evident at first episode (78). The effect sizes are greater in schizophrenia than bipolar disorder (79,80), and the amygdala may actually be large or normal in bipolar disorder (79), perhaps particularly in younger patients. This merits intensive study as a possible discriminator, although there are technical difficulties in reliably extracting volumes in such a small structure.

A number of automated support vector machine (SVM) analyses have recently been applied to sMRI data in schizophrenia (81). Generally, 80-90% of patients can be identified from their similarity to a group pattern for schizophrenia (82-84), although these studies do tend to rather circularly use group differences to inform the group classification, and do not convincingly agree on the anatomical patterns of differentiation. The challenges for such studies are to distinguish schizophrenia from bipolar disorder, to generate individual scan readings, to cross test various models on various software routines, and to compare them with other diagnostic techniques including other approaches to brain imaging.

Functional brain imaging and electrophysiology

Hypofrontality

The relative underactivation of PFC is one of the most consistent findings in schizophrenia research. Zakzanis and Heinrichs (85) found an overall effect size from 21 resting positron emission tomography (PET) studies of –0.64, a 60% overlap in data distributions, and an even greater effect from 9 activated PET studies of –1.13, a 40% overlap, although they did not examine for heterogeneity or publication bias. As currently reported, functional MRI (fMRI) studies do not lend themselves to the calculation of overall effect sizes, but hypofrontality is clearly evident in dorsolateral PFC on working memory studies (86) as it is in (left) inferior PFC on verbal memory tasks (87). Functional imaging studies and especially fMRI also tend to be analysed in relative rather than in absolute terms, preferable for diagnostic evaluations. Nonetheless, several classification studies have found that dorsolateral PFC activation on various tasks might distinguish schizophrenia from bipolar disorder (88,89), and similarly high diagnostic accuracy (>80%) has been reported in default-mode network activity (90) and on resting fMRI (91). However, a recent study found less discrimination, perhaps because task performance differences clouded the picture (92). It remains to be seen how such an approach would cope with the most difficult differential, i.e. when those with bipolar disorder in the sample are experiencing active psychotic symptoms.

Positron emission tomography (PET)

PET has also been used to assay neurotransmitter receptors in vivo, and dopamine D2 receptors in particular. This has been a controversial field, but D2 receptors are increased overall, with an effect size of 1.47 across 17 post-mortem and PET studies (93), including some medication naïve subjects. Furthermore, there is a very consistent literature dem-

onstrating increased pre-synaptic activity in the striatum, as indexed by greater amphetamine-promoted dopamine release and greater F-DOPA uptake in schizophrenia (94). A preliminary classification study is also encouraging (95), although making a distinction between schizophrenia and bipolar disorder with psychotic symptoms is arguably unlikely.

Electrophysiology

A small number of studies have provided data on the sensitivity and specificity of EEG findings in the differential diagnosis of schizophrenia, with very mixed results (96). Several measures of neuronal responses to stimuli, especially the P300 and P50, show large effect sizes versus controls, but large amounts of unexplained heterogeneity between studies (97). They also tend to show almost as large effects in relatives, suggesting a greater loading on trait rather than state effects, and possibly less utility for diagnosis. Mismatch negativity does, however, show promise in these regards (see Table 3) and has possible specificity (98). Finally, a solitary but impressive study has considered exploratory eye movements in 145 patients with schizophrenia from seven World Health Organization collaborative centres and found more than 85% sensitivity and specificity against depression and healthy controls (99), although a recent Japanese multisite study was less successful (100).

EARLY DIAGNOSIS

Diagnoses have value for communication and prognostication, but particularly for planning action. Early diagnosis is actually akin to accurate prognostication within a group as to who will develop the disorder of interest and who will not. Studies of early diagnosis therefore require lengthy follow-up, and any predictors should ideally be unambiguously defined and measured, and improve upon what can be achieved in current practice. Again, therefore, we first consider the potential role of psychotic symptoms in early diagnosis.

Clinical features

Psychotic symptoms as predictors

A range of childhood psychopathologies have been shown to predict schizophrenia. The strongest of these have included: self-reported psychotic symptoms at age 11, which increased the risk 16x of schizophreniform disorders at age 26 (101); schizophrenia spectrum personality disorder (PD) at mid-teens in Israeli army conscripts males, increasing the risk of schizophrenia by 21.5 times (102); and diagnoses of alcohol abuse, any PD, or substance abuse in Swedish army conscripts aged 18 or 19, increasing the risk of subsequent schizophrenia (OR 5.5, 8 and 14, respectively) (103). These statistical effects are, however, insufficiently replicated and too prone to high false positive rates for clinical use.

Early diagnosis becomes more practically and ethically straightforward when people present as patients with prodromal symptoms. Klosterkotter et al (104) followed 160 prodromal patients over a decade and found that ten "basic symptoms", including subtle disturbances of mental life such as stress sensitivity, had PPVs of more than 70%. This has yet to be replicated, however. The most common approach has been to use the ultra high risk (UHR) criteria devised as a means to predict transition to psychosis in clinic attenders in Melbourne (105). The transition rates to psychosis (not just schizophrenia) were as high as 54% within 12 months at first, with PPV/NPV both more than 80% (106), but these figures have steadily fallen with time and application in different settings, so that transition rates can now be as low as 14% after 12 months and 19% after 18 months (107).

Several prospective cohort studies have followed children or adolescents at high genetic risk as they are offspring or otherwise related to patients with schizophrenia. Thought disorder and negative symptoms, behavioural or neuromotor dysfunction, and attention and memory impairment are fairly consistent predictors in these studies (108), but only two studies have reported data in terms of clinical prediction. In the New York High Risk Project (NYHRP), the predictive power of symptoms for adulthood schizophreniform psychosis was not that high (107). In the Edinburgh High Risk Study (EHRS), in which the baseline risk of transition to schizophrenia was 21/162 (13%), psychotic symptoms at interview only had a PPV of 25%, a schizotypal PD at interview only had a PPV of 29% and the strongest behavioural predictor of any sort was a self-completed questionnaire for schizotypal traits (the Rust Inventory of Schizotypal Cognitions, RISC, PPV 50%). All of the foregoing did, however, have NPVs more than 90%, and the RISC figures correspond to an LR+ of >5 (109).

Risk factor prediction

These prospective cohort studies of young people at high genetic risk have also established a number of behavioural abnormalities in childhood and adolescence that predict subsequent psychosis, usually with greater power than family history, migration, OCs or regular cannabis use (108). In the EHRS, none of those risk factors was a statistically significant predictor of schizophrenia, but several aspects of childhood behaviour, as elicited from the mothers with the Achenbach scale, were (109). Tarbox and Pogue-Geile (110) recently summarized this literature and concluded that "poor undifferentiated social functioning" is a moderately sensitive predictor of schizophrenia among children aged 7–8 in the general population; whereas, among high risk children, poor social functioning may be quite sensitive to schizophrenia as early as age 5-6. However, given an estimated effect size (d) of about 1, and an OR of about 5-6, it would be mistaken to try to predict psychosis on this basis. Even with the elevated baseline risk of 13% in the EHRS, the sensitivity and specificity of such behaviours were too low (109).

Physical examination and neuropsychological test prediction

In the NYHRP, the offspring were tested with neurobehavioral measures at 7-12 years of age and assessed in mid-adulthood for schizophrenia-related diagnoses. Childhood deficits in attention, verbal memory, and gross motor skills identified 83%, 75%, and 58%, respectively, of those with psychoses; 50% were identified by all three variables combined. Encouragingly, the three variables had low deficit rates in the offspring of two other parental groups and were not associated with other psychiatric disorders in any group, but false positive rates were 18-28%, which the authors rightly regarded as insufficient evidence for antipsychotic drug prescribing (111). Michie et al (112), similarly, reported a false positive rate of 21% as unacceptably high in children assessed for sustained attention deficits. Worse, NSS were not predictors of symptoms or schizophrenia in EHRS (113), and cognitive tests were at most weak predictors (114).

Indeed, Pukrop et al (115) recently reviewed 32 relevant cognitive studies and found that investigations of neurocognitive baseline assessments in high-risk samples are inconsistent in terms of the deficits found. Longitudinal studies tend to favour measures of processing speed and of verbal memory and learning as predictive of psychosis, but the weak predictive effects, negative studies and unstable performance argue against the usefulness of cognitive tests in early diagnosis, at least in isolation.

Multivariate prediction

Several studies around the world have now examined the predictive performance of combinations of symptoms and other variables, with mixed results. Even though features like bizarre thinking and schizotypy are commonly replicated, they tend to do so as part of multivariate models which are dissimilar (104,105,107). The North American Prodrome Longitudinal Study (NAPLS) followed up 291 prospectively identified treatment-seeking patients with prodromal syndromes criteria, 35% of whom developed schizophrenia. Of 77 variables, five baseline features contributed uniquely to the prediction of psychosis: a genetic risk for schizophrenia with recent deterioration in functioning (one of the UHR criteria), higher levels of unusual thought content and suspicion/paranoia, greater social impairment, and a history of substance abuse (116). Prediction algorithms combining 2 or 3 of these variables resulted in dramatic increases in positive predictive power (up to 80%) compared with the UHR prodromal criteria alone. The equally impressive European Prediction Of Psychosis (EPOS) study established high inter-rater reliability for the >60 items they examined and optimal prediction with six variables (positive symptoms, bizarre thinking, sleep disturbances, schizotypal PD, highest functioning in the past year, and years of education). This combination gives a positive likelihood ratio above 10 (107). It awaits replication, however, and did not replicate the predictive power of either the Bonn (104) or NAPLS criteria (116).

Blood tests

In theory, the genomic biomarkers described above could potentially predict schizophrenia at an early stage of development, many years before onset. There are, however, only two studies which have taken blood before diagnosis, and both of these in adults rather than children, perhaps for practical and ethical reasons. In the EHRS, NRG1 status was associated with the onset of psychotic symptoms (117), whereas the COMT Val/Met allele polymorphism was the only schizophrenia predictive blood test (Val allele present PPV 39%, NPV 93%; 118). This result gains partial support from replicated work showing a COMT-cannabis interaction (119), although there was no such interaction in the EHRS. Clearly, these results require clarification before genotyping could be employed as a diagnostic marker in high risk groups.

Neuroimaging

There are now a number of studies of people at genetic high risk or with prodromal symptoms who have been imaged at baseline and subsequently examined for transition status, some with follow-up imaging. Reductions of grey matter (GM) density in orbito-frontal cortex (120-122) and medial temporal lobe (120,122) are now clearly replicated in the prodrome to schizophrenia, although the numbers are small. Three studies have taken these analyses further into the clinical domain. Schobel et al (124) found that increases in hippocampal CA1 cerebral blood volumes on contrast enhancement predicted subsequent psychosis with PPV 71% and NPV 82%. Koutsouleris et al (125) found overall SVM classification accuracies of around 90% in discriminating between at risk groups and healthy controls. A receiver operator characteristic curve analysis of GM change in the inferior temporal lobes in the EHRS showed that these were more strongly predictive of schizophrenia than any other variable in that study, with a likelihood ratio of more than 10 (126; PPV 60%, NPV 92%).

It would, of course, be much easier and cheaper to be able to use one baseline scan to predict schizophrenia, and several groups have provided proof of concept studies, although the results are confusing. As Smieskova et al (127) showed in a recent systematic review of the literature, cross-sectional voxel-based morphometry studies have replicated decreased GM in frontal and cingulate cortex in the pre-psychotic, yet whole brain volumes and/or global GM volumes were consistently increased. Indeed, in the EHRS, increased PFC folding on the first scan had a PPV of 67%, our strongest baseline predictor (128). This points to a dramatic reduction in volumes around onset, which could be focus for future investigations, and suggests that analysis techniques which can allow for baseline increases and decreases as well as change may have the best diagnostic performance.

PREDICTING ANTIPSYCHOTIC DRUG TREATMENT RESPONSE

Treatment response is pertinent to clinically relevant pathophysiology to the extent that available treatments address the fundamental disease process or processes rather than being simply ameliorative in some way. We can be confident that antipsychotic drugs treat the hyperdopaminergia associated with positive psychotic symptoms, and even though it is not clear that this is the primary disease process in schizophrenia, there is substantial evidence that this represents a common pathway to acute delusions and hallucinations.

Clinical predictors

Several historical variables have been repeatedly associated with a good response to antipsychotic drugs (including symptom severity, early subjective and objectively rated response to the drug, and the duration of untreated psychosis), but very few researchers have examined their diagnostic properties in prediction (129,130). Recent examples include an attempt to use baseline Positive and Negative Syndrome Scale (PANSS) scores to predict response at week 2, but the predictive values were low (131). Leucht et al (132) have shown that predicting non-response on the Brief Psychiatric Rating Scale (BPRS) at 4 weeks with a PPV of >80% was only possible if there had been absolutely no improvement at all in the first two weeks. The prediction of remission might be improved by the inclusion of 4- and 6-week assessments, but the increase in prediction accuracy is modest at best and unlikely to be clinically useful (133).

The Drug Attitude Inventory is a 30 item self report inventory which has good psychometric properties and diagnostic performance, perhaps because it captures elements of both an early subjective response and positive attitudes to medication (134), which are both associated with compliance. This and standardized symptom severity and outcome ratings might be usefully incorporated into routine clinical practice, at least to help reliably determine people's attitudes to treatment and whether they have benefitted sufficiently to stay on a treatment.

Biological predictors

Biomarkers of treatment response do not have stiff competition, but they still have a long way to go. Higher antipsychotic drug plasma levels and raised homovanillic acid (HVA) and other peripheral markers in plasma (and CSF) have been repeatedly related to response, but the replicability, diagnostic performance and practicality of this are unclear (135). Further, plasma measures are themselves often at best indirect measure of cortical activity. Most potential pharmacogenetic predictors of antipsychotic drug response have also fallen at the stage of reproducibility. Intriguing findings that the COMT Val allele might predict olanzapine response (136), that the 102-T/C 5-HT2A receptor gene is associated with clozapine response (137), and that the DRD3 Ser allele is associated with poor clozapine response (138) all await external replication. Only the Del allele within the -141C Ins/Del DRD2 polymorphism is consistently associated with (poorer) antipsychotic drug response relative to the Ins/Ins genotype, but even this effect is too small for clinical use (139). The genetics of antipsychotic drug response may therefore be as complicated as the genetics of schizophrenia, and the pharmacogenetics of psychosis might also require multiple gene testing.

Imaging predictors of response

In sharp contrast with the diagnosis and early diagnosis literature reviewed above, structural imaging measures are clearly not associated with treatment response or resistance (140,141). There are, however, quite a number of studies showing that more abnormal computed tomography/sMRI appearances are associated with a generally poor prognosis and a bad outcome. Functional imaging measures show much greater promise, with both reduced basal ganglia metabolism and increased striatal D2 receptor occupancy being repeatedly linked to antipsychotic drug treatment response (135,142).

There is also a strikingly consistent literature on the EEG and treatment response in schizophrenia, in which increased pre- and/or post-treatment alpha-wave EEG activity predicts response to antipsychotics in five out of the six studies we are aware of (143-148). There is enough replication here to justify further studies of PET and EEG of antipsychotic drug response and to begin to evaluate this in terms of their potential clinical significance. Where PET prediction of response could be really useful is in predicting treatment resistance to first or second generation antipsychotics and, even better, response to clozapine, and perhaps also in measuring the response to a single test dose as a means to establish drug and dosage choice for a given patient. Those questions need, however, to be considered in detail by additional studies. The greater availability and lesser cost of EEG make this the most promising potential predictive biomarker of antipsychotic drug response in psychosis for routine clinical use.

CONCLUSIONS AND RESEARCH DIRECTIONS

We have considered the ability of symptoms and signs, and a range of potential biomarkers, as methods of objectively diagnosing schizophrenia in established cases, in predicting transition to psychosis in people at high risk for clinical or genetic reasons, and in predicting treatment response to antipsychotic medication. We have identified what we consider are the best bets for future research evaluation and provided some pointers about how these studies should be conducted and reported (Table 4). Some will say this is all premature. It would certainly be foolish to think that we are ready to employ these measures in clinical practice, but we think that it is long overdue to start considering the variables and methods

Table 4 Summary of research findings

- Particular psychotic symptoms are not in themselves strong associates or predictors of schizophrenia, because of their relative rarity, the difficulties in reliably eliciting them and their lack of specificity.
- Developmental abnormalities (social, sensorimotor, intellectual), whether elicited in the history or on examination, merit formal evaluation as potential diagnostic aids, but these may simply be trait markers.
- A number of genetic markers of schizophrenia have been identified, but the impact of such testing in clinical practice needs to be established.
- Of currently available technological approaches, structural brain imaging looks most promising as a diagnostic aid, and in the early detection of psychosis (at least within high risk populations).
- Functional imaging should be more sensitive, but is more expensive and technically demanding, and may have particular value in differential diagnosis and response prediction.
- Imaging and other approaches should be further improved by genotyping and/or other biomarkers as they become available – although with each additional test false negatives tend to become more of a problem.
- Ideally, clinically significant test results should be examined in clinical trials to establish whether the time and expense involved impacts favourably on patient outcome.

which can take us towards objective diagnostic testing in psychiatry, and to report data in terms of predictive values and likelihood ratios, or at least in such a way as these can be calculated.

The current "gold standard" for the diagnosis of schizophrenia allows reliable diagnoses to be made and communicated, and has some predictive validity in terms of denoting a poor prognosis in most patients. It is frequently stated that these criteria lack biological validity, yet there is no doubt that they have allowed aspects of the pathophysiology of schizophrenia and other psychoses to be elucidated. The symptomatic and biological boundaries between schizophrenia and bipolar disorder may not be discrete (149,150), but where there have been direct comparisons we have been able to highlight some promising leads. We fully acknowledge, and indeed it is a key motivator to writing this article, that our diagnostic gold standard is tarnished and can be variably applied. Replacing this with another set of subjective criteria would, however, be comparable to rearranging deck chairs on the Titanic. We should aim much higher as a profession – towards objective, etiological and/or pathophysiological measures. We have been overcautious in pursuing this agenda in psychiatry, as a medical discipline, perhaps in part because of the hype and then failure of the dexamethasone suppression test in depression (151).

We regard the diagnosis section of this paper as the most important part, because a suitable patient population is available to all clinicians, a diagnosis is usually already made, and this is therefore where an objective approach would have most impact. Epidemiological risk factors need to be formally evaluated in terms of how much they should rightfully increase diagnostic suspicion (or likelihood), especially when considered with other factors, and as potential causal specifiers for psychosis. We also need to determine if there are any objective, reliable "soft signs", and how these and brief cognitive tests of intellectual decline from premorbid function may perform in clinical practice in terms of their practicality and utility in patients with acute psychosis. Meanwhile, geneticists need to establish how we will know a causal gene when we see one, and how we will manage the patients carrying it. Imaging "biomarkers" perhaps have most promise for diagnostics, but the imaging community needs to develop quantitative techniques that can be applied to individual patients and apply these to the critical distinction between schizophrenia and bipolar disorder with psychotic symptoms. Amygdala volumes may require standardization by age and account for medication if they are to be a distinguishing feature, while dorsolateral PFC activation patterns will require standardization by performance and perhaps IQ, although resting state functional imaging studies may circumvent this.

Making diagnoses at earlier stages in the illness and therapeutic response predictions are not lesser priorities but do seem less practical propositions. Risk factors are all too rare and insufficiently powerful predictors of psychosis to be of great diagnostic value in essentially healthy people, quite apart from the ethical issues inherent in predictive genetic testing and possible prescription of unproven treatments for large numbers of people years before a few become ill. Early diagnosis becomes more practical and ethically straightforward nearer to the time of onset, when the severity of symptoms, thought disruption, schizotypy, cannabis use and brain imaging again look to have promise. It is, however, at least debatable to what extent a predictive test for schizophrenia, or indeed of antipsychotic drug response, would be used, even if predictors were strong, given the limited resources for early intervention services, the restricted choice of treatments currently available, and the lack of availability of imaging and genetic technologies in most clinical settings even in so-called developed nations.

Even more important than the specifics at this stage is the general approach. The one critical aspect of diagnostic studies that is often forgotten is the necessity of a reliable test of the proposed diagnostic aid in a second independent and preferably similarly large cohort, also conducted blind to diagnosis. As fitted models of multiple variables always perform in an "optimistic manner", or are "over-fitted" on the model-development data, cross-validation in an independent sample is needed to control for tailor-made modelling. We are not aware of any examples of this having been done in a truly independent cohort for any of the findings we have described. This requires large scale clinical research studies, which may require support from a variety of informatics approaches, including computational models of the brain/mind, normative and illness databases for comparisons, multivariate prediction algorithms and so on (152,153). Multilevel models including neurobiological, sociobiographical, and environmental variables may increase predictive accuracy, but each additional domain also brings potential variations according to study setting, levels of ex-

posure and inter-rater reliability, as well increasing the risk of false negatives.

The biggest stumbling block clinical researchers may face in trying to set up such studies and change diagnostic practice in psychiatry is concern about how certain one needs to be of an etiological risk factor or pathophysiological mechanism and its specificity before it can be used as a diagnostic aid or test. This is, of course, a legitimate question, but it misses the key point – at least from a clinical perspective – of whether or not the presence of a marker in an individual takes it beyond a threshold where diagnosis or some management strategy which follows from it is likely to be of benefit. Establishing the requisite measures and thresholds will require formal studies in their own right. Clinicians will need to participate in large simple studies to identify the most clinically useful symptoms and signs and tests. This is how medicine works and, with additional study, advances. It is the way psychiatry needs to travel if we are to start to use objective indices to inform psychiatric classification and practice. The future of psychiatry as a medical discipline may depend on it.

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Looking for a "biological test" to diagnose "schizophrenia": are we chasing red herrings?

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The developments in the rest of medicine have shown us that the ability of a diagnosis to predict treatment and prognosis is usually improved once one has a firm biological test. General treatment of "heart failure" was rather poor when the same treatment was used for all forms of heart failure, while the precise diagnosis of valvular dysfunction, myocarditis and ischaemic heart disease led to more precise treatments, better outcomes and better ability to predict outcome. That has been the fond hope in biological psychiatry, and Lawrie et al carefully and systematically analyze how far we have come to realizing it in schizophrenia.

Their article carefully reviews data from risk factors, clinical signs and symptoms, genetics, blood-based markers and imaging "markers" with respect to their sensitivity, specificity and predictive value. The paper achieves two important goals. It is a thoughtful synthesis of such evidence, presented from the perspective of sensitivity, specificity and likelihood ratios. Furthermore, by drawing attention to the lack of useful clinical biological tests, it reminds us of the journey ahead. While I laud the authors' effort, I question whether it is even feasible, at present, to look for a biological "test" in psychiatry just as they do in the rest of medicine.

The way "tests" are evaluated in the rest of medicine is versus a "gold standard". A simple blood test often is used to substitute for a definitive pathological diagnosis. A simple ECG recording is used to substitute a complex invasive angiogram. Thus, in medicine, indices of sensitivity, specificity, likelihood ratio etc. are all premised on measuring a new test against the definitive "gold standard". No test can better the "gold standard". But, what today would be the "gold standard" for the diagnosis of schizophrenia? It would have to be DSM (or the ICD) (1). There is no other option. Given that our current and foreseeable DSM/ICD labels are empirical and pragmatic collections of clinical symptoms, the looking for a biological finding to predict this heterogeneous collection of symptoms is shaky.

The second major problem at present is the "artificiality" of the current data from a clinical perspective. The extant data in genetics, imaging and biological markers of schizophrenia has been collected in individuals who fully and unambiguously meet the classical DSM criteria and are usually contrasted to perfectly healthy, one might say "hypernormal", normal volunteers (2). Where is the problem in distinguishing two such people? Classical schizophrenia is easily distinguished from perfect normalcy by even an untrained observer. The real challenge in the clinic is to distinguish the nearly-psychotic depressed-looking individual from the nearly-depressed psychotic-behaving individual and firmly classifying one into major depression and the other into schizophrenia (if either of these have a deeper meaning – see the gold standard problem above). Very few studies have attempted this at present. And therefore any predictive value derived from current data separating classical illness from perfect normalcy is artificially inflated.

So, we are in a Catch-22. Until we have a gold standard we are unlikely to find meaningful biological tests. And until we have a better biological understanding we cannot redefine the illness to make it more valid. What's the way out?

A solution lies in the pursuit of biologically defined "subtypes". There is little hope of, or purpose in, replacing the well-established and relatively standardized method of diagnosing schizophrenia clinically (which has taken a 100 years to get to) with an *ad hoc* biological test of limited clinical value. It would be too disruptive and would yield little benefit. Thus, the DSM-5 and ICD-11 carry on the tradition of their ancestors (1). In the meantime, what biological psychiatry should seek are biological tests that can either improve treatment choice or predict differential prognosis. This requires a shift in the research we do. The emphasis is not anymore in finding biological differences versus supernormal controls. The focus is on prediction within the phenomenologically defined diagnosis. Thus, I can foresee meeting a new patient, diagnosing his/her to have a DSM-6/ICD-12 schizophrenia, and then telling him/her "you have a schizophrenia of the 'hypofrontal' subtype, and this means that you will not respond well to standard antipsychotics and therefore let's start with clozapine instead"; or meeting another young man and saying "you have a schizophrenia with 'conserved executive function'; in this subtype we find that antipsychotics can be stopped after two years, provided there is active involvement in cognitive-behavioural therapy".

What fish you catch, is largely a function of where you fish. Rather than focussing on schizophrenia versus normal controls with biological tests – something fraught with several taxonomic (dimensional vs. categorical) and practical challenges – let's use the umbrella diagnosis and "subtype" it. And let's judge the game empirically – let the test that best improves or best predicts real-life outcome of patients win the prize.

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Diagnostic markers for schizophrenia: do we actually know what we're looking for?

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Lawrie et al have written a thoughtful review of the evidence for diagnostic markers of schizophrenia, covering epidemiological risk factors, physical signs, neurocognitive and neuroimaging features and gene- or protein-based biomarkers. However, behind this mass of data lie four unasked questions, the answers to which are critical to the success of any attempt to improve diagnosis.

What is the illness we are trying to diagnose? It is commonplace nowadays for researchers to acknowledge that schizophrenia is not actually a unitary disorder, but is more likely to be a group of disorders that share syndromal characteristics. A brief examination of a number of neuropsychiatric disorders demonstrates that they can symptomatically be indistinguishable from schizophrenia. For example, Niemann-Pick type C disease may present with psychosis as the sole initial manifestation (1), as may metachromatic leukodystrophy (2). Yet, their genetic bases are completely different, and by pooling them as "psychotic disorders" we would merely add noise to our search for diagnostic markers. It is trite, but nonetheless true, that a clear definition of what we are trying to diagnose is key.

Should different dimensions of schizophrenia be considered separately? As Lawrie et al note, the current gold standard diagnosis of "schizophrenia" is "tarnished". An alternative approach to diagnosing "schizophrenia" is to "deconstruct" the syndrome (3,4). That is, to consider various dimensions of the "illness" and investigate risk factors, markers, course, outcome and treatment for these. For example, at a basic level, positive psychotic symptoms and negative symptoms could be examined separately. This may be too simplistic a division. Positive symptoms are likely to be heterogenous in origin and outcome, and could be divided into three (bizarre experiences, persecutory ideation and magical thinking) (5), four (the previous three but perceptual abnormality as well) or even five factors (essentially the previous four but with magical ideation divided into paranormal beliefs and grandiosity). These positive symptoms are likely to have different associations with other psychopathological dimensions, different underlying aetiologies, and hence different risk factors, markers and course. The recent finding that negative symptoms and conceptual disorganization co-occur in the community provides evidence for this approach. This builds on past work that has long suggested that there is a "neurodevelopment" or "nuclear syndrome" characterized by early onset, male gender, and cognitive impairment (6), that is likely to have a poorer prognosis, in terms of functional recovery, than "schizophrenia" without these features. Kirkpatrick and colleagues have referred to this syndrome, with the addition of marked avolition, as the deficit syndrome (7). It is on this background of thinking and evidence that the Psychosis Work Group of the DSM-5 Committee is planning on testing a set of dimensions, including hallucinations, delusions, disorganization, restricted affect, avolition, cognition impairment, anxiety, depression and mania (8). These dimensions could therefore become targets for research and treatment development (8). It may well be that people currently diagnosed as "schizophrenia" will require different treatments from each other depending on the relative prominence of each dimension, which is likely to be more precise an indicator of underlying pathology than a simple diagnosis of "schizophrenia". The blanket approach of antipsychotics and perhaps cognitive-behavioural therapy may not be appropriate to all. For example, some individuals with apparent "schizophrenia", but without evidence of neurodevelopmental pathology, may recover in the absence of antipsychotics (9).

At what stage in the illness are we trying to diagnose it? Schizophrenia does not present similarly at all stages of the illness. Lawrie et al provide a good overview of attempts at early diagnosis, although many of the studies they cite do not have schizophrenia as the final outcome. For example, many of the clinical high risk studies (including our own) use a transition to "psychosis" as the outcome of interest (10).

Finally, a critical question for the psychiatric community generally is: what difference does a diagnosis of schizophrenia make? Does it affect treatment or prognosis? A patient presenting with positive psychotic symptoms in the absence of an obvious immediate cause (such as seizures or recent drug use) is likely to be treated initially with a low dose of antipsychotics, and perhaps provided with a psychological intervention such as cognitive behavioural therapy. Whether or not this patient has a schizophrenia diagnosis, this initial treatment regimen is unlikely to change. Equally, a diagnosis of schizophrenia (at least, one reached after only a brief period of illness) does not provide much indication of prognosis. Recovery is common, as is diagnostic revision.

The aim of Lawrie et al is laudable – to more precisely be able to diagnose schizophrenia through the use of a clinical arsenal, from blood tests and neuroimaging to good history taking and physical examination. However, such an approach is doomed without first establishing the nature of the illness, the extent to which diagnostic markers vary with course, and the relevance of the diagnosis for treatment and prognosis.

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Is there a schizophrenia to diagnose?

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Lawrie et al provide a useful review of the diagnostic process and the potential application of various biological parameters in different settings: diagnosis, differential diagnosis, early diagnosis and prediction of treatment response. They conclude that a number of measures have the potential to increase the rigour of clinical assessments in psychiatry and improve diagnostic precision. While I agree with much of what they write and share their concerns about the de-medicalization of psychiatry, I do have one major concern: I am not convinced that we can be certain that schizophrenia is necessarily a valid diagnostic entity.

Because we are still largely ignorant of the underlying pathogenesis of schizophrenia and other severe psychiatric disorders, we are forced to rely upon a diagnostic process that is largely descriptive and syndromic, with disease categories that are highly heterogeneous and overlapping. Lawrie et al's response to this is to suggest that we need to seek biological validators of schizophrenia that can be used to distinguish it from other disorders. But this assumes that Kraepelin's original dichotomous conceptualization of the functional psychoses was correct. What if the underlying structure is different? Perhaps there are many schizophrenias or perhaps the functional psychoses are better conceived of in dimensional terms (1-3).

In the last three years, the application of novel genomic approaches to disorders such as schizophrenia, bipolar disorder, autism and attention-deficit/hyperactivity disorder (ADHD) has yielded a number of important new insights. Highlights include increasing evidence that common risk alleles are shared by schizophrenia and bipolar disorder (4) and evidence that specific submicroscopic deletions and duplications of segments of DNA, known as copy number variants (CNVs), confer risk of schizophrenia and other neurodevelopmental disorders such as autism, ADHD, epilepsy and intellectual disability (4,5). These findings not only challenge the aetiological basis of current diagnostic categories but, together with evidence for frequent comorbidity (which is often obscured by the application of rigid diagnostic categories in research studies), suggest that we should view the functional psychoses as members of a group of related and overlapping syndromes that result in part from a combination of genetic and environmental effects on brain development and which are associated with specific and general impairments of cognitive function. These findings also suggest that many biological and psychological correlates of disease will not map neatly onto diagnostic categories and therefore will be of questionable utility to diagnosis at least where current criteria are concerned. Furthermore, they do suggest that a simple categorical approach to diagnosis might not capture the complexity that exists and that other models might be more useful for research and clinical practice (3).

To my mind, the search for the mechanistic underpinning of psychiatric disorders in the immediate and near future needs to be focussed on two distinct domains. First, we should seek to refine our understanding of the major psychopathological syndromes/dimensions, such as psychosis, negative symptoms, mood disturbance and cognitive impairment, that occur in different combinations in our diagnostic categories (3). This should include detailed cognitive and neurocognitive studies. This will give us better and more objective measures of psychopathology, allowing us to target therapies and measure their response more effectively as well as giving us greater insights into how these syndromes might arise. Second, we need to characterize these

syndromes/dimensions at the level of cellular and neuronal function by focussing on the biological systems implicated by genetic and other biological studies. This work will need to include cellular and animal models as well as the study of endophenotypes that are related to fundamental neuronal and systems function.

A combination of these top-down and bottom-up approaches might ultimately allow us to trace the links between underlying biology, environmental factors and manifest psychopathology. In the meantime, I would argue that, at least as far as research is concerned, we need to worry less about how we place our patients into specific diagnostic groups and more about defining phenotypes to suit the specific hypotheses we are testing. In the clinic too, perhaps we should admit that we treat syndromes like psychosis, depression and mood instability rather than diagnoses, and focus more on improving the way we measure these than on refining the way we place patients into categories that in all likelihood do not represent real underlying disease entities.

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Biomarkers in schizophrenia: we need to rebuild the Titanic

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Lawrie et al have made a remarkable effort to take stock of the number of current clinical and neurobiological measures which may serve as potential objective diagnostic and prognostic markers, and may move future clinical, therapeutic and pathophysiological research in schizophrenia in a promising direction. They argue that replacing current diagnostic criteria for this illness by another set of subjective criteria would be comparable to rearranging deck chairs on the Titanic. We cannot agree more, and believe that we should look at salvaging the Titanic itself.

The major challenge in developing biomarkers of diagnostic value lies in the limitations of the current diagnostic and classificatory approaches. While the current diagnostic approaches have clearly improved reliability of diagnoses with the recurrent revisions of the DSM, the validity of disorders such as schizophrenia remains in question.

First, the *content validity* of the schizophrenia construct is seriously limited by the substantive heterogeneity of the disorder in cross-sectional presentations, neurobiological characteristics as well as the etiological factors implicated (1). It is commonplace in the schizophrenia literature for authors to invoke heterogeneity as an explanation for inconsistent findings. Heterogeneity must be viewed as a problem to be addressed rather than as an explanation or a solution, and is the strongest reason to revisit the long-entrenched and inadequate conceptualization of this disease entity (2).

The *predictive validity* of schizophrenia as a construct is hampered by the fact that the longitudinal course of this illness is highly variable (3-5), as is the response to different treatments (6). Furthermore, the *discriminate validity* of schizophrenia is limited by its blurred boundary with other major disorders such as bipolar disorder. Overlap between these disorders is seen in neurobiology, genetics, symptomatology as well as treatment response, posing a central challenge to the century-old Kraepelinian view that these are distinct illnesses (7). At the heart of this debate is the core concept of schizoaffective disorder as an entity that combines the features of both illnesses. Psychiatric disorders generally do not meet the time-honored dictates that symptom constellations (syndromes) would have specific pathology which would lead to specific etiology. In this context, Robins and Guze (8) proposed four tenets of a valid psychiatric diagnosis. These include the need for a distinct signature in phenomenology, course, family history, and biology. Schizoaffective disorder fails to meet these criteria, being characterized by having overlaps with schizophrenia and bipolar disorder in each of these domains (6,9). The interface between schizophrenia and the continuum of "health" is also fuzzy, leading to the intermediate syndromes of schizotypal and brief psychotic disorders.

An increasingly held view is that the pathophysiological heterogeneity of schizophrenia may be resolved by elucidating independent families of intermediate phenotypes that traverse across structural, functional, neurochemical and molecular domains, and map on to psychopathological dimensions, but are agnostic to diagnostic categorization (10). As progress is made toward these goals, it is possible that the current entity of schizophrenia will be deconstructed and rebuilt as phenotypically overlapping, but etiopathologically distinct component entities. Biomarkers of the kind Lawrie et al review may be of better value to identify and "diagnose" such entities, perhaps in the not too distant future.

Lawrie et al suggest other key scenarios beyond diagnosis where current

clinical practice operates in the dark: early detection and predicting response to treatment. It is in these venues that the application of our understanding of the pathophysiology of schizophrenia may make an earlier impact in the clinical world. The ability to identify the cohort that is likely to develop these disorders may enable effective preventive interventions with non-pharmacologic means such as cognitive behavior therapy and cognitive remediation, and pharmacological interventions such as omega3 fatty acids and low-dose atypical antipsychotics. One can also envision in the relatively near future biomarker screens that may predict treatment response and side effects irrespective of diagnosis.

In conclusion, the paper by Lawrie et al provides a useful, quantitative appraisal of the state of our understanding of schizophrenia as we now know it and how that understanding impacts clinical care. Some of the more prognostic issues outlined by the authors regarding early identification and prediction of outcome have the potential to be dramatically affected by our ability to understand this disease in biological terms. We are in agreement with their conclusion that diagnosis by biomarkers is not currently feasible and would add that, for various reasons mentioned above, this particular issue may not be where our biological understanding of schizophrenia makes the most immediate impact in the clinical world. That may change, however, as our current Titanic-like construct of schizophrenia gives way to component entities defined across phenomic, genomic, enviromic and endophenomic dimensions (11).

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Objective tests for schizophrenia: window to the future

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Lawrie et al review findings from phenomenological, epidemiological, proteomic, genomic, and brain imaging studies of patients with or at risk for schizophrenia, addressing the question whether these findings provide an objective basis for prediction, diagnosis, and/or prognosis. The field has advanced significantly over the past 20 years, such that the associations of schizophrenia with many risk factors and markers are "beyond a reasonable doubt". At the same time, however, translating findings in these domains into objective algorithms for prediction/diagnosis/prognosis is likely to remain a promise rather than reality for the foreseeable future. Several considerations motivate this somewhat more dour perspective.

First, at the present time, no particular risk factor is known to be sufficient to cause the disorder, and it remains unknown what aggregations of risk factors are sufficient. In other words, how much, or what combinations, are enough? Given the multiplicity of the causes of schizophrenia and other mental disorders, it seems likely that there will be several combinations, making it highly unlikely that we will ever have a simple heuristic, or single diagnostic test, for use in the clinic. However, multivariate algorithms may eventually prove feasible. It would seem likely that the most parsimonious algorithms would include markers of pathophysiology (e.g., glutamatergic and/or dopaminergic signaling) rather than etiologic risk factors, since there are likely to be many causal combinations or routes into such final common pathways.

Second, efforts to surface such multivariate classification algorithms would be greatly enhanced if all studies began considering their data within the rubric of classification/prediction (i.e., sensitivity and specificity, positive and negative predictive power, etc.), in addition to the traditional group comparisons of means. Currently, very few studies even consider the issue of classification, despite the fact that there is a general interest in investigations of "biomarkers" and despite the availability of many elegant mathematical and statistical approaches (e.g., machine learning). In this sense, the efforts of Lawrie et al are commendable and timely, representing perhaps the opening "salvo" in calls for such a sea change.

Third, for any predictive/diagnostic/prognostic algorithm to be successful,

we must define the conditions under which it is expected to perform best. In their review, Lawrie et al appear to hold the segregation of schizophrenia and bipolar disorder as the ultimate litmus test that most markers have yet to achieve. Yet, at their genomic roots, these two syndromes may have more in common than not, in which case such segregation at the level of biomarkers would not necessarily be expected. At the very least, future classification approaches should model syndromal outcomes both within and outside of the lenses provided by our current diagnostic classification systems.

Clearly there are many other points of interest in the debate about objective tests for schizophrenia. The issues noted above represent a few suggestions for an emerging field that carries the hopes and dreams of millions of patients and family members on its shoulders.

Clinical handling and understanding of schizophrenia should be based on pathophysiological findings and theories

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Lawrie et al's paper focuses on reliable diagnostic tools, early diagnosis and prediction of response to pharmacological treatment in schizophrenia, providing a very useful overview of the existing evidence.

However, achieving a reliable and early diagnosis of schizophrenia with clinical and biological methods is important but not sufficient, since the diagnosis itself and in particular early diagnosis leaves the clinician with many open questions as to prognosis and the appropriate treatment of the individual patient. Furthermore, to limit the consideration of treatment prediction to the response to pharmacological treatment may be reductive. Finally, even psychiatrists working in clinical practice are asked almost every day by patients, relatives or friends to explain schizophrenia. Therefore, even if the clinician is not a scientist or philosopher, he will be very interested to know what to respond to this question which refers to the etiopathophysiology of this human condition. In the following, I will briefly touch these points.

The diagnosis of schizophrenia is polythetic. It is possible that two patients with the same diagnosis do not share even one symptom. Further, course, social impairment and treatment may vary enormously between patients. Knowledge about this heterogeneity is still very limited, but is of paramount interest for the clinician and therefore deserves particular attention even if empirical studies are still scarce and inconclusive. For instance, several clinical and biological similarities of catatonia with motor disorders and obsessive compulsive disorder have been identified, which point to common pathophysiological mechanisms (1). In brief remitting psychoses, hints to a distinct pathophysiology have been found (2,3). These new pathophysiological findings are relevant for the definition of the diagnostic categories and therefore of direct clinical interest.

In the last decade, important and empirically validated non-pharmacological techniques have been developed, which are linked to pathophysiological hypotheses. For instance, standardized diagnostic batteries (4) and detailed neurocognitive interventions (5,6) have been developed following hypotheses inspired by neuropsychological findings. There is also an example of an efficacious therapy derived from a pathophysiological mechanism revealed by biological research: the evidence on the role of the components of the left hemispheric language system in the generation of auditory verbal hallucinations has led to the development of fMRI-guided transcranial magnetic stimulation of left temporal brain regions for their treatment (7-9).

The question of the origin of schizophrenia still remains open. The practically endless catalogue of findings in various fields, from humanities to empirical psychology, systems physiology and molecular biology, does not match the needs of clinicians to give their patients a useful model of their condition. People will lose confidence in our discipline, if one psychiatrist explains the disorder as caused by a transmitter dysregulation, another as a genetic deficit, one more as a consequence of an information overflow and the next as a product of social environment. There is urgent need to search for and discuss unifying theories of schizophrenia pathophysiology, which may allow connecting the findings at the various methodological levels, and help us to understand the heterogeneity of the disorder. The situation is not as desperate as it seems, since there are recent developments which deserve attention. For instance, there are several indications that part of our patients with the diagnosis of schizophrenia suffer from structural and functional disorders of modules of the left hemispheric language system, including the primary auditory cortex, the superior posterior temporal lobe and the arcuate fascicle (10-12). For the understanding of schizophrenia as a clinical entity, this has a double meaning. First, some symptoms like incoherence, alogia and auditory hallucinations are linked to subtle structural changes of the cerebral cortex and to chronic or episodic functional dysregulation of language production and perception. A simple but important implication for therapy and clinical handling of these patients is the need to adapt standard colloquial and cognitive therapies to the verbal capacities of these patients. The second meaning of these findings is the inverse conclusion, i.e. that not all schizophrenic patients have deficits in their language functions. There are probably other pathophysi-

ological mechanisms that may cause phenomena like delusions of existential threat or the motor phenomena of catatonia (13,14).

In conclusion, in addition to the important questions summarized by Lawrie et al, we emphasize the clinical importance of some pathophysiological findings and hypotheses for the development of valid taxonomies, of non-pharmacological interventions, and of comprehensive models for the group of schizophrenias.

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A desperate search for biomarkers in schizophrenia. What is going wrong?

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In their excellent review, Lawrie et al search for suitable biomarkers to establish the diagnosis of schizophrenia, and to predict the transition to psychosis and the response to treatment. They conclude that currently the diagnosis of schizophrenia by means of clinical criteria is reliable and that replacing this with another set of subjective criteria would be "comparable to rearranging deck chairs on the Titanic". Despite their substantial effort to distil biomarkers out of the literature, the authors remain unsuccessful. What is the background and what can be done to change this lack?

Concerning biomarkers, we seem to envy the rest of medicine. In cardiology, for instance, we have a wealth of markers like ECG or blood parameters, helping to establish a firm diagnosis. Even when we look at neurology, a discipline obviously working on the same organ we deal with, disease phenotypes like stroke, epilepsy or multiple sclerosis are easy to define. These disorders have a clear morphological substrate and often well identified etiological factors. Schizophrenia is a network disorder in which we find local abnormalities and a disconnection syndrome, but we are not able to discover a common neuropathological substrate or a set of established risk genes. The behavioural phenotype encompasses virtually all aspects of human behaviour. Therefore, we need to reduce the complexity of the phenotype under examination. Our task consists in designing simple experiments to answer a few questions or just one question. We need to focus on one "neurofunctional pathway" rather than leaving the interpretation of our data to "neuronal network hypotheses".

We can rely on sophisticated research tools, namely molecular genetics and brain imaging, but the differences to be detected in schizophrenia are exiguous and heterogeneous. And we still look for a static lesion explaining at least part of the psychopathology of schizophrenia. In a recent randomized trial, however, we could demonstrate that hippocampal volume reduction, one of the structural hallmarks of schizophrenia, is reversible with aerobic exercise over a period of three months (1). Therefore, our concept of a static neurodevelopmental lesion and/or degenerative brain process in schizophrenia might be wrong. We have to realize that any detrimental factor to the brain, such as obstetric complications, cannabis abuse or chronic psychotic symptoms, will lead to regenerative brain efforts. Therefore, it is vital to define the phase of illness of each patient under study.

Interestingly, there is consistent evidence for a heterogeneous outcome in schizophrenia. About 20 to 30% of patients with schizophrenia show a very favourable, around 20% a fair and the remaining 50% a more unfavourable outcome (2). Despite this evidence, there are no studies trying to define the

neurobiological basis of these different long-term outcomes. It would be a good start if neurobiological findings were interpreted on the background of the long-term outcome of the patients included in the study.

In summary, Lawrie et al's paper points to a wealth of neurobiological data from schizophrenia research, which currently are not helpful in identifying biomarkers for establishing the diagnosis, predicting the transition to psychosis or responding to treatment. This underscores the need to reduce the complexity of our observed phenotypes and to develop more focused study designs. Furthermore, in order to reach a better understanding of the neurobiological basis of schizophrenia, we need to focus on the different phases of illness, distinguishing prodromal, first- and multiple-episode cases. Finally, stratifying our findings on the background of the long-term outcome of the included patients could help us to develop a more sophisticated interpretation of our neurobiological data on schizophrenia.

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Income-related inequalities in the prevalence of depression and suicidal behaviour: a 10-year trend following economic crisis

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The issue of health inequalities has steadily gained attention in South Korea, as income inequality widened and social polarization increased following the country's economic crisis in the late 1990s. While official figures indicate a general trend of worsening mental health, with rapidly rising rates of suicide and depression in particular, the extent of socio-economic inequality with respect to mental health problems has not been well elucidated. This study aimed to measure income-related inequalities in depression, suicidal ideation and suicide attempts in South Korea and to trace their changes over a 10-year period (1998-2007). The concentration index approach was employed to quantify the degree of income-related inequalities, using four waves of the Korea National Health and Nutrition Examination Survey data. The study found persistent pro-rich inequality in depression, suicidal ideation and suicide attempts over the past decade (i.e., individuals with higher incomes were less likely to have these conditions). The inequalities actually doubled over this period. These findings imply a need for expanded social protection policies for the less privileged in the population.

Key words: Depression, suicidal ideation, suicide attempt, income, inequality, concentration index, South Korea

(World Psychiatry 2011;10:40-44)

Persistent health inequalities between socio-economic groups have been observed in both developed and developing countries (1). Tackling such disparities has featured prominently in the policy agenda globally in recent years. The World Health Organization (2,3), the World Bank (4), and the United Nations Development Programme (5) have all emphasized its importance and made this issue a priority. South Korea is no exception. The New Health Plan 2010, established in 2005, aims to reduce health inequality and ultimately improve overall quality of life of the nation (6).

In South Korea, the issue of health inequalities has gained increasing attention with the widening income inequality and increasing social polarization following the country's economic crisis in the late 1990s (7). There have been widespread concerns that such social changes may also widen the health gap between socioeconomic groups (7). Recent studies examining this issue were largely consistent in reporting persistent and/or widening health inequality (7-9).

Despite growing awareness of mental health issues and their explicit presence in the New Health Plan 2010, the extent of socioeconomic inequality with respect to mental health problems in South Korea has not been thoroughly examined. Official figures (10,11) indicate a general trend of worsening mental health, with rising rates of suicide and depression in particular. The suicide rate rose dramatically from the national average of 13.0 per 100,000 in 1997 to 26.0 in 2008 (11), the highest among countries belonging to the Organization for Economic Cooperation and Development (OECD) (12). Similarly, the lifetime prevalence of major depression rose from 3.1% in 2001 (13) to 5.6% in 2006 (10), although it is still lower than that reported in Western countries (14-17).

A variety of factors may influence mental health, some of which are potentially amenable to change by individuals or society (e.g., income, education, housing, neighbourhood, relationships, and employment). The mechanisms through which such factors affect the development of mental health problems are contentious (18-20). However, many of them are, directly or indirectly, related to income.

This study aimed to measure the magnitude of income-related inequalities in the prevalence of depression, suicidal ideation and suicide attempts in South Korea and trace the change in the inequalities over the past 10 years.

METHODS

Data for this study were taken from four waves (1998, 2001, 2005 and 2007) of the Korea National Health and Nutrition Examination Survey (KHANES), a nationally representative cross-sectional household health survey conducted by the Ministry of Health and Welfare, in which subjects were selected from non-institutionalized civilians through a stratified multistage probability sampling design.

The present analysis was based on individuals aged at least 19 years (N=27745 for 1998, N=27413 for 2001, N=25487 for 2005, and N=3335 for 2007). The analysis on suicidal behaviour was based on a subset of the KHANES data (Health Awareness and Behaviour data) (N=8991 for 1998, N=8072 for 2001, N=7802 for 2005, and N=3335 for 2007). All data were weighted to represent the structure of the South Korean population.

The survey gathered information from respondents through face-to-face interviews, including socio-economic status, self-reported health status, incidence of acute and chronic illness, health behaviour (e.g., exercise, smoking, alcohol consumption), and health service utilization and spending on health.

Information on depression, suicidal ideation and suicide

attempts was obtained through self-report of whether the respondents: a) had been diagnosed with depression by a physician in the past 12 months ("yes" vs. "no"), b) had ever felt like dying in the past 12 months ("yes" vs. "no"), and c) had ever attempted suicide(s) in the past 12 months ("yes" vs. "no"). Income was defined as the average monthly gross income, and divided by an equivalence factor (equal to the number of household members powered to 0.5), to adjust for differences in household size and composition (8,21).

The concentration index (CI) approach (22,23) was employed to measure the extent of income-related inequalities in the prevalence of depression, suicidal ideation and suicide attempts (henceforth referred to as "illness" for ease of reference). The concentration curve can be plotted with the cumulative percentage of the illness on the vertical axis corresponding to the cumulative percentage of income distribution on the horizontal axis. The CI is defined as twice the area between the concentration curve and the 45° line, which ranges from a minimum value of -1 to a maximum of +1 and occurs when illness in an entire population is concentrated in the very poorest or very richest, respectively. A zero value indicates complete equality in the prevalence of the illness regardless of income level.

Depression, suicidal ideation or suicide attempts may be correlated with age and gender, both of which could possibly be unequally distributed across income groups. Hence, our study also calculated age- and gender-standardized CIs to control for the confounding impact of demographic variables. The prevalence of the illness was standardized by age and gender using the indirect standardization method (24). This was done by "correcting" the actual distribution of the illness prevalence by comparing it with the distribution that would be observed if all individuals had the same mean age-gender effect as the entire population.

In addition, age and gender could also be correlated with other socio-economic factors such as educational attainment and employment status, for which we do not want to standardize (since income was used as a proxy for the general socio-economic status of an individual), but which we nevertheless want to control for in order to tease out the independent impacts of age and gender on the illness. The prevalence of depression was thus adjusted for age and gender at the mean level of other non-confounding factors (i.e., educational attainment, employment status, urbanicity of the residential area, and marital status).

The CIs for (standardized) prevalence of the illness were calculated using the Newey-West regression (25). All analyses were conducted using STATA SE/10 (26).

RESULTS

Figures 1-3 show the concentration curves for depression, suicidal ideation and suicide attempts, respectively, based on the four waves of the household survey data (1998, 2001, 2005 and 2007). The concentration curves plot the cumula-

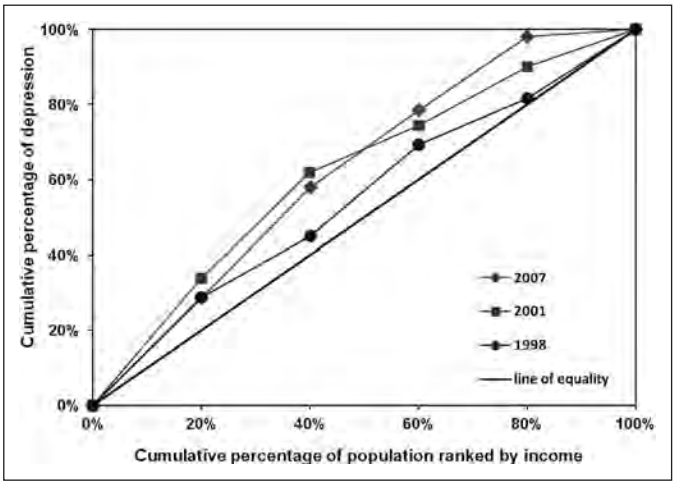

Figure 1 Concentration curves for depression in South Korea from 1998 to 2007

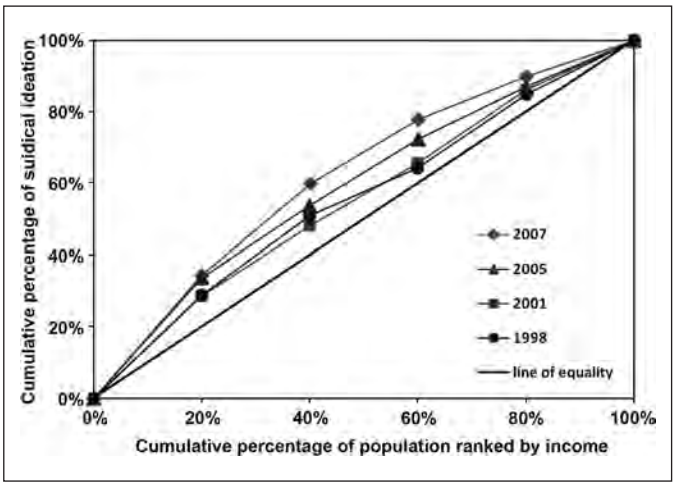

Figure 2 Concentration curves for suicidal ideation in South Korea from 1998 to 2007

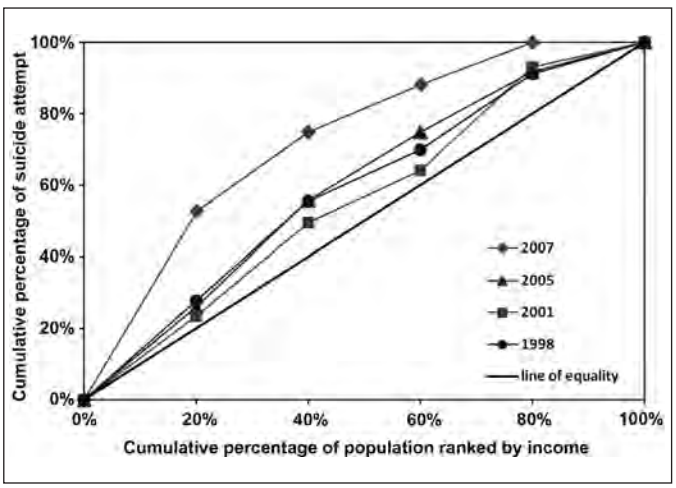

Figure 3 Concentration curves for suicide attempts in South Korea from 1998 to 2007

tive percentage of each psychopathology on the vertical axis against the cumulative percentage of the sample ranked by income on the horizontal axis, beginning with the poorest and ending with the richest. The curves provide an indication of the nature of inequality in the prevalence of each psychopathology across income groups.

All curves were above the equality lines, implying that all three psychopathologies were more highly concentrated in lower income groups across years. The inequality observed was more pronounced in recent years, especially for suicide attempt, as indicated by the curves being even further away from the equality lines. In all three cases, the curves also tended to have the steepest slopes for the lowest income group, but the slopes in the other income groups exhibited different patterns across years. This suggests that the lowest income groups have the highest risk for depression, suicidal ideation or suicide attempt, a trend that is persistent across years, while the impact of income on these cases varied over time for the other income levels, especially for depression. For instance, the impact of income on depression was greater in the lowest income group as well as in the middle income group in 1998, while this was observed for only up to the second lowest income group in 2001, and by and large, till the second highest income group in 2007. On the other hand, suicidal ideation and suicide attempt exhibited clearer income-gradient curves in recent years.

As shown in Table 1, all the CIs were negative, implying the existence of pro-rich inequalities in the prevalence of depression, suicidal ideation and suicide attempt across the years (i.e., poorer groups are doing worse). The magnitude of the CIs doubled between 1998 and 2007 in all three instances, although they exhibited a different trend of the inequalities.

The CI for depression fell sharply from -0.126 (SE: 0.068) in 1998 to -0.278 (SE: 0.068) in 2001, and remained relatively constant thereafter (CI and its SE in 2007: -0.287 and 0.114). The CI for suicidal ideation fell over time, but its fall was rather gradual: it was -0.138 (SE: 0.012) in 1998 and gradually decreased to -0.250 (SE: 0.028) in 2007. In contrast, the CI for suicide attempt increased from -0.221 (SE: 0.062) in 1998 to -0.175 (SE: 0.075) in 2001 and -0.179 (SE: 0.089) in 2005, but plunged to -0.400 (SE: 0.116) in 2007.

After standardizing the distributions for the age and gender composition of income rank, smaller CIs were obtained in general (see Table 1), which suggests that, if every individual had the same mean age-gender effect as the entire population, the expected distribution of the illness would be less unequal. Nevertheless, the CIs still indicated pro-rich inequalities, implying that even if we control for the age-gender effect on income, the latter still plays a substantial role in the prevalence of depression, suicidal ideation and suicide attempts. In fact, after standardizing the demographic composition of income rank while controlling for the correlation with other socioeconomic factors such as educational attainment and employment, the CIs became closer to the unstandardized ones. This suggests that the impact of the demographic confounders on the income-related inequality in the prevalence of the three psychopathologies is rather small, while income has a major impact, either directly or indirectly, through other socio-economic variables.

DISCUSSION

This study represents the first attempt to quantify the magnitude of income-related inequality in mental health in South Korea. The study also analyzed whether such inequality changed in the 10-year period following the country's major economic crisis of the late 1990s. The data provide evidence of persistent pro-rich inequalities in depression, suicidal ideation and suicide attempts over the past decade (1998-2007). The magnitude of the inequalities across all three psychopathologies was found to double during this period, although they exhibited different trends. For depression, inequality increased sharply between 1998 and 2001, and remained relatively stable thereafter. Similarly, inequality in the prevalence of suicidal ideation increased over time, but the increase was rather gradual. In the case of suicide attempts, inequality decreased between 1998 and 2001, but surged between 2005 and 2007.

While it is not clear why the trend of inequality differed between depression and suicide attempts, one explanation might be found in the multi-faceted impact of the economic

Table 1 Unstandardized and standardized concentration indices (CI) for depression in South Korea from 1998 to 2007

			Standardized CI (SE)	
		Unstandardized CI (SE)	Age and gender only	Age and gender + other factors*
Depression	1998	-0.126 (0.068)	-0.084 (0.068)	-0.093 (0.068)
	2001	-0.278 (0.068)	-0.211 (0.068)	-0.270 (0.068)
	2007	-0.287 (0.114)	-0.175 (0.113)	-0.266 (0.117)
Suicidal ideation	1998	-0.138 (0.012)	-0.120 (0.011)	-0.145 (0.012)
	2001	-0.159 (0.015)	-0.123 (0.015)	-0.156 (0.015)
	2005	-0.200 (0.015)	-0.142 (0.015)	-0.184 (0.015)
	2007	-0.250 (0.028)	-0.166 (0.027)	-0.209 (0.027)
Suicide attempts	1998	-0.221 (0.062)	-0.259 (0.062)	-0.333 (0.062)
	2001	-0.175 (0.076)	-0.195 (0.072)	-0.232 (0.072)
	2005	-0.179 (0.089)	-0.227 (0.089)	-0.352 (0.089)
	2007	-0.400 (0.116)	-0.285 (0.116)	-0.390 (0.114)

*Other factors controlled for were educational attainment, employment status, urbanicity and marital status

crisis, which broke out in late 1997 and unfolded over 1998. Following the crisis, the unemployment rate rose sharply from below 3.0% in 1997 to 7.0% in 1998 (27). The Gini coefficient, a measure of the magnitude of income inequality, also rose to above 0.3 in 1999 for the first time, and it increased to 0.325 in 2008 (28). Such a crisis is likely to have brought about rising poverty, greater insecurity, and stresses from social exclusion, which would plausibly have a major impact on the mental health of individuals, especially those in lower income groups. However, its impact on depression and suicidal acts may have not been evident in the same temporal fashion. The onset of depression is likely to involve a prolonged course of symptoms prior to clinical diagnosis. On the contrary, the emergence of suicide acts may reflect an acute response to the crisis. For instance, there was a surge in suicide rates in 1998: it was 13.6 per 100,000 population in 1997 but rose to 18.8 in 1998 and subsided thereafter (12).

Our study found that pro-rich inequalities doubled over the ten years for all three psychopathologies, and the inequalities also became prominently income-gradient in recent years, particularly for suicide attempts. While our study did not examine income-related inequality in the prevalence of suicide due to the paucity of data, such a trend may be similar to that of suicide attempts. Given the "epidemic" suicide phenomena in contemporary Korea (29), our findings urge for extended social protection policies for the less privileged populations.

The CIs in our study indicated that the magnitude of inequality might be greater in mental health than for general health. Based on the same KHANES data set which were employed in the present study, Shin and Kim (30) reported CIs of -0.0116 for 1998, -0.0179 for 2001 and -0.0278 for 2005 in their assessment of income-related inequality in self-reported general health. While their study also showed an inequality in general health in favour of the rich, the magnitudes were notably smaller than those found in our analyses. This observation is consistent with the international literature. Mangalore et al (31) reported a CI of -0.10572 for neurotic disorder and -0.43936 for probable psychosis in the UK, indicating a much greater inequality than that reported for self-reported (general) health (CI = -0.0129) (22). In Spain, Costa-Font and Gil (18) also reported greater income-related inequality in depression (CI = -0.1551) than in self-reported health (CI = -0.0066) (22).

While income may not have a clear link with depression or suicidal behaviour, it can serve as a proxy for the general socio-economic condition of an individual. In other words, its impact on depression or suicidal behaviour may be understood as a reflection of the complex links with a myriad of socio-economic factors (e.g., unemployment). Decomposition of income-related inequality would be a topic that deserves further research.

The present study has a number of limitations that should be noted in the interpretation of the findings. Firstly, although we used nationally representative survey data sets, which are commonly considered one of the most reliable data source in health-related research, the validity and reliability of psychometric measures employed in the KHANES survey had been implicitly assumed rather than explicitly ascertained. Secondly, the analyses were based on a series of cross-sectional surveys, which precludes causal inference, a problem shared with almost all studies of health inequalities. The cross-sectional data, nevertheless, provide some early evidence in an area where there is currently no good source of representative panel data for mental health in South Korea. Thirdly, we used self-reported data, which is potentially subject to both recall bias and social desirability bias. While recall bias in reporting a formal diagnosis of depression is very unlikely, social desirability can lead to underreporting due to the stigma attached to mental illness. In addition, access to care is likely to vary by socio-economic status. Since the KHANES study measured "doctor-diagnosed depression", depressed individuals in lower income groups might have been underrepresented in the survey due to potential barriers like financial difficulties in seeking professional help. It is therefore plausible that the actual income-related inequality in the prevalence of depression may be greater.

In conclusion, our study showed the existence of significant pro-rich inequalities in the prevalence of depression, suicidal ideation and suicide attempts. The inequalities in each instance have doubled over the past ten years, accompanied by widening income inequality following the nation's economic crisis in the late 1990s. Furthermore, our results suggest that income-related inequality was more pronounced in mental health than in general health. These findings imply the need for expanded social protection policies for vulnerable populations and for a strengthening of the mental health safety net.

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Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis?

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The constructs of atypical depression, bipolar II disorder and borderline personality disorder (BPD) overlap. We explored the relationships between these constructs and their temperamental underpinnings. We examined 107 consecutive patients who met DSM-IV criteria for major depressive episode with atypical features. Those who also met the DSM-IV criteria for BPD (BPD+), compared with those who did not (BPD-), had a significantly higher lifetime comorbidity for body dysmorphic disorder, bulimia nervosa, narcissistic, dependent and avoidant personality disorders, and cyclothymia. BPD+ also scored higher on the Atypical Depression Diagnostic Scale items of mood reactivity, interpersonal sensitivity, functional impairment, avoidance of relationships, other rejection avoidance, and on the Hopkins Symptoms Check List obsessive-compulsive, interpersonal sensitivity, anxiety, anger-hostility, paranoid ideation and psychoticism factors. Logistic regression revealed that cyclothymic temperament accounted for much of the relationship between atypical depression and BPD, predicting 6 of 9 of the defining DSM-IV attributes of the latter. Trait mood lability (among BPD patients) and interpersonal sensitivity (among atypical depressive patients) appear to be related as part of an underlying cyclothymic temperamental matrix.

Key words: Atypical depression, borderline personality disorder, bipolar II disorder, cyclothymic temperament

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The relationship between atypical depression, borderline personality disorder (BPD) and bipolar II disorder (BP-II) remains understudied. Previous work by us (1,2) and others (3-6) suggests a considerable overlap in both clinical manifestations and long-term traits of patients within this broad realm.

The rubric "atypical depression" includes a large subset (7,8) of depressive states characterized by reactive mood, a pattern of stable interpersonal sensitivity (exaggerated vulnerability to feeling hurt by criticism or rejection) and reverse vegetative symptoms such as increased appetite and hypersomnia. In its original description, atypical depression was also invariably associated with phobic-anxious symptomatology and preferential response to monoamine oxidase inhibitors (9).

The related concept of "hysteroid dysphoria" (10) has been used to describe a subgroup of depressed patients, usually women, whose hallmark is an extreme intolerance of personal rejection, with a particular vulnerability to loss of romantic relationships. The stormy lifestyle of these patients suggests a link to BP-II and related cyclothymic or "soft" bipolar conditions (11-13).

Regrettably, most clinical studies of atypical depression exclude definite bipolar disorder (9,10,14). Such exclusion appears unjustified on the basis of the observation of similar rates of atypicality in unipolar and bipolar I depressives (15) and of higher rates in BP-II compared to unipolar patients (16). Follow-up data also show a frequent bipolar outcome in atypical depressives (15,17).

In a previous study (2), we observed that 32.6% of 86 major depressive patients with DSM-IV atypical features met criteria for strictly defined BP-II and 72% met our criteria for bipolar spectrum disorder (major depression plus hypomania and/or cyclothymic or hyperthymic temperament). Family history for bipolar disorder validated these clinical observations. Lifetime comorbidity with anxiety disorders (panic disorder-agoraphobia, social phobia and obsessive-compulsive disorder) and both cluster B (dramatic, emotional or erratic) and C (anxious or fearful) personality disorders was very common. These findings suggested that the "atypicality" of depression is related to an affective temperamental dysregulation, which could explain why atypical depressive patients are often given "borderline" diagnoses (18).

In the present report, we expand our sample size and extend the aim of our analyses to compare previous course, symptomatic features, family history, and axis I and axis II comorbidity in atypical depressive patients with (BPD+) or without (BPD-) a concomitant diagnosis of BPD. Moreover, in order to better characterize this personality profile in atypical depressives, we explore its temperamental underpinnings and links with other personality disorders.

METHODS

A consecutive sample of 107 patients who met DSM-IV criteria for major depressive episode with atypical features (14 males and 93 females, mean age 31.5±8.8 years, range 16-55 years), was recruited in a three-year period at the Institute of Psychiatry of the University of Pisa. The subjects

came from a variety of sources, about equally divided between self-referrals, referrals from general practitioners and various medical specialists and psychiatrists. Exclusion criteria were a lifetime history of schizophrenia or other psychotic disorder, organic mental syndrome and serious or uncontrolled medical diseases. All patients provided written informed consent for participation in the study.

The Axis I diagnostic evaluation was conducted by the Structured Clinical Interview for DSM III-R (19) and the Semi-structured Interview for Depression (SID, 20). The SID, developed as part of the Pisa-San Diego Collaborative Study on Affective Disorders, has been used with 2500 patients at the time of this writing: its reliability for diagnostic assessment of patients and their temperaments has been documented elsewhere (21,22). Family history data were collected by the Family History Research Diagnostic Criteria (23). Temperaments were defined by our operational criteria, reported elsewhere (2, 24), which represent the University of Tennessee (25) modification of the Schneiderian descriptions (26). Cyclothymic temperament was defined according to Akiskal (27).

We considered two levels for the diagnosis of BP-II, based respectively on the "conservative" DSM-IV threshold of ≥ 4 days for hypomania, and the ≥ 2 days threshold embodied in the SID, which has been validated in large clinical and epidemiologic populations (28,29).

The diagnosis of atypical depression required mood reactivity (i.e., mood brightens in response to actual or potential positive events), plus two or more of the following features: significant weight gain or increase in appetite, hypersomnia, leaden paralysis, long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) resulting in significant social or occupational impairment, and absence of melancholic and catatonic features during the same episode. For the diagnosis of major depression with atypical features, we attained excellent inter-rater reliability (kappa = 0.94).

For the current and lifetime diagnosis of body dysmorphic disorder (BDD), we used a semi-structured interview (30). The diagnosis of borderline, histrionic, narcissistic, avoidant, dependent and obsessive-compulsive personality disorders was performed by the corresponding sections of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II, 31).

For symptomatological assessment, psychiatrists completed the following rating scales: the Atypical Depression Diagnostic Scale (ADDS, 32), a semi-structured interview designed to determine the presence and the severity, on a scale ranging from 1 to 6, of atypical features during the current depressive episode, the Hamilton Rating Scale for Depression (HRSD, 33) and its modified form for reverse vegetative features (34). Patients also completed the Hopkins Symptoms Check List (HSCL-90, 35).

Comparative analyses for familial, epidemiological, clini-

Table 1 Demographic and clinical features in patients with atypical depression with (BDP+) or without (BDP-) borderline personality disorder

	BDP+ (n=46)	BDP- (n=61)	t or β^2 (df=2)	p
Gender (% females)	87.0	86.7	0	0.99
Age (years, mean±SD)	30.0±7.7	32.7±9.4	-1.61	0.11
Age at onset (years, mean±SD)	22.2±7.8	23.2±8.2	-0.6	0.54
Age at first treatment (years, mean±SD)	24.6±8.9	26.3±10	-1	0.3
Age at first hospitalization (years, mean±SD)	18.2±15.0	18.3±17	0	0.98
Duration of current episode (months, mean±SD)	7.3±7.3	14.0±17.8	-2.41	0.02
Duration of illness (years, mean±SD)	7.7±6.0	9.5±7.6	-1.28	0.2
No. previous depressive episodes (mean±SD)	3.3±2.8	4.0±4.0	-1.02	0.32
No. hospitalizations (mean±SD)	1.1±1.8	1.5±2.8	-0.82	0.42
Residual (interepisodic) symptoms (%)	84.4	77.6	0.76	0.4
No. lifetime suicide attempts (mean±SD)	1.1±1.6	0.9±1.9	0.38	0.7
Suicide attempts in current episode (%)	32.6	15±24.6	0.84	0.04
Family history in first-degree relatives (%)				
Major depression	52.2	50.8	0.06	0.8
Bipolar disorder	10.9	9.9	0.22	0.73
Panic disorder-agoraphobia	8.7	16.4	1.37	0.24
Obsessive-compulsive disorder	4.3	5.0	0.55	0.46
Generalized anxiety disorder	4.3	0	2.7	0.1
Eating disorders	4.3	4.9	0.08	0.77
Alcohol abuse	2.2	5.0	0.55	0.46
Substance abuse	4.3	0	2.70	0.1

Table 2 Diagnosis distribution and comorbidity with Axis I and II disorders in patients with (BDP+) or without (BDP-) borderline personality disorder

	BDP+ (n=46)	BDP- (n=61)	β^2 (df=2)	p
Depressive types (%)				
Bipolar I	2.2	0	1.34	0.2
Bipolar II	26.1	21.3	0.33	0.6
Bipolar III (pharmacologic hypomania)	6.2	8.2	0.15	0.7
Bipolar NOS (cyclothymic/hyperthymic temperaments)	50.0	42.6	0.57	0.4
Bipolar spectrum (total)	84.8	72.1	3.62	0.06
Major depressive disorder, recurrent	8.7	24.6	4.54	0.03
Major depressive disorder, single episode	4.4	3.3	0.83	0.8
Anxiety disorders (%)				
Panic disorder	23.9	16.4	0.94	0.3
Panic disorder with agoraphobia	50.0	42.6	0.58	0.4
Obsessive-compulsive disorder	17.3	18.0	0.01	0.9
Social phobia	9 (19.6)	18 (29.5)	1.37	0.2
Generalized anxiety disorder	4 (8.7)	4 (6.6)	0.17	0.7
Other Axis I disorders (%)				
Body dysmorphic disorder	55.8	36.1	3.99	0.05
Anorexia nervosa	0	1.7	0.76	0.3
Bulimia nervosa	26.1	9.8	4.95	0.03
Alcohol related disorders	13.0	4.9	2.25	0.1
Substance related disorders	15.2	13.1	0.10	0.8
Axis II disorders (%)				
Histrionic	33.3	19.7	2.55	0.1
Narcissistic	31.1	9.8	7.66	0.006
Obsessive-compulsive	34.8	29.5	1.29	0.6
Dependent	63.0	34.4	8.63	0.003
Avoidant	73.3	52.5	4.76	0.03
Affective temperaments (%)				
Depressive	17.4	27.9	0.23	0.2
Hyperthymic	8.7	21.3	1.37	0.08
Cyclothymic	58.7	27.9	11.72	0.001

cal and course characteristics of subgroups were conducted using the Student's t-test for dimensional variables (or the Mann-Whitney U-test, when appropriate) and the χ^2 analysis for categorical variables (or the Fisher exact-test, when appropriate). A two-tailed significance level of $p<0.05$ was set. To assess the symptomatological picture associated with BPD, a series of multivariate analyses of variance was performed with the ADDS item scores, the HRSD factor and total scores, the item scores for reverse vegetative features of the HRSD and the HSCL-90 factor scores as dependent measures and the diagnosis of BPD as independent class variable. Finally, we undertook an analysis of the explanatory power of affective temperaments and personality disorders (predictors) using a standard backward stepwise logistic regression procedure for diagnosis and each criterion of BPD.

RESULTS

The rate of definite bipolar disorders (bipolar I and II) in the entire sample was 24.3% (n=26); pharmacological hypomania raised this rate to 31.8%. Broadening the bipolar spectrum to include major depressions in association with hyperthymic or cyclothymic temperaments (which in the DSM-IV schema might be subsumed under bipolar NOS) gave a yield of 77.6% (n=83).

The comparison between BPD+ and BPD- patients did not show significant differences in sex distribution, index age, age at onset of mood disorder, age at first treatment, age at first hospitalization, number of previous depressive episodes, number of hospitalizations, presence of residual symptomatology, stressors and lifetime or current history of suicide attempts (Table 1).

The two groups also showed similar rates of family history for mood, anxiety and eating disorders as well as alcohol and substance abuse. Only length of the current episode (shorter in BPD+) and rate of suicide attempts (higher in BPD+, in part definitional) distinguished the two groups.

As far as diagnostic distribution for Axis I is concerned (Table 2), our data did not reveal significant differences between BPD+ and BPD-, with the exception of non-bipolar recurrent major depression, that was more represented in BPD-. It is noteworthy that bipolarity, whether narrowly or broadly defined, did not distinguish the two groups.

Regarding the lifetime comorbidity with anxiety disorders (also shown in Table 2), panic disorder and agoraphobia were the most common in both groups; obsessive-compulsive disorder, social phobia and generalized anxiety were

Table 3 Symptomatological features in patients with (BDP+) or without (BDP-) borderline personality disorder

	BDP+ (n=46)	BDP- (n=61)	t value	p
Atypical Depression Diagnostic Scale (mean±SD)				
Usual reactivity	53.3±25.5	44.4±18.3	2.09	0.04
Maximum reactivity	70.2±15.8)	65.1±12.1	1.90	0.06
Interpersonal sensitivity	4.8±0.9	4.5±0.9	1.86	0.07
Quality of relationships	4.3±1.0	3.5±0.8	2.05	0.04
Functional impairment	4.3±1.0	3.9±0.8	2.51	0.01
Avoidance of relationships	3.9±1.0	3.5±1.1	2.02	0.05
Other rejection avoidance	4.0±1.2	3.6±1.1	2.07	0.04
Leaden paralysis	4.6±1.2	4.2±1.3	1.72	0.09
Increased appetite	3.2±1.8	3.5±1.6	-0.86	0.4
Increased food intake	3.1±1.8	3.3±1.6	-0.84	0.4
Weight gain	2.4±1.6	2.8±1.4	-1.51	0.1
Weight gain-increased appetite	2.3±2.0	2.5±2.0	-0.82	0.4
Hypersomnia	3.5±3.1	2.9±2.8	1.06	0.3
Hamilton Rating Scale factors (mean±SD)				
Anxiety-somatization	0.9±0.3	0.9±0.4	-0.003	0.99
Weight	0.2±0.5	0.1±0.3	1.48	0.1
Cognitive disturbances	1.0±0.5	0.8±0.4	2.04	0.04
Diurnal variations	1.2±0.7	1.0±0.7	1.63	0.1
Retardation	1.4±0.4	1.3±0.5	1.60	0.1
Sleep disturbance	0.5±0.5	0.5±0.5	-0.02	0.98
Total	21.2±5.2	18.8±6.2	2.05	0.04
Hamilton Scale for reverse symptoms (mean±SD)				
Lack of energy	2.9±0.8	2.9±0.9	0.15	0.9
Social withdrawal	1.7±1.0	1.8±1.1	-0.67	0.5
Increased appetite	1.4±1.2	1.5±1.1	-0.28	0.8
Increased food intake	1.3±1.2	1.5±1.1	-0.55	0.6
Carbohydrate craving	1.5±1.2	1.6±1.1	-0.42	0.7
Weight gain	0.7±0.8	0.9±0.8	-1.60	0.1
Hypersomnia	1.9±1.7	1.5±1.5	1.30	0.2
Hopkins Symptoms Check List-90 (mean±SD)				
Somatization	1.7±0.9	1.4±0.8	1.5	0.15
Obsessive-compulsive	2.1±0.9	1.9±1.0	1.9	0.1
Interpersonal sensitivity	1.9±1.0	1.5±0.9	2.3	0.02
Depression	2.4±0.9	2.1±0.9	1.2	0.25
Anxiety	2.0±1.0	1.5±0.9	2.5	0.01
Anger-hostility	1.7±1.0	0.9±0.7	4.0	0.0001
Phobic anxiety	1.3±1.0	1.0±0.7	1.7	0.09
Paranoid ideation	1.9±1.0	1.4±0.9	2.9	0.005
Psychoticism	1.4±0.8	1.0±0.7	2.5	0.01

less prevalent, but again, their rates were similar in BPD+ and BPD- patients. Body dysmorphic disorder and bulimia nervosa occurred more frequently in BPD+ than BPD-, while substance and alcohol related disorders were equally represented in the two groups. Personality disorders belonging to the anxious and dramatic clusters were highly represented in both groups. Narcissistic, dependent and avoidant personality disorders were significantly more common in BPD+ than BPD- patients. Of the affective temperaments, cyclothymic disposition was significantly more prevalent in the BPD+ group.

On multivariate analyses of variance, BPD+ and BPD- patients differed with respect to ADDS items scores (F=2.23, df=12/94, p=0.016) and HRCL-90 factor scores (F=2.51, df=9/97, p=0.013), but not to HRSD factor and total scores, and item scores for reverse vegetative features of the HRSD. Subsequent univariate analyses confirmed that BPD+ patients had significantly higher scores on the ADDS items covering reactivity of mood, interpersonal sensitivity, functional impairment, avoidance of relationships and other rejection avoidance, and on the HSCL-90 obsessive-compulsive, interpersonal sensitivity, anxiety, anger hostility, paranoid ideation and psychoticism factors (Table 3).

On the standard backward stepwise logistic regression, cyclothymic temperament, and dependent, avoidant and narcissistic personality disorders were predictors for BPD (Table 4). Among the BPD+ patients, cyclothymic temperament contributed significantly to 6 out of 9 DSM criteria: efforts to avoid real or imagined abandonment, unstable and intense interpersonal relationships, identity disturbance, impulsivity, recurrent suicidal behavior or self-mutilating behavior, affective instability, and marked reactivity of mood.

Dependent personality disorder was a significant variable

Table 4 Odd ratios and confidence intervals for DSM-IV diagnosis and criteria of borderline personality disorder

	Affective temperaments			Personality disorders				
	Hyperthymic	**Depressive**	**Cyclothymic**	**Dependent**	**Avoidant**	**Hystrionic**	**Narcissistic**	**Obsessive-compulsive**
Borderline personality disorder*****			2.02 (1.6-2.5)	1.50 (1.1-1.9)	1.62 (1.1-2.1)			1.81 (1.2-2.4)
Efforts to avoid real or imagined abandonment*****			1.64 (1.2-2.1)	2.17 (1.8-2.6)				
Unstable and intense interpersonal relationships*****			2.66 (2.2-3.2)		1.94 (1.4-2.4)	3.83 (3.1-4.5)		
Identity disturbance***			1.74 (1.3-2.2)		1.66 (1.2-2.1)			
Impulsivity*****			2.23 (1.8-2.6)				1.75 (1.2-2.3)	
Recurrent suicidal behavior, or self-mutilating behavior*			1.67 (1.3-2.1)					
Affective instability, marked reactivity of mood****			1.67 (1.2-2.1)			2.06 (1.4-2.7)		
Chronic feelings of emptiness**								
Inappropriate, intense anger or difficulty controlling anger								
Transient, stress-related paranoid ideation or severe dissociative symptoms								

*p<0.01; **p<0.007;***p<0.003; ****p<0.002; *****p<0.0001

only for efforts to avoid real or imagined abandonment; avoidant personality for unstable and intense interpersonal relationships and for identity disturbance; histrionic personality for unstable and intense interpersonal relationships, and for affective instability and marked reactivity of mood; and narcissistic personality for impulsivity.

DISCUSSION

Extending our earlier findings (2) in a much larger sample, the present study found that, when adopting "narrow criteria" based on DSM-IV, 24% of atypical depressives could be classified as bipolar. Using broader criteria, 78% could be considered to belong to the "soft" bipolar spectrum. The latter included depressions with history of hypomania shorter than four days and antidepressant-associated hypomania, as well as depressive episodes arising from cyclothymic and hyperthymic temperaments beyond the thresholds for BP-II in the DSM-IV schema. We are not the only research team reporting high rates of bipolar spectrum disorders in atypical depressives (16,36,37).

In our sample, 43% of atypical depressive patients met DSM-IV criteria for BPD. However, this was not the most common Axis II disorder: avoidant and dependent personality disorders, probably related to the presence of interpersonal sensitivity and separation anxiety, were even more prevalent.

BPD+ patients, when compared to BPD-, were characterized by a higher rate of comorbidity with Axis II disorders of the anxious and dramatic clusters, in particular narcissistic, avoidant and dependent personality disorders. The most significant association was, however, with cyclothymic temperament. These findings support the observation that borderline characterologic features are related to the mood instability of the cyclothymic type (4,6,12).

According to the logistic regression, the presence of cyclothymic attributes explains most, but not all, of the relationship between atypical depression and BPD, including avoidance of abandonment, unstable relationships, identity disturbance, impulsivity, self-injurious behavior, affective irritability and reactivity. Avoidant and dependent traits, more related to the presence of phobic-anxious attitudes, also appear relevant to the diagnosis of BPD, as well as to the prediction of several BPD criteria, such as unstable and intense interpersonal relationships, identity disturbance and efforts to avoid real or imagined abandonment. The presence of narcissistic personality appears to be related to impulsivity, while histrionic personality accounts for unstable and intense interpersonal relationships, affective instability, and marked mood reactivity. In a recent study, hypomanic symptoms have been shown to predict an increase in narcissistic and histrionic personality features in suicidal young adults: it is unclear whether "mood symptoms might impact personality" ("scar hypothesis") or vice versa (38).

According to Henry et al (39), BDP and BP-II are charac-

terized by different types of affective lability: shifts from anger and anxiety to euthymia are associated with BDP, whereas shifts from euthymia to depression and elation and vice versa are characteristic of BP-II patients. In our patients, mood lability, hostility and anxious-avoidant-sensitive traits appear to be related, within a cyclothymic temperamental matrix. Other authors interpreted the affective instability of BPD as a form of prolonged ultra-rapid cycling with extreme rapid mood switching (40), closely resembling classic descriptions of cyclothymia (1).

In a more hypothetical vein, we submit that cyclothymic disposition might represent the mediating core characteristic in this complex pattern of mood, anxiety, and impulsive disorders. Anxious-sensitive symptomatology and hostile-impulsive-addictive behavior, rather than being considered independent comorbidities, might represent core features of such cyclothymic diathesis (41,42), largely pinpointed by a common familial trait (43,44). The coexistence among mood, anxiety and impulsive disorders and BPD has been reported by Zanarini et al (45) in a large population of severe personality disorder inpatients and in a subsequent prospective follow-up of over 6 years (46). More recently, a lifetime pattern of complex Axis I comorbidity of disorders of affect (mood and anxiety disorders) and of impulse (alcohol-substance use and eating disorders) was found to have strong positive predictive power for the BPD diagnosis (47). Unfortunately these authors did not examine cyclothymic and other bipolar spectrum disorders with specific measures. This is a common omission among "borderline" researchers, possibly based on a DSM-IV convention. According to this manual, "mood lability" distinguishes BPD from BP-II. However, this can be questioned, because in a large sample of major depressive patients examined prospectively in the National Institute of Mental Health collaborative study of depression, mood lability was the most specific predictor of BP-II outcome (48).

Certainly, prospective studies with greater methodological sophistication are needed to clarify the relationship of the putative temperamental and developmental variables to the complex affective patterns we have described. However, a proper consideration of "soft" bipolarity in borderline-atypical depressive patients (50) is extremely important in order to protect them from antidepressant-induced switches or rapid cycling and make them accessible to pharmacological and psychological approaches focused on abrupt shifts in mood and consequent impulsive, hostile, and aggressive behavior.

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Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care

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The lifespan of people with severe mental illness (SMI) is shorter compared to the general population. This excess mortality is mainly due to physical illness. We report prevalence rates of different physical illnesses as well as important individual lifestyle choices, side effects of psychotropic treatment and disparities in health care access, utilization and provision that contribute to these poor physical health outcomes. We searched MEDLINE (1966 – August 2010) combining the MeSH terms of schizophrenia, bipolar disorder and major depressive disorder with the different MeSH terms of general physical disease categories to select pertinent reviews and additional relevant studies through cross-referencing to identify prevalence figures and factors contributing to the excess morbidity and mortality rates. Nutritional and metabolic diseases, cardiovascular diseases, viral diseases, respiratory tract diseases, musculoskeletal diseases, sexual dysfunction, pregnancy complications, stomatognathic diseases, and possibly obesity-related cancers are, compared to the general population, more prevalent among people with SMI. It seems that lifestyle as well as treatment specific factors account for much of the increased risk for most of these physical diseases. Moreover, there is sufficient evidence that people with SMI are less likely to receive standard levels of care for most of these diseases. Lifestyle factors, relatively easy to measure, are barely considered for screening; baseline testing of numerous important physical parameters is insufficiently performed. Besides modifiable lifestyle factors and side effects of psychotropic medications, access to and quality of health care remains to be improved for individuals with SMI.

Key words: Physical illness, severe mental illness, bipolar disorder, depression, schizophrenia, psychotropic medication, health disparities

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A number of reviews and studies have shown that people with severe mental illness (SMI), including schizophrenia, bipolar disorder, schizoaffective disorder and major depressive disorder, have an excess mortality, being two or three times as high as that in the general population (1-21). This mortality gap, which translates to a 13-30 year shortened life expectancy in SMI patients (4,5,22-27), has widened in recent decades (11,28-30), even in countries where the quality of the health care system is generally acknowledged to be good (11). About 60% of this excess mortality is due to physical illness (27,31).

Individuals with SMI are prone to many different physical health problems (Table 1). While these diseases are also prevalent in the general population, their impact on individuals with SMI is significantly greater (31,32).

Although many factors contribute to the poor physical health of people with SMI (33), the increased morbidity and mortality seen in this population are largely due to a higher prevalence of modifiable risk factors, many of which are related to individual lifestyle choices (31). However, this is not the whole story. It seems that the somatic well being of people with a (severe) mental illness has been neglected for decades (15), and still is today (7,34-39,40,41). There is increasing evidence that disparities not only in health care access and utilization, but also in health care provision contribute to these poor physical health outcomes (33-39). A confluence of patient, provider, and system factors has created a situation in which access to and quality of health care is problematic for individuals with SMI (31). This is not totally surprising as we are today in a situation in which the gaps, within and between countries, in access to care are greater than at any time in recent history (42). Therefore, this growing problem of medical comorbidities and premature death in people with SMI needs an urgent call to action.

This paper highlights the prevalence of physical health problems in individuals with SMI. Furthermore, contributing factors are considered that impact on the physical health of these people, such as psychotropic medications (antipsychotics, antidepressants and mood stabilizers), individual lifestyle choices (e.g., smoking, diet, exercise), psychiatric symptoms, as well as disparities in the health care. This is a selective, rather than a systematic review of clinical data on physical health problems in people with SMI, as we did not include all physical diseases. We searched MEDLINE (1966 – August 2010) for epidemiological, morbidity and mortality data on the association between physical illnesses and schizophrenia, bipolar disorder and major depressive disorder. We com-

bined the MeSH terms of these psychiatric disorders with the different MeSH terms of major general physical disease categories. We included pertinent reviews to identify prevalence figures and factors contributing to the excess morbidity and mortality rates. Reference lists of reviews were searched for additional relevant studies. Moreover, if necessary to obtain more specific information, for some of the general physical disease categories (e.g., respiratory diseases), we also used specific physical illnesses as a search term.

PHYSICAL DISEASES LINKED TO SMI AND/OR PSYCHOTROPIC TREATMENT

Obesity

Obesity is becoming a significant and growing health crisis, affecting both developed and developing countries (43,44). People with obesity have shorter life spans and are at increased risk for a number of general medical conditions, including type 2 diabetes mellitus, DM (relative risk, RR >3), cardiovascular disease, CVD (RR >2-3), dyslipidemia (RR >3), hypertension (RR >2-3), respiratory difficulties (RR >3), reproductive hormone abnormalities (RR >1-2) and certain cancers (e.g., colon) (RR >1-2) (22,45-49,50).

Several methods are available to assess overweight and obesity. Body mass index (BMI) is a direct calculation based on height and weight (kg/m^2). A BMI ≥25 kg/m^2 corresponds to overweight, a BMI ≥30 kg/m^2 to obesity (31). BMIs ≥30kg/m^2 are known to shorten life expectancy (48,51). However, based on evidence for higher morbidity and mortality risk at BMIs below 30 Kg/m^2 in Asian populations, the threshold for the definition of overweight in these populations is modified to a BMI ≥23 Kg/m^2 and the threshold for obesity to a BMI ≥25 Kg/m^2. Waist circumference (WC), measuring abdominal or central adiposity, is emerging as a potentially more valid and reliable predictor of risk for CVD, type 2 DM, and other metabolic risk-related conditions, compared with BMI (31). Accumulating evidence argues that lower cutoff points for WC should be used for Asians, as this population is prone to obesity-related morbidity and mortality at shorter WCs (52-56). The International Diabetes Federation (IDF) provides sex-and race-specific criteria in defining WC to identify people with central obesity, thus adjusting this criterion to make it also useful in non-Caucasian populations (Table 2). However, long-term prospective studies are still required to identify more reliable WC cut points for different ethnic groups, particularly for women (57).

Obesity in SMI patients

SMI and obesity overlap to a clinically significant extent (45). Increasing evidence suggests that persons with SMI are, compared to the general population, at increased risk for overweight (i.e., BMI =25-29.9, unless Asian: BMI =23-24.9), obesity (i.e., BMI ≥30, unless Asian: BMI ≥25) and abdominal obesity (see Table 2) (63-75), even in early illness phase and/or without medication (76-78). The risk of obesity in persons with SMI, however, varies by diagnosis. People with schizophrenia have a 2.8 to 3.5 increased likelihood of being obese (79). Several Canadian and US studies reported rates of obesity (BMI ≥30) in patients with schizophrenia of 42-60% (63,79,80). On the other hand, those with major depres-

Table 1 Physical diseases with increased frequency in severe mental illness (from 15)

Disease category	Physical diseases with increased frequency
Bacterial infections and mycoses	Tuberculosis (+)
Viral diseases	HIV (++), hepatitis B/C (+)
Neoplasms	Obesity-related cancer (+)
Musculoskeletal diseases	Osteoporosis/decreased bone mineral density (+)
Stomatognathic diseases	Poor dental status (+)
Respiratory tract diseases	Impaired lung function (+)
Urological and male genital diseases	Sexual dysfunction (+)
Female genital diseases and pregnancy complications	Obstetric complications (++)
Cardiovascular diseases	Stroke, myocardial infarction, hypertension, other cardiac and vascular diseases (++)
Nutritional and metabolic diseases	Obesity (++), diabetes mellitus (+), metabolic syndrome (++), hyperlipidemia (++)

(++) very good evidence for increased risk, (+) good evidence for increased risk

Table 2 Ethnicity-specific cutoff values of waist circumference indicating abdominal obesity (see 57-62)

	European, sub-Saharan Africans, Mediterranean and Middle Eastern populations	South Asians, Chinese, and ethnic South and Central Americans	Japanese	Northern Americans
Men	≥94 cm	≥90 cm	≥90 cm	≥102 cm
Women	≥80 cm	≥80 cm	≥82-85 cm	≥88 cm

sion or bipolar disorder have a 1.2 to 1.5 increased likelihood of being obese (BMI ≥30) (44,69,70,81,82). Clinical research has suggested that up to 68% of treatment-seeking bipolar disorder patients are overweight or obese (83). One study found an obesity rate (BMI ≥30) of 57.8% among those with severe depression (84).

In patients with SMI, as in the general population, obesity is associated with lifestyle factors (e.g., lack of exercise, poor diet), but also with illness-related (negative, disorganized and depressive symptoms) and treatment-related factors, including weight liability of certain psychotropic agents. Adverse effects, such as sedation, should also be considered as potential contributors to weight gain in addition to, still not fully elucidated, medication induced effects on appetite and food intake (45,73,50,85-87).

Obesity and psychotropics

Weight gain during acute and maintenance treatment of patients with schizophrenia is a well established side effect of antipsychotics (AP), affecting between 15 and 72% of patients (26,50,77,88-98). There is growing evidence for similar effects in patients with bipolar disorder (65,83,99). There is a hierarchy for risk of weight gain with AP that has been confirmed in different studies and meta-analyses (88,92,100-106). Weight gain is greatest with clozapine and olanzapine (107,108), while quetiapine and risperidone have an intermediate risk. Aripiprazole, asenapine, amisulpride and ziprasidone have little effect on weight. A recent systematic review of randomized, placebo controlled trials of novel AP in children and adolescents (<18 years old) identified the same hierarchy for risk of weight gain for this vulnerable population (109). Among the conventional AP, so-called low-potency agents, such as chlorpromazine and thioridazine, have a higher risk than high-potency drugs, such as haloperidol (110-112). No agent, however, should be considered as truly weight-neutral, as the proportion of individuals experiencing ≥7% weight gain is greater with any atypical AP than with placebo (92), and all AP have been found to cause significant weight gain in AP-naïve or first-episode patients (113-115). Even amisulpride, ziprasidone and low-dose haloperidol demonstrated notable weight gain of 9.7 kg, 4.8 kg and 6.3 kg respectively at endpoint in a 12-month trial of AP in first-episode patients (102). Equally, antidepressants (AD) such as paroxetine (116), and mood stabilizers, such as lithium and valproate (117-119), have been associated with weight gain (Table 3).

The high interindividual variability in medication-induced weight gain suggests that genetic factors influence the risk to gain weight (50,122). Studies of genetic predictors of weight gain under AP therapy have mainly but not exclusively (131) focused on HTR2C (132-135) and LEPR (135,136) gene polymorphisms. Although the results are promising, the role of genetic factors in predicting this severe side effect remains an option for the future.

Metabolic syndrome

Obesity is also associated with the metabolic syndrome (MetS), a clustering of abnormalities that confers a 5-6-fold

Table 3 Weight gain liability of psychotropic agents used in SMI (see 45,63-65,87,95,99,104,120,121-130)

Drug class	Weight loss	Relatively weight neutral	Weight gain
Antidepressants	Bupropion Fluoxetine	Citalopram Duloxetine Escitalopram Nefazodone Sertraline Venlafaxine	*Substantial* Amitriptyline Imipramine Mirtazapine *Intermediate* Nortriptyline Paroxetine
Anticonvulsants/ Mood stabilizers	Topiramate Zonisamide	Lamotrigine Oxcarbazepine	*Substantial* Lithium Valproate *Intermediate* Carbamazepine Gabapentin
Antipsychotics	Aripiprazole (in pre-treated individuals) Molindone (in pre-treated individuals) Ziprasidone (in pre-treated individuals)	Amisulpride Aripiprazole Asenapine Fluphenazine Haloperidol Lurasidone Perphenazine Ziprasidone	*Substantial* Chlorpromazine Clozapine Olanzapine *Intermediate* Iloperidone Quetiapine Risperidone Thioridazine Zotepine

increased risk of developing type 2 DM and a 3-6 fold increased risk of mortality due to coronary heart disease (137-144).

There is also evidence supporting the hypothesis that the MetS or components of the MetS may be important etiologic factors for certain cancers (e.g., colon cancer) (145,146).

Although some controversy exists whether the MetS is a true syndrome (57,147-149), and despite differences in specific criteria among the definitions (Table 4), there is agreement that the major characteristics of the syndrome include central obesity, hypertension, dyslipidemia, glucose intolerance or insulin resistance (45,137,150). Studies show large variations in prevalence estimates of the MetS across definitions, countries or regions, gender, ethnicity, and age groups (137). Countries in North and South America (151-154) reported a relatively higher prevalence than other countries or regions in the world (137).

MetS in SMI patients

The MetS is highly prevalent among treated patients with schizophrenia. Depending on used MetS criteria, gender, ethnicity, country, age groups and AP treatment, percentages vary considerably (between 19.4% and 68%) (155-167). However, there is little debate that people with schizophrenia exhibit a higher MetS prevalence than their peers in the general population across the world (168). MetS rates in patients with bipolar disorder and schizoaffective disorder have been reported to be 22-30% (143,169,170) and 42% (171), respectively.

Table 5 summarizes the potential of various AP medication to cause or exacerbate the metabolic syndrome. Nevertheless, lifestyle and behavioral patterns (smoking, physical inactivity, dietary habits) also play important roles in the prevalence of the MetS in SMI populations (118,168,176).

Disparities in health care

The proportion of SMI patients not receiving tests for assessing metabolic risk factors, even for factors relatively simple and easy to measure, such as obesity and blood pressure, is high (141,177-181). At present, neither psychiatrists nor primary care physicians carefully screen or monitor patients receiving AP medication for metabolic risk factors (173). Even after FDA (Food and Drug Administration) and ADA (American Diabetes Association)/APA (American Psychiatric Association) recommendations for novel AP, the frequency of baseline glucose and lipid testing showed little change. Several large-scale pharmacoepidemiologic studies of individuals initiating a novel AP (with non-psychiatric large control groups) reported low mean baseline metabolic testing rates, varying between 8% and less than 30% (181-183) and follow-up assessments done in only 8.8% of patients. Likewise, most children starting treatment with novel AP do not receive recommended glucose and lipid screening. In a related study in children receiving AP treatment, similarly low metabolic monitoring rates were found (184). The MetS remains, thus, widely underdiagnosed and undertreated among patients with SMI.

Diabetes mellitus

Three to four percent of the world's population have DM, which leads to a markedly increased risk of blindness, renal failure, amputation and cardiovascular disease, and reduces life expectancy by 10 or more years. Currently, 70% of people with DM live in developing countries, and while DM is increasing across the world, its greatest increase will be in these countries. By 2030 more than 80% of people with DM will live in developing countries (195).

There are well-defined biological and behavioral risk factors for type 2 DM (195). The most important of these are overweight and obesity (RR: 4.10-17.5)(196), particularly abdominal obesity, and physical inactivity (RR: 1.12-2.18) (196-205). Other behavioral risk factors include certain dietary patterns (over and above any effect on obesity), such as diets low in whole grains and other sources of fibre, as well as smoking (206).

Identifying people at high risk of DM is important because it has been demonstrated that intensive interventions in this group can reduce the incidence of DM. In individuals at high risk, a combination of moderate weight loss, increased physical activity and dietary advice can lead to a 60% reduction in DM incidence (207,208).

DM in SMI patients

Evidence suggests that the prevalence of DM in people with schizophrenia as well as in people with bipolar disorder and schizoaffective disorder is 2-3 fold higher compared with the general population (103,209-216). The risk of DM in people with depression or depressive symptoms is 1.2-2.6 times higher compared to people without depression (217-225).

The reason for the increased risk of DM in SMI patients is multifactorial and includes genetic and lifestyle factors as well as disease and treatment specific effects. An increase in well-established DM risk factors in these patients partially accounts for much of the increased risk (16,226). However, additional factors (disease, treatment) are important as well, and research suggests that, compared to the general population, the prevalence of DM in schizophrenia patients is 4 to 5 times higher in different age groups (15-25: 2% vs. 0.4%; 25-35: 3.2% vs. 0.9%; 35-45: 6.1% vs. 1.1%; 45-55: 12.7% vs. 2.4%; 44-65: 25% vs. 5.8%) (227).

Table 4 Working definitions of the MetS (see 57,185-194)

Criteria	WHO (1998,1999)	EGIR (1999)	NCEP ATP III (2001,2004)	AACE/ACE (2003)	IDF (2005)	IDF & AHA/NHLBI (2009)
Required factor	IGT, IFG or DM type 2, and/or insulin resistance	Insulin resistance or hyperinsulinemia	None	At least one of the specified risk factors (e.g., obesity, sedentary lifestyle, age>40)	Central obesity	None
	plus any 2 or more of the following	**plus any 2 of the following**	**but any 3 or more of the following**	**plus 2 or more of the following**	**plus any 2 of the following**	**but any 3 or more of the following**
Additional factors						
Obesity	Waist-to-hip ratio >0.90 (men) Waist-to-hip ratio >0.85 (women) and/or BMI>30 kg/m^2	WC≥94 cm (men) WC≥80 cm (women)	WC≥102 cm (men) WC≥88 cm (women)	BMI>25 kg/m^2 or WC>102 cm (men) WC>89 cm (women) (10-15% lower for non-Caucasians)		Elevated WC and country-specific definitions as defined by the IDF and AHA/NHLBI until more data are available
Triglycerides	≥150 mg/dL (≥1.7 mmol/L) **and/or**	>177 mg/dL (>2.0 mmol/L)	≥150 mg/dL (≥1.7 mmol/L) or on elevated triglycerides Rx	>150 mg/dL	≥150 mg/dL (≥1.7 mmol/L) or on lipid abnormality Rx	≥150 mg/dL (≥1.7 mmol/L) (Rx for elevated triglycerides is an alternate indicator)
HDL - cholesterol	<35 mg/dL (<0.9 mmol/L) (men) <39 mg/dL (<1.0 mmol/L) (women)	<40 mg/dL (<1.0 mmol/L) (men and women) or on dyslipidemia Rx	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on reduced HDL-cholesterol Rx	<40 mg/dL (men) <50 mg/dL (women)	< 40 mg/dL (<1.03 mmol/L) (men) <50 mg/dL (<1.29 mmol/L) (women) or on lipid abnormality Rx	<40 mg/dL (<1.0 mmol/L)(men) <50 mg/dL (<1.3 mmol/L)(women) (Rx for reduced HDL-cholesterol is an alternate indicator)
Blood pressure	≥160/90 mm Hg (later modified as ≥140/90 mm Hg)	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg or on hypertension Rx	>130/85 mm Hg	≥130/85 mm Hg or on antihypertensive Rx	≥130/85 mm Hg (antihypertensive Rx in a patient with a history of hypertension is an alternate indicator)
Glucose	IGT, IGF (≥110 mg/dL) (≥6.1 mmol/L), or DM type 2	IGT or IFG (≥110 mg/dL) (≥6.1 mmol/L) (but not DM)	≥110 mg/dL (≥6.1 mmol/L) (includes DM) (later modified as ≥100 mg/dL) (≥5.6 mmol/L) or on elevated glucose Rx	110-125 mg/dl	≥100 mg/dL (≥5.6 mmol/L) or previously diagnosed type 2 DM	≥100 mg/dL (≥5.6 mmol/L) (Rx of elevated glucose is an alternate indicator)
Other	Microalbuminuria (urinary albumin excretion rate ≥20 μg/min or albumin: creatinine ratio ≥20 mg/g) (later modified as ≥30 mg/g)					

WHO: World Health Organization; EGIR: European Group for the Study of Insulin Resistance; NCEP ATP III: National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); AACE/ACE: American Association of Clinical Endocrinologists/American College of Endocrinology; IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; DM: diabetes mellitus; BMI: body mass index; WC: waist circumference; Rx: treatment; HDL: high-density lipoprotein.

DM and psychotropic medications

Atypical AP seem to have a stronger diabetogenic risk than conventional AP (96,228,229), the risk being 1.3 fold higher in people with schizophrenia taking atypical AP compared with those receiving conventional AP (230). However, the risk of DM-related adverse events differs between atypical AP. Of the atypical AP, specifically olanzapine (231-234) and clozapine (232,234,235) and, to a lesser extent, quetiapine (236) and risperidone (237), are associated with an increased risk of DM (80) in people who have schizophrenia or bipolar disorder (238,239). A recent large-scale pharmacoepidemiologic study (including 345,937 patients who purchased antipsychotics and 1,426,488 unexposed individuals)

Table 5 Approximate relative likelihood of metabolic disturbances with AP medication (172-175)

Medication	MetS
Chlorpromazine	High (?, limited data)
Clozapine	High
Olanzapine	High
Quetiapine	Moderate
Amisulpride	Mild
Iloperidone	Mild (?, limited data)
Risperidone	Mild
Sertindole	Mild
Asenapine	Low (?, limited data)
Aripiprazole	Low
Haloperidol	Low
Lurasidone	Low (?, limited data)
Perphenazine	Low
Ziprasidone	Low

found low to moderate, but significantly increased rates of incident DM compared with the general population for clozapine (RR=1.45), olanzapine (RR=1.29) and risperidone (RR=1.23). Rates increased two or more times with ziprasidone and sertindole. Aripiprazole, amisulpride and quetiapine did not have a significantly increased rate (240).

In the only study to date in first-episode patients, DM development was promoted in patients with schizophrenia by initial treatment with olanzapine (hazard ratio, HR=1.41) and mid-potency conventional AP (HR=1.60), as well as by current treatment with low-potency conventional AP (odds ratio, OR=1.52), olanzapine (OR= 1.44) and clozapine (OR=1.67). Current aripiprazole treatment reduced DM risk (OR= 0.51) (241). An analysis of the FDA's DM-related adverse events database (ranging from new-onset hyperglycemia to life-threatening ketoacidosis), found the following adjusted reporting ratios for DM relative to all drugs and events: olanzapine 9.6 (9.2-10.0); risperidone 3.8 (3.5-4.1); quetiapine 3.5 (3.2-3.9); clozapine 3.1 (2.9-3.3); ziprasidone 2.4 (2.0-2.9); aripiprazole 2.4 (1.9-2.9); haloperidol 2.0 (1.7-2.3) (242). However, a systematic review of 22 prospective, randomized, controlled trials found no difference in the incidence of glycaemic abnormalities between placebo cohorts and AP medication cohorts, as well as no significant difference between any of the AP medications studied in terms of their association with glycaemic abnormalities (243). Although the latter analysis was restricted to mostly short-term trials, this inconsistency of findings suggests that medication effects interact with patient, illness, cohort and study-specific factors.

AD may also increase the risk of DM, probably partly due to side effects such as sedation, increased appetite, and weight gain (244-248). However, although increasing, specific data on the risk of DM associated with the use of AD are sparse. Given the heterogeneity and small sample sizes of the few currently available studies, it is unclear whether or not specific AD themselves may increase the risk of DM. Nevertheless, it seems that an increased risk of DM is associated with the concurrent use of tricyclic AD and serotonin reuptake inhibitors (SSRIs) (OR=1.89) (249), the long-term use of both tricyclic AD (incidence rate ratio, IRR=1.77) and SSRIs (IRR=2.06) in at least moderate daily doses (250), as well as the use of AD medication in high-risk patients (251).

Furthermore, although understudied, certain mood stabilizers, especially valproate, have been associated with an elevated risk for the development of insulin resistance (252,253), conferring a risk for DM, which is possibly related to weight gain (254), and/or fatty liver infiltration (255), but also to valproate itself (256).

Disparities in health care

There is evidence that diabetes patients with mental health conditions are less likely to receive standard levels of diabetes care (35,257,258). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, non-treatment rate for DM was 45.3% (35). One study (n=76,799), examining the impact of mental illness on DM management, found the unadjusted OR to be 1.24 (1.22-1.27) for no hemoglobin A(1c) testing, 1.25 (1.23-1.28) for no low-density lipoprotein cholesterol testing, 1.05 (1.03-1.07) for no eye examination, 1.32 (1.30-1.35) for poor glycemic control, and 1.17 (1.15-1.20) for poor lipaemic control (257). Despite clear guidance and a high prevalence of undiagnosed DM, screening rates for metabolic abnormalities in people with SMI remain low, which may lead to prolonged periods of poor glycaemic control (259-263). Delayed diagnosis results in prolonged exposure to raised blood glucose levels, which can, among other things, cause visual impairment and blindness, damage to kidneys with the potential consequence of renal failure, and nerve damage (264).

Diabetic ketoacidosis

Although diabetic ketoacidosis (DKA), a potentially fatal condition related to infection, trauma, myocardial infarction or stroke (265), occurs most often in patients with type 1 DM, it may be the first obvious manifestation of type 2 DM. Symptoms include: increased thirst and urination, nausea and vomiting, abdominal pain, poor appetite, unintended weight loss, lethargy, confusion and coma.

The incidence of DKA is nearly (266) or more (267) than 10-fold greater in those with schizophrenia compared to the general population. Cases of DKA have been reported with the atypical AP clozapine (235,268), olanzapine (233,269), quetiapine (236), risperidone (237), aripiprazole (270-272) and ziprasidone (242). However, not all atypical AP appear to have the same propensity to cause this complication (273). The incidence of DKA for each atypical AP over a 7-year period was as follows: clozapine, 2.2%; olanzapine, 0.8%; and risperidone, 0.2% (267). However, higher incidence rates for clozapine and olanzapine can be due to reporting and detection biases (more DKA cases may be re-

ported for these agents since doctors in general are more careful about clozapine and olanzapine and therefore detect and report such cases with these agents more frequently). Within the class of conventional AP, cases of DKA have been reported with chlorpromazine (274,275), but no such cases have been reported for other conventional AP. The mortality of reported cases of DKA varies between 15.4% and 48% (233,235-237), which is up to ten times higher than the 4% rate in the general population (276).

Cardiovascular diseases

The term cardiovascular diseases (CVD) refers to any disease that affects the cardiovascular system. Coronary heart disease and cerebrovascular disease are the principal components of CVD and make the largest contribution to its global burden (277,278). CVD accounts for 17.1 million or 29% of total worldwide deaths (279). While there are downward trends in CVD mortality in most developed countries due to successful secondary prevention, the mortality rates in developing countries are rising (280). A staggering 82% of worldwide CVD deaths take place in developing countries (279). Global trade and food market globalization have led to a transition toward a diet that is energy dense and nutrient poor. The resultant increases in obesity are accompanied by physical inactivity. In addition, tobacco consumption is increasing at alarming rates in developing countries (281). Finally, people in developing countries have less access to effective and equitable health care services which respond to their needs (279).

The conventional risk factors for CVD are smoking, obesity, hypertension, raised blood cholesterol and DM. Many other factors increase the risk of CVD, including unhealthy diet, physical inactivity and low socioeconomic status (282, 283). Table 6 shows the summary prevalence of CVD risk factors in developed and developing countries, based on the World Health Organization (WHO) comparative risk factor survey data. The risk of late detection of CVD risk factors and consequent worse health outcomes is higher among people from low socioeconomic groups due to poor access to health care. This gradient exists in both rich and poor countries (284,285).

CVD in SMI patients

The preponderance of evidence suggests that patients with major depression, bipolar disorder and schizophrenia are at significantly higher risk for cardiovascular morbidity and mortality than are their counterparts in the general population (2,9,11,23,28,29,287-295). Moreover, in SMI patients, CVD is the commonest cause of death (2,25,33, 218,289,290,296-300).

The prevalence of CVD in people with schizophrenia and bipolar disorder is approximately 2- to 3-fold increased, particularly in younger individuals (5,16,25,29,297,299,301,302). A recent review of all published larger (>100 patients) studies between 1959 and 2007 found the mortality risk for CVD to be 35% to 250% higher among persons with bipolar spectrum disorders compared to the general population (6). People with depression have a 50% greater risk of CVD (22). Besides the fact that depression is an independent risk factor for aggravating morbidity and mortality in coronary heart disease (303), the main factor mediating the link between depression and coronary events seems to be lack of physical activity (304).

The aetiology of this excess CVD is multifactorial and likely includes genetic and lifestyle factors as well as disease specific and treatment effects (16). People with SMI have significantly higher rates of several of the modifiable risk factors compared with controls. They are more likely to be overweight or obese, to have DM, hypertension, or dyslipidemia and to smoke (25,95,229,178,305-308). The excess CVD mortality associated with schizophrenia and bipolar disorder is widely attributed to the 1-5 fold RR of the modifiable CVD risk factors in this group of patients compared with the general population (Table 7).

Coronary heart disease in SMI patients

Coronary heart disease refers to the failure of coronary

Table 6 Economic development and risk factors for cardiovascular disease in WHO subregions (see 280,286)

	Poorest countries in Africa, America, South-East Asia, Middle East	Better-off countries in America, Europe, South-East Asia, Middle East, Western Pacific	Developed countries of Europe, North America, Western Pacific
Mean body mass index	19.9 - 26.0	22.9 - 26.0	23.4 - 26.9
Physical inactivity (% with no physical activity)	11 - 23	15 - 24	17 - 20
Low fruit and vegetable intake: average intake per day (grams)	240 - 360	190 - 350	290 - 450
Blood pressure (mean systolic pressure mmHg)	125 - 133	124 - 133	127 - 138
Mean cholesterol (mmol/L)	4.8 - 5.1	4.6 - 5.8	5.1 - 6.0

Table 7 Estimated prevalence and relative risk (RR) of modifiable risk factors for cardiovascular disease in schizophrenia and bipolar disorder compared to the general population (see 4,305,309)

Modifiable risk factors	Schizophrenia		Bipolar disorder	
	Prevalence (%)	RR	Prevalence (%)	RR
Obesity	45-55	1.5-2	21-49	1-2
Smoking	50-80	2-3	54-68	2-3
Diabetes mellitus	10-15	2-3	8-17	1.5-3
Hypertension	19-58	2-3	35-61	2-3
Dyslipidemia	25-69	≤5	23-38	≤3
Metabolic syndrome	37-63	2-3	30-49	2-3

circulation to supply adequate circulation to cardiac muscle and surrounding tissue, a phenomenon that can result in a myocardial infarction. During the 21st century, coronary heart disease will remain the leading cause of death in developed countries, will become the leading cause of death in developing countries, and therefore, will emerge as the leading cause of death in the world (25). The risk of coronary heart disease seems to be 2-3.6-fold higher in patients with schizophrenia (25,299). One large study found that the ten-year coronary heart disease risk was significantly elevated in male (9.4% vs. 7.0%) and female (6.3% vs. 4.2%) patients who have schizophrenia compared to controls (p=0.0001) (101). People with bipolar disorder have a 2.1 fold higher risk (299). The RR of myocardial infarction in people with major affective disorder was found to be 1.7 to 4.5 (310-313). Depression is an even stronger risk factor for cardiac events in patients with established coronary heart disease: prospective studies have shown that depression increases the risk of death or nonfatal cardiac events approximately 2.5-fold in patients with coronary heart disease (314).

Cerebrovascular disease in SMI patients

Cerebrovascular disease is a group of brain dysfunctions related to disease of the blood vessels supplying the brain, and can result in a cerebrovascular accident or stroke. The risk of cerebrovascular accident seems to be 1.5 to 2.9 fold higher in patients with schizophrenia (40,41,299,302,315, 316) and 2.1 to 3.3 fold higher in patients with bipolar disorder (299,317). The RR of developing cerebrovascular accident for patients with major affective disorder was found to be 1.22 to 2.6 (318,319). Obesity, DM, CVD as well as depressive symptoms are recognized as risk factors for cerebrovascular accident (317,320).

CVD and psychotropics

In addition to weight gain and obesity related mechanisms, there appears to be a direct effect of AP that contributes to the worsening of CVD risk (96,97,121,321). A recent publication demonstrated that atypical AP D_2 antagonism could have a direct effect on the development of insulin resistance (322). Evidence was found that higher AP doses predicted greater risk of mortality from coronary heart disease and cerebrovascular accident (299).

Overall, SSRIs appear safe in cardiac populations, with few cardiac side effects (287,311), while studies have found an increased risk of adverse cardiac events in patients using tricyclic AD (311,323,324). Tricyclic AD commonly increase heart rate by over 10%, induce orthostatic hypotension, slow cardiac conduction, and increase the risk of arrhythmias. Although it can have some cardiac conduction effects, in general, lithium can be safely used in cardiac patients (287).

Sudden cardiac death and psychotropics

Patients with schizophrenia have been reported to be three times as likely to experience sudden cardiac death as individuals from the general population (325,326). In patients with AP monotherapy, a similar dose-related increased risk of sudden cardiac death was found for both conventional and atypical AP, with adjusted RRs of 1.31 vs. 1.59 (low dose, chlorpromazine equivalents <100mg), 2.01 vs. 2.13 (moderate dose, chlorpromazine equivalents 100-299mg) and 2.42 vs. 2.86 (high dose, chlorpromazine equivalents ≥300mg), respectively (327). In large epidemiological studies, a dose dependent increased risk of sudden cardiac death has been identified in current users of tricyclic AD (328).

There is a consensus that QTc values >500 msec, or an absolute increase of 60 msec compared with drug-free baseline, puts a patient at significant risk of torsade de pointes, ventricular fibrillation and sudden cardiac death (94,329, 330). Most AP and some AD may be associated with QTc prolongation (331). Patients using AP have higher rates of cardiac arrest or ventricular arrhythmias than controls, with ratios ranging from 1.7 to 5.3 (332-335). AP associated with a greater risk of QTc prolongation include pimozide, thioridazine and mesoridazine among the conventional AP (94,335,336) and sertindole and ziprasidone among the atypical AP (94,337). However, the largest randomized study to date (n=18,154) did not find a statistically significant difference in the risk of sudden cardiac death between ziprasidone and olanzapine treated patients with schizophrenia

(338,339). Similarly, another large randomized study (n=9,858) observed no significant differences between sertindole and risperidone recipients in cardiac events, including arrhythmias, requiring hospitalization. However, cardiac mortality in general was higher with sertindole (337). These large randomized studies, which focused on a low incidence serious side effect, suffer from the problem that they did not enrich samples for cardiac risk, so that they lack power and, possibly, generalizability. Cases of torsade de pointes have been reported with thioridazine, haloperidol, ziprasidone, olanzapine, and tricyclic AD. Although SSRIs have been associated with QTc prolongation, no cases of torsade de pointes have been reported with the use of these agents. There are no reported cases of lithium-induced torsade de pointes (328).

Disparities in health care

SMI patients have the highest CVD mortality but the least chance of receiving many specialized interventions or circulatory medications. Evidence suggests that people with schizophrenia are not being adequately screened and treated for dyslipidemia (up to 88% untreated) and hypertension (up to 62% untreated) (35,306,340-343). The care of these patients shows a significant deficit in the monitoring of cholesterol values and the prescription of statins (25,35,40,344). They also have low rates of surgical interventions, such as stenting and coronary artery bypass grafting (40,41,291, 297,345). A poorer quality of medical care contributes to excess mortality in older people with mental disorders after heart failure (346). Another important barrier is the lack of seeking medical care by SMI patients themselves, even during acute cardiovascular syndromes (25).

Viral diseases

Patients with SMI are at increased risk for a variety of chronic viral infections, of which the most serious are the diseases associated with human immunodeficiency virus (HIV) and hepatitis C virus.

HIV positivity

The prevalence of HIV positivity in people with SMI is generally higher than in the general population, but varies substantially (1.3-23.9%) (347-370). The high frequency of substance abuse, sexual risk behaviors (e.g., sex without a condom, trading sex for money and drugs), and a reduced knowledge about HIV-related issues contribute to this high HIV prevalence (364,371-376). Therefore, it is important that patients with SMI are tested for HIV (377). However, studies investigating HIV testing rates among individuals with a SMI indicate that fewer than half of these patients (percentages ranging from 17% to 47%) have been tested in the past year (378-394).

Since many patients with SMI are exposed to atypical AP, which have been associated with metabolic abnormalities, and since patients infected with HIV and on highly active antiretroviral therapy may also develop metabolic abnormalities, this group of patients is at particularly high risk for developing MetS and ultimately CVD (395).

Hepatitis

Across different continents, markedly elevated rates of hepatitis virus infection have been reported in persons with SMI compared to the general population (364,396-403). The largest study to date found prevalence rates of hepatitis B virus (23.4%) and hepatitis C virus (19.6%) in SMI patients to be approximately 5 and 11 times the overall estimated population rates for these infections. Overall, an estimated 20-25% of persons with SMI are infected with hepatitis C virus (360,404-407).

The most common transmission routes for persons with SMI are drug-use behaviors and sexual behaviors related to drug use (404-406). Therefore, especially patients with SMI and substance use disorders (including dependency) should have routine screening and treatment for hepatitis C virus infection to prevent associated morbidity and mortality (400,407,408). Interventions exist that are specifically designed to facilitate integrated infectious disease programming in mental health settings for people with SMI and to overcome provider- and consumer-level barriers at a modest and specified cost (409). A recent study showed that the assignment of people with SMI to the "STIRR" (Screening, Testing, Immunization, Risk reduction counseling, medical treatment Referral) intervention had high levels (over 80%) of participation and acceptance of core services (testing for hepatitis C, immunization against hepatitis, knowledge about hepatitis) (407).

Respiratory tract diseases

Up until 50 years ago, respiratory diseases, such as pneumonia and tuberculosis, accounted for the majority of deaths amongst people with SMI who lived in institutions (2). Today, respiratory diseases are still more prevalent in people with SMI (8,410-417).

Tuberculosis

Studies consistently show a higher incidence of tuberculosis among patients with schizophrenia compared with the general population (422-426). In some countries, tuberculosis still occurs so frequently that mental hospitals have special wards for people with both tuberculosis and schizophrenia (15). If untreated, up to 65% of people with active tuberculosis will die of the disease. However, chemotherapy is

effective and the vast majority of people with drug-susceptible forms of tuberculosis are cured if properly treated (427).

Pneumonia

A nationwide, population-based study found schizophrenia to be associated with a 1.37 times greater risk of acute respiratory failure and a 1.34-fold greater risk of mechanical ventilation (428). Filik et al (414) found that people with SMI have a higher prevalence of angina and respiratory symptoms and impaired lung function when compared with the general population. Significant barriers to prompt and appropriate medical care for pneumonia still persist for patients who have schizophrenia (428).

Chronic obstructive pulmonary disease

The prevalence of chronic obstructive pulmonary disease, i.e. chronic bronchitis and emphysema, is significantly higher among those with SMI than comparison subjects (429-433). In a study of 200 outpatients in the US, 15% of those with schizophrenia and 25% of those with bipolar disorder had chronic bronchitis, and 16% of people with schizophrenia and 19% of people with bipolar disorder had asthma. These rates were significantly higher than those of the matched controls from the general population. The authors also found that, even when smoking was controlled for as a confounder, both people with schizophrenia and bipolar disorder were more likely to suffer from emphysema (430). Although the association remains unclear, a higher incidence of chronic obstructive pulmonary disease in the past two decades has been associated with the side effects of phenothiazine conventional AP (434).

Cancer

Cancer risk in SMI patients

Given that obesity and unhealthy lifestyle behaviors are known risk factors for a number of cancer types (149,435-438), one would expect to see higher cancer rates in patients with SMI. However, studies exploring the relationship between SMI and all cancer types together have shown conflicting results (30,439). Some studies have demonstrated a decreased cancer risk in schizophrenia (440-448). On the other hand, other studies found an increased (9,21,28,449-451) or no different (292,419,452,453) overall risk of cancer in patients with schizophrenia compared to the general population. In the population of bipolar spectrum disorders, deaths from cancer are not higher (8,288,416,417,454-456) or only slightly elevated (417,418,456) compared with the general population, despite the higher number of risk factors for cancer (such as obesity) in this population. This discrepancy of results may be a result of various confounding factors that could artificially lower the rates of diagnosed and reported cancer in SMI populations. For example, people with SMI are less likely to receive routine cancer screening (457-460). Furthermore, patients with SMI have a shorter life expectancy, so they may die from cardiovascular reasons before reaching the expected age of death from cancer (30). Another tentative hypothesis is that AP have antitumour properties (448) or that the disease itself has a possible protective effect, including a tumor suppressor gene or enhanced natural killer cell activity (461,462). Nevertheless, a problem with most of the existing data base analyses is that etiologically disparate cancer types were lumped together. An important analysis of cause-specific excess deaths associated with underweight, overweight, and obesity in the general population found that obesity was associated with an increased mortality from cancers considered obesity-related but not with mortality from other cancers (463).

Cancer risk and psychotropics

Because of the possible, but still controversial, role of prolactin in breast cancer, the assumption has been made that exposure to prolactin-raising dopamine antagonists could result in breast cancer. The current study database on AP and breast cancer risk is very limited (464). The majority of the studies in which the risk of breast cancer has been investigated in patients treated with conventional AP (465-468) did not uncover an increased risk of breast cancer, an exception being the cohort study by Wang et al (469).

Musculoskeletal diseases

Osteoporosis in SMI patients

Schizophrenia, schizoaffective states, major depression and bipolar disorder are known to be associated with low bone mineral density (BMD) (470). In comparison with the general population, untreated patients with schizophrenia appear to have an increased risk of developing osteoporosis. On the one hand, this is because of the disease itself, on the other hand, because of risk factors related to their lifestyle (e.g., smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, polydipsia) (470-476). Although the association between depression and loss of BMD has been reported inconsistently, most studies have found low BMD in patients with depressive symptoms or major depressive disorder (477-483). Two recent meta-analyses confirmed that depression is associated with low BMD and should be considered as an important risk factor for osteoporosis, although this increased risk may be mediated by AD (484,485). However, physiologic changes and the adoption of poor health behaviors are two prominent ways in which depression is hypothesized to directly affect BMD (486).

Osteoporosis and psychotropics

Although it has been suggested that raised prolactin levels provoked by AP medication can lead to an increased risk of osteoporosis in patients with schizophrenia (471, 487), clinical data implicating AP-induced hyperprolactinemia as a possible major risk factor for bone loss are limited and contradictory (488,489). Some studies (490-493) found a relationship between the use of prolactin-raising medication and low BMD in patients with chronic schizophrenia, while others (474,489,494-498) failed to find a relationship between prolactin, AP and osteoporosis. Nevertheless, the available data seem to indicate that hyperprolactinemia with associated hypogonadism may be a risk factor (488), leading to bone mineral loss in women as well as men (499).

The majority of studies directly examining the relationship between AD and BMD in humans report that the use of these medications is associated with low BMD (486). However, this finding seems to be restricted to the SSRI class of AD (500-502).

Data describing the epidemiology of osteoporotic fracture and psychotropics in patients with SMI are limited. Regarding AP, conflicting results exist (503). Some of these studies have reported higher prevalence rates of osteoporotic fractures in patients with chronic schizophrenia, entirely or partly independent of the use of AP (504,505). Other studies (506-510) have found significant increases (OR=1.2-2.6) in the risk of fractures associated with AP. For AD, a dose-response relationship was observed for fracture risk (504,508). SSRIs seem to be associated with the highest adjusted odds of osteoporotic fractures (OR=1.5) (504,505, 508). A meta-analysis showed a 33% increased risk of fractures with SSRIs compared to non-SSRI AD. The RR of fractures in this meta-analysis was 1.60 for AD and 1.59 for AP (511). Although lithium has a potentially negative impact on bone metabolism (470), it is associated with lower fracture risk (OR=0.6) and, thus, seems to be protective against fractures (504,505).

Urological, male/female genital diseases and pregnancy complications

Sexual dysfunction in SMI patients

Sexual dysfunction in SMI patients has received little attention from clinicians (512,513). This low awareness has a significant negative impact on patients' satisfaction with treatment, adherence, quality of life and partner relationships (450). Although there are relatively few systematic investigations concerning sexual disorders in schizophrenia (514), sexual dysfunction in schizophrenia is, compared to normal controls, estimated to be more frequent (515-519) and to affect 30-80% of women and 45-80% of men (512,515, 520-523). This dysfunction can be secondary to the disease itself and to comorbid physical disorders, or be an adverse event of AP (520,524,525). Sexual dysfunction is also a common symptom of depression (526-530). Up to 70% of patients with depression may have sexual dysfunction (466). Approximately 25% of patients with major depression may experience problems with erection or lubrication (531).

Patients with SMI are likely to engage in high-risk sexual behavior, putting them at risk of sexually transmitted diseases. However, findings suggest that sexual health education for these people tends to produce a reduction in sexual risk behavior (532).

Sexual dysfunction and psychotropics

Psychotropic drugs are associated with sexual dysfunction (514). To date, only few studies (534-547) have directly compared the sexual functioning associated with different atypical AP. These studies suggest that the relative impact of AP on sexual dysfunction can be summarized as: paliperidone = risperidone > haloperidol > olanzapine ≥ ziprasidone > clozapine ≥ quetiapine > aripiprazole (503,520,536). Conventional AP cause less sexual dysfunction than risperidone but more than the other novel AP (520,522).

AD therapy (except for mirtazapine, nefazodone and bupropion) frequently induces or exacerbates sexual dysfunction, which occurs in approximately 50% of patients (548). Although sexual dysfunction has been reported with all classes of AD (549), SSRIs are associated with higher rates (550-552). Published studies suggest that between 30% and 60% of SSRI-treated patients may experience some form of treatment-induced sexual dysfunction (553,554).

Pregnancy complications, SMI and psychotropics

There is an extensive literature reporting an increased occurrence of obstetric complications among women who have schizophrenia (15). During pregnancy, it is important to evaluate the safety of psychotropic drugs. Most women with a SMI cannot stop taking their medication, as this would interfere with their activities of daily living, especially taking care of an infant (555). There is a paucity of information, with a lack of large, well designed, prospective comparative studies during pregnancy. However, no definitive association has been found up to now between the use of AP during pregnancy and an increased risk of birth defects or other adverse outcomes (555,556). Among AD, SSRIs and, possibly, serotonin and noradrenaline reuptake inhibitors (SNRIs) have been associated with preterm labor, respiratory distress, serotonin rebound syndrome, pulmonary hypertension and feeding problems in the neonate (557-559). Furthermore, a number of mood stabilizers have been associated with fetal malformations, including carbamazepine and valproate (560,561). Current evidence seems to suggest that Fallot's tetralogy is not considerably elevated with lithium compared to the rate in the general population (560).

Stomatognathic diseases

Oral health in SMI patients

Dental health has been consistently found to be poor in people with SMI (562-573). A study using an overall dental status index (DMF-T) in chronically hospitalized patients with mental disorders (mostly schizophrenia) found a mean score of 26.74 (out of a possible 32), one of the highest reported in the literature (571). According to another study, only 42% of patients with schizophrenia brush their teeth regularly (at least twice a day) (573). This poor dental health leads to functional difficulties. In one large study (n=4,769), 34.1% of the patients with SMI reported that oral health problems made it difficult for them to eat (572).

Factors which influence oral health include: type, severity, and stage of mental illness; mood, motivation and self-esteem; lack of perception of oral health problems; habits, lifestyle (e.g., smoking), and ability to sustain self-care and dental attendance; socio-economic factors; effects of medication (dry mouth, carbohydrate craving); and attitudes and knowledge of dental health teams concerning mental health problems (569,574).

Oral health and psychotropics

AP, AD and mood stabilizers all cause xerostomia (575). This reduction in salivary flow changes the oral environment and leads to caries, gingivitis and periodontal disease (576).

Disparities in health care

Oral health status is a frequently disregarded health issue among SMI patients (498), with low rates of dental examination within the past 12 months (569,577-579). In one study of a mixed psychiatric population, 15% had not been to a dentist in the last 2 years (579), while in another only 31% of schizophrenia patients had visited a dentist during a three year period (577). In the latter study, non-adherence to annual dental visits was predicted by substance abuse diagnosis, involuntary legal status, living in an institution, admission to a psychiatric facility for a minimum of 30 days, and male gender, whereas clozapine treatment, novel AP treatment, at least monthly outpatient visits, and age > 50 years were associated with a lower risk for inappropriate dental care.

Taken together, these findings confirm the urgent need for an intervention program to improve oral health outcomes among patients with SMI, by facilitating access to dental care and addressing modifiable factors such as smoking and medication side effects (571,572), especially because oral diseases are preventable and social inequity in oral health avoidable (580). Moreover, improving dental health status and care are relevant, as poor dental status is associated with endocarditis and reduces social and work opportunities.

Other physical health conditions in people with SMI

This review is by no means exhaustive. We speculate that perhaps most medical illnesses occur with greater frequency in SMI, which in itself serves as a vulnerability factor (587).

Haematological diseases, which may in themselves be primary problems in patients with SMI, have frequently been described in the literature as potential serious complications of psychotropic medications. AP (e.g., clozapine, haloperidol, olanzapine, phenothiazines, quetiapine, risperidone, ziprasidone), AD (e.g., amitriptyline, clomipramine, imipramine) as well as lithium are associated with blood dyscrasias. Clozapine (approximately 0.8%) and phenothiazines (chlorpromazine approximately 0.13%) are the most common causes of drug-related neutropenia/agranulocytosis. AD are rarely associated with agranulocytosis. With appropriate management, the mortality from drug-induced agranulocytosis in Western countries is 5-10% (before the use of antibiotics this percentage was 80%) (582).

Some physical conditions, although important, are rarely studied, underreported and not systematically assessed. Although a common side effect of AP that can be severe and lead to serious consequences and even death, constipation has been given relatively little attention. The most reported complications of this physical condition are paralytic ileus, faecal impaction, bowel obstruction and intestine/bowel perforations. Constipation has most widely been reported for clozapine, although it can be associated with other AP as well. Prevalence of constipation in randomized controlled trials for different AP is: zotepine 39.6%, clozapine 21.3%, haloperidol 14.6% and risperidone 12% (583). Next to medication effects, lifestyle and diet factors can contribute to the occurrence of constipation in people with SMI (sedentary life, low physical activity, diet low in fibre, limited fluid intake) (584). Clinicians should actively and systematically screen and monitor symptoms and possible complications of constipation (585-588).

CONCLUSIONS

In summary, many physical disorders have been identified that are more prevalent in individuals with SMI. In addition to modifiable lifestyle factors and psychotropic medication side effects, poorer access to and quality of received health care remain addressable problems for patients with SMI. Greater individual and system level attention to these physical disorders that can worsen psychiatric stability, treatment adherence, and life expectancy as well as quality of life will improve outcomes of these generally disadvantaged populations worldwide. The barriers to somatic monitoring and interventions in persons with SMI will be summarized in the second part of this educational module, where monitoring and treatment guidelines as well as recommendations at the system level (state and health care institutions) and individual level (clinicians, patients, family) will be provided.

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Burnout in psychiatrists, general practitioners and surgeons

Burnout is a serious consequence of chronic exposure to work-related stressors. Three key dimensions of this response are emotional exhaustion, feelings of cynicism and detachment, as well as a sense of lack of personal accomplishment and ineffectiveness. According to research reports, 40-60% of general practitioners (1) and 46-93% of emergency physicians suffer from burnout (2). It has been suggested that some health workers are more prone to the burnout syndrome than others. In particular, it has been reported that psychiatrists may be more vulnerable to experiencing burnout than other physicians and surgeons (3).

We compared the level of burnout among 160 physicians (70 general practitioners working in public health centers, and 50 psychiatrists and 40 surgeons employed at university clinics). The assessment was carried out by the Maslach Burnout Inventory.

The total burnout score was moderate in all three examined groups. However, there were significant differences between the groups in the dimensions of burnout. General practitioners had a higher score for emotional exhaustion than the other two groups ($F=5.546$, $df=156$, $p<0.01$). Surgeons had the highest depersonalization ($F=15.314$, $df=156$, $p<0.01$) and the lowest personal accomplishment score ($F=16.079$, $df=156$, $p<0.01$). Psychiatrists had the lowest and surgeons the highest total burnout score.

Physicians with greater daily number of patients were more prone to emotional exhaustion but had higher sense of personal accomplishment. Older physicians with more years of practice and greater daily numbers of patients were less prone to depersonalization. There was no statistically significant gender difference on the total burnout score, but emotional exhaustion was higher in women ($t=-3.460$, $p<0.01$) and lack of personal accomplishment in men ($t=-2.132$, $p<0.05$).

These findings, which in general are in line with previous reports concerning correlates of burnout in the medical profession, do not confirm that psychiatrists are at higher risk for burnout than other physicians. Although the sample size was small and the design cross-sectional, this study may be of interest, because the perception that psychiatry is a particularly distressing medical specialty may contribute to the current decline in recruitment of young doctors into the profession (4-7).

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ERRATUM

It has been brought to our attention that in Table 4 of the paper "Metabolic syndrome in people with schizophrenia: a review", by de Hert et al, published in the February 2009 issue of *World Psychiatry*, there was a factual error: in the study by Saddichha et al, listed in the table, the number of patients was 99 instead of 433, and the prevalence of metabolic syndrome was 18.2% instead of 34.0%.

The 15th World Congress of Psychiatry (Buenos Aires, September 18-22, 2011)

The organization of the World Congress of Psychiatry is proceeding very actively. An outstanding scientific programme is being built up. The 24 Keynote Lectures and the 18 Core Symposia have been finalized. The Lectures are outlined in Table 1. The selection of the Regular Symposia, Workshops, WPA Section and Zonal Symposia, Oral Communications and Posters, among the several thousand submissions received, is ongoing. The development of the scientific programme can be followed by visiting the website wpa-argentina2011.com.ar.

Table 1 15th World Congress of Psychiatry - Keynote Lectures

- Classifications and diagnostic systems in psychiatry: our heritage and our future (*N. Sartorius*)
- Past, present, future of the genetics of mental disorders (*P. McGuffin*)
- Community mental health care: recent developments and new trends (*G. Thornicroft*)
- Supported employment for people with serious mental illnesses (*R.E. Drake*)
- The evidence base for psychodynamic therapy (*P. Fonagy*)
- Cognitive-behavioral psychotherapies: their heritage and future (*K. Shear*)
- Intermediate phenotypes in schizophrenia genetics (*D.R. Weinberger*)
- Neuroimaging in psychosis: our heritage and our future (*P. McGuire*)
- The epidemiology of mental disorders: heritage and future (*R.C. Kessler*)
- Suicide in a changing world (*M. Phillips*)
- Personality disorders: past, present, and future (*A.E. Skodol*)
- Getting to the fundamentals of eating disorders (*J. Treasure*)
- Schizophrenia: the beginning, the change, the future (*W.T. Carpenter Jr.*)
- Clinical approach to bipolar disorder (*E. Vieta*)
- Clinical approach to major depression (*M.E. Thase*)
- Anxiety disorders: an integrative approach (*D.J. Stein*)
- Advances in the understanding and treatment of addictive disorders (*C.P. O'Brien*)
- The indelible lessons of trauma: the propensity to remember and forget (*A.C. McFarlane*)
- Brain plasticity in healthy, hyperactive and psychotic children (*J. Rapoport*)
- The heritage and future of women's mental health (*D. Stewart*)
- Psychiatry and general medicine: from theory to practice (*T.N. Wise*)
- Successful cognitive and emotional aging (*D. Jeste*)
- Culture and mental health: realities and promises (*R.D. Alarcón*)
- Ethics and human rights in psychiatry: an axiographic framework (*F. Lolas*)

The official language of the Congress will be English. Simultaneous translations into Spanish and Portuguese will be available for Keynote Lectures, Core Symposia and selected Regular Symposia. There will be a special track in the scientific programme with Symposia and Oral Communication Sessions in Spanish or Portuguese.

An extremely attractive programme of tours for Congress participants and accompanying persons has been organized. Details can be found on the website of the Congress.

This is going to be a memorable event. Psychiatrists from all countries of the world are cordially invited to attend.

WPA papers and documents 2009-2010

Several papers and documents have been produced by the WPA in 2009 and 2010, as part of the implementation of the Action Plan approved by the General Assembly (1-3).

Four guidances have been developed by international task forces. Three of them have already appeared in *World Psychiatry* and the fourth is in publication. They deal with steps, obstacles and mistakes to avoid in the implementation of community mental health care (4), how to combat stigmatization of psychiatry and psychiatrists (5), mental health and mental health care in migrants (6), and protection and promotion of mental health in children of persons with severe mental disorders. Translations of these guidances in several languages are already available on the WPA website (www.wpanet.org). Further translations are forthcoming.

Three books have been produced within the WPA programme on depression in persons with physical diseases. They deal with depression and diabetes (7), depression and heart disease (8), and depression and cancer (9). Three corresponding sets of slides are available in several languages (fifteen in the case of the set on depression and diabetes) on the WPA website.

Two surveys have been conducted with the WPA Member Societies. The results of the survey on reducing the treatment gap for mental disorders have been already published (10). The results of the survey on views and attitudes of psychiatrists in the various countries of the world concerning diagnosis and classification of mental disorders, carried out in collaboration with the World Health Organization as part of the process of development of the ICD-11, will appear in a forthcoming issue of *World Psychiatry*.

A set of recommendations for relationships of psychiatrists and psychiatric associations with the pharmaceutical industry has been produced by the WPA Standing Committee on Ethics and is available on the WPA website.

An educational module on physical illness in patients with severe mental disorders has been developed by an in-

ternational task force (11). The first part of this module appears in this issue of *World Psychiatry* (12). The second part will be published in the next issue. Two sets of slides based on these papers can be found on the WPA website.

A series of recommendations on best practices in working with service users and family carers has been produced by an international task force (13). The final text is available on the WPA website. A paper commenting on these recommendations will be published in a forthcoming issue of *World Psychiatry*.

A template for graduate and postgraduate education in psychiatry and mental health has been produced by an international task force (14). The text is available on the WPA website.

WPA Member Societies and psychiatrists of all countries of the world are welcome to use the above materials for clinical, educational and research purposes and to promote their dissemination and translation in further languages.

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