World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 12, Number 3 *October 2013*

WILEY Blackwell **NEW IMPACT FACTOR: 8.974** ISSN 1723-8617

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Adherence to psychiatric treatments and the public image of psychiatry

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Accepting the idea that a person you love has a psychotic disorder is not easy. You will tend to deny the seriousness of the problem and to believe or hope that those experiences or behaviours will just go away, that this is only an existential crisis which will clear up spontaneously.

Accepting the idea that your loved one has to take an antipsychotic medication which is going to interfere with his mental processes and may have significant physical side effects is also not easy. You may prefer a less invasive treatment such as a talk therapy, or hope that a psychosocial approach providing friendship skills, job counseling and a supportive environment be sufficient. These sentiments may re-emerge periodically as the pharmacotherapy is ongoing.

Nowadays, consulting the Internet will be a common coping strategy under these circumstances. You will try to explore what scientists, or people who have faced the same situation, think about psychiatric diagnoses and pharmacological treatments.

Well, if you are a close relative or a friend of a person with a psychotic disorder who has been prescribed an antipsychotic medication, and you are navigating the Internet during these days, you will have a shocking experience. You will read on prominent websites that "psychiatric diagnosing is a kind of spiritual profiling that can destroy lives and frequently does" (1); that "psychiatry is a pseudoscience, unworthy of inclusion in the medical kingdom" (2); that "psychiatric drugs are toxins to the brain; they work by disabling the brain" (1); and that "psychiatric drugs increase the chronicity of major mental disorders over the long term" (3). You will read that "the way psychiatry is now practiced" is marked by "the frenzy of diagnosis, the overuse of drugs with sometimes devastating side effects, and widespread conflicts of interest" (4). You will learn that psychiatric diagnoses, contrary to those made by the other medical specialties, are not based on biological tests, being therefore invalid (e.g., 5), and that psychotropic drugs are not only useless, but "worse than useless": their prescription explains why the incidence of mental disorders is continuously increasing worldwide (6).

One could argue that all this is not surprising, that we can find on the Internet all kinds of rubbish, and that psychiatry has always been under attack. But that appraisal would not be correct. In more than 30 years of work at the international level, I have never seen such a massive campaign in so many countries against the validity of psychiatric diagnoses and the efficacy of psychiatric treatments, especially medications, and I have never experienced such a weak and ambiguous response by our profession, with so many prominent figures in the field just arguing against each other and actually reinforcing the bad public image of psychiatry. We can be sure that patients and families are watching all this, and that the impact on the adherence to our treatments is going to be sensible.

Of course, everybody is free to say what he wants, even if driven by ideological acrimony or vested interests, and someone may believe in good faith that innovative ways of diagnosing and treating mental disorders will emerge in the medium or long term as an outcome of this quarrel. However, I think it is fair to our present-day patients and their families, as well as to the many thousands of psychiatrists who honestly exercise their profession worldwide, to emphasize some points which may help them swim against this current.

The first point is that the unavailability of laboratory tests does not invalidate psychiatric diagnoses. It is not true that psychiatry is unique in the field of medicine in making diagnoses which are not "based on biological tests". There are, indeed, several non-psychiatric conditions (migraine and multiple sclerosis being good examples) which are diagnosed today without specific laboratory tests, and many others which have been correctly diagnosed for decades on the basis of their clinical picture before any laboratory test became available (7). Furthermore, most laboratory tests in medicine are "probabilistic, not pathognomonic, markers of disease" (8): they "will helpfully revise diagnostic probabilities, rather than conclusively rule in or rule out a diagnosis" (7), and their results will have to be interpreted using clinical judgment. Moreover, the availability of laboratory tests has not prevented some non-psychiatric diseases which lie on a continuum with normality – such as hypertension and diabetes – to be the subject of controversy as to the appropriate "threshold" for the diagnosis (e.g., 9). In fact, whether blood pressure or glycemic levels are normal or pathological depends on the clinical outcomes they predict, and the relevant evidence may under some circumstances (e.g., during pregnancy for glycemia) be unclear or controversial (e.g., 10). Indeed, "the lack of a gold standard against which to judge different claims around how to define disease" and the "highly subjective decisions" needed to evaluate "what constitutes sufficient distress or risk to warrant a definition of caseness" have been recently identified as

general problems in medicine (see 9). So, assuming that the availability of laboratory tests automatically allows making "yes or no" diagnoses in the other branches of medicine is incorrect, and stating that psychiatric diagnoses are invalid because laboratory tests are not available is misleading.

The second point is that, although the boundaries between most mental disorders and the range of normality remain controversial (as for hypertension and diabetes, those boundaries do not "exist in nature", but are fixed on the basis of clinical utility (11)), there is now a reasonably wide agreement among psychiatrists about the prototypes of major mental disorders. The most significant contribution of the DSM-III has actually been the clear, explicit and precise delineation of those prototypes, which has been largely incorporated in the ICD-10, rather than the provision of thresholds in terms of number and duration of symptoms, whose empirical basis remains limited and which are rarely used in clinical practice. The prototypical forms of major mental disorders are a clinical reality, not a fiction, and patients and families can be confident that well-trained clinicians are able to recognize these forms in ordinary practice. There is indeed a "grey zone" between the prototypical forms of major mental disorders and the range of normality, but the skilled clinician will handle the cases falling in that zone with great caution, usually adopting a stepwise approach in which the first stage is watchful waiting. The characterization of earlier and milder forms of major mental disorders is currently an active research focus (see 12).

The third point is that psychiatric medications are not less effective, when prescribed for their target conditions, than those used by other medical specialties. Actually, according to a recent review of meta-analyses (13), the efficacy of antipsychotics in the acute treatment of schizophrenia, as assessed by the standardized mean difference from placebo, is similar to that of antihypertensives in the treatment of hypertension and of corticosteroids in the treatment of asthma. Even more, the efficacy of long-term antipsychotic treatment in preventing relapses in schizophrenia, as assessed by the same measure, is almost six times higher than the efficacy of angiotensin-converting enzyme (ACE) inhibitors in preventing major cardiovascular events in people with hypertension. One could argue that the effectiveness of psychiatric medications in ordinary clinical practice is lower than their efficacy as emerging from controlled trials, that those medications have significant side effects, and that researchers' financial conflicts of interests may have biased the results of trials, but all these arguments may also apply to medications used by other specialties (while psychiatry is unique among medical disciplines as to the impact of commentators' ideological conflicts of interests on the way the available evidence is presented). Of course, it is always important to emphasize that antipsychotic treatment has to be prescribed within the frame of a valid therapeutic alliance and complemented, whenever possible, by evidence-based psychosocial interventions.

These are some core facts on which, I believe, most psychiatrists could agree, mentioning them in their interactions with patients, families, students, residents and journalists, even if on the same occasion they deliver further messages which may reflect their own theoretical orientation, clinical experience or research interests, and which may be less widely shared by the profession.

We must keep the trunk of the tree, which all of us share, distinct from the branches, which we may share or not. Otherwise, we will have to blame ourselves if in the future the problem of adherence to psychiatric treatments will become even harsher and more widespread than it is today.

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DOI 10.1002/wps.20081

Urbanicity, social adversity and psychosis

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In recent years, there has been increasing interest in research on geographical variation in the incidence of schizophrenia and other psychoses. In this paper, we review the evidence on variation in incidence of schizophrenia and other psychoses in terms of place, as well as the individual- and area-level factors that account for this variation. We further review findings on potential mechanisms that link adverse urban environment and psychosis. There is evidence from earlier and more recent studies that urbanicity is associated with an increased incidence of schizophrenia and non-affective psychosis. In addition, considerable variation in incidence across neighbourhoods has been observed for these disorders. Findings suggest it is unlikely that social drift alone can fully account for geographical variation in incidence. Evidence further suggests that the impact of adverse social contexts – indexed by area-level exposures such as population density, social fragmentation and deprivation – on risk of psychosis is explained (confounding) or modified (interaction) by environmental exposures at the individual level (i.e., cannabis use, social adversity, exclusion and discrimination). On a neurobiological level, several studies suggest a close link between social adversity, isolation and stress on the one hand, and monoamine dysfunction on the other, which resembles findings in schizophrenia patients. However, studies directly assessing correlations between urban stress or discrimination and neurobiological alterations in schizophrenia are lacking to date.

Key words: Urbanicity, social adversity, psychosis, schizophrenia, social fragmentation, isolation, discrimination, stress

(World Psychiatry 2013;12:187–197)

In recent years, interest has been increasing in the role of the social environment in the origins of schizophrenia and other psychotic disorders (1). One area of research that has received particular attention is the association between social risk factors – such as urbanicity, social adversity and exclusion – and psychosis (2-4). Understanding geographical variation in the incidence of psychosis and identifying social factors that account for this variation may provide valuable insights into the etiology of, and treatment for, psychosis (1,5).

In this paper, we review the evidence on: a) variation in the incidence of schizophrenia and other psychoses in terms of place; b) individual- and area-level factors that explain this variation, including social stress and exclusion; and c) potential mechanisms that link adverse urban environment and psychosis.

GEOGRAPHICAL VARIATION IN INCIDENCE

The first studies on geographical variation in the incidence of schizophrenia and other psychoses were conducted in Chicago (6-9) and Bristol (10) since the 1920s.

Faris and Dunham (9), in their pioneering study in Chicago, were the first to report that first admission rates of schizophrenia were highest in the city centre. While rates of schizophrenia decreased as the distance from the centre increased, rates of affective psychosis (i.e., psychotic depression, bipolar disorder with psychotic features) were more evenly distributed across central and peripheral areas (9). Building on this work, other early studies reported a similar pattern in nine other American cities (11).

In the first study outside of the USA, Hare (12) found higher rates of schizophrenia in inner-urban areas of Bristol. In this study, rates also varied within inner-urban areas across neighbourhoods (12). Consistent with Faris and Dunham (9), variation in incidence of affective psychosis and, in addition, depression was limited (12).

Subsequent studies carried out in Nottingham (13,14) and Mannheim (15,16) also reported that rates of schizophrenia, but not affective psychosis, were elevated in inner-urban areas. However, in contrast to Hare (12), they found only limited variation within these areas across neighbourhoods. Notably, there was also evidence of higher rates of depression in inner-urban areas (13-16).

Elevated rates in inner-urban areas

Later studies produced similar findings in a number of countries (i.e., the UK, Denmark, Finland, Germany, Ireland, Scotland, Sweden, and the United States) (17-39). Mortensen et al (28), in a study of Danish registry data, found that urbanicity was associated with a more than 2-fold increased risk of schizophrenia. Similarly, urbanicity has been shown to be associated with a 2- to 3-fold increase in the incidence of non-affective psychosis (22,25). This broadly concurs with findings from most other studies, reporting that degree of urbanicity (indexed by population density) is associated with an approximately 1.5- to 4-fold increase in rates of schizophrenia and other non-affective psychoses (40-43). Consistently, Vassos et al (31) estimated in a recent meta-analysis a pooled effect of 2.37 (95% CI 2.01–2.81) for exposure to urban environment on the incidence of schizophrenia. A similar effect was observed when estimates were extended to all non-affective psychoses (OR 2.38, 95% CI 1.6-3.5).

As in earlier studies, evidence on geographical variation in the incidence of affective psychosis was less consistent.

While Marcelis et al (26) reported significantly higher rates of affective psychosis in those exposed to urban areas, most studies investigating this issue found no evidence to support geographical variation in incidence (21,25,30,36,44). Concerning depression, rates in inner-urban areas have been found to be elevated, though to a lesser degree than for non-affective psychosis (37,45,46).

Variation across neighbourhoods

In line with the earlier study by Hare (10) in Bristol, and in contrast to what was found in Nottingham (13,14) and Mannheim (15,16), later studies investigating the incidence of psychosis at the neighbourhood level reported at least some variation across neighbourhoods within cities (39,47-60). Standardized incidence ratios of schizophrenia (57,59,60), non-affective psychosis (56) and all psychotic disorders (47) have been shown to vary considerably across neighbourhoods. Further, statistically significant random effects of neighbourhoods, indicating geographical variation in the incidence of schizophrenia (57,60) and non-affective psychosis (57), have been found.

However, to date, only three studies have reported on the magnitude of this variation (39,56,59). In these studies, estimates of the proportion of variation in incidence attributable to the neighbourhood level ranged from 4% (39,57) to 12% (4) for schizophrenia and from 2% (39) to 11% (5,56) for non-affective psychosis. These estimates are broadly in line with what has been reported for neighbourhood-level variation in depression (61-66). As in the earlier studies (9,10), later studies did not find evidence in support of variation in the incidence of affective psychosis across neighbourhoods (56).

Several studies in migrant and minority ethnic groups suggest that the risk of schizophrenia and other psychoses is substantially increased in first as well as second generation migrants (43,67,68), and that this risk is especially high in some groups that are potentially exposed to high levels of social exclusion and racist discrimination, e.g., individuals from the Black African and Black Caribbean group (69-73).

While a multitude of individual- as well as area-level factors – including poverty, access to health care, social support, rates of drug use and their respective neurobiological correlates – may contribute to the higher rates of psychosis, cannabis use appears not to explain the higher rates in Black Caribbean migrants (1), and access to health care may be less relevant than institutional exclusion prior to first presentation to mental health services (41,74-76). The finding that lack of social cohesion and support is associated with the higher rates emphasizes the relevance of social exclusion as a stress factor, which in animal experiments has been shown to interact with brain networks implied in the development of psychotic disorders (4,77-81).

Drift or causation?

An important question from the above findings is whether the elevated rates of schizophrenia in urban areas are a cause or a consequence of the disorder or its prodrome. While for a long time the most commonly accepted explanation was that it is selection into urban areas following onset of disorder or its prodrome (drift), rather than exposure to urban environment (causation), that increases risk, early studies were limited in addressing this question (24,41).

A number of studies have since investigated temporality and dose-response gradient, predominantly focusing on the association of urbanicity with schizophrenia. There is good evidence from studies investigating temporality of this association to suggest that the risk of schizophrenia and other non-affective psychosis increases as degree of urbanization at birth increases (17,21,22,28). In contrast, evidence on a dose-response relationship of urban birth with affective psychosis and depression remains limited (21,26,46).

In an attempt to discriminate exposure to urbanicity at birth and time of illness onset, Marcelis et al (27) used Dutch national psychiatric case register data to demonstrate an approximately 2-fold increased incidence of schizophrenia in individuals born in urban areas. However, no increase in incidence was observed in those not exposed at birth but living in an urban environment at the time of illness onset (27). Lewis et al (24) further reported an increased risk of schizophrenia in those brought up in an urban environment. In the only study to date that sought to disentangle the effects of urban birth and upbringing, Pedersen and Mortensen (18) found that it is exposure to urban environment during upbringing rather than urbanicity at birth that increases the risk of schizophrenia later in life. What is more, there was strong evidence of a dose-response relationship between cumulative exposure to urbanicity during upbringing and risk of schizophrenia (18). A dose-response gradient for urbanicity has also been reported for other non-affective psychosis (21,37) and depression without psychotic features (37), though not for affective psychosis (21). These findings, taken together, suggest that it is unlikely that social drift alone can fully account for geographical variation in incidence (41). This raises the question of what it is in the urban environment that places more individuals at risk of non-affective psychotic disorders.

INDIVIDUAL- AND AREA-LEVEL RISK FACTORS

Various environmental factors have been proposed to account for geographical variation in the incidence of schizophrenia and other non-affective psychoses ever since the first evidence has been reported. These can be broadly grouped into environmental exposures of individuals living in inner-urban areas (i.e., individual-level exposures) and

exposure to characteristics of these areas (i.e., area-level exposures) (see Table 1).

Individual-level factors

Based on evidence of an association between exposure to early neurodevelopmental insults and risk of schizophrenia (91), and assuming these insults may be more common in inner-urban areas, their impact on early brain development has been posited to contribute to the higher rates of psychosis in these areas.

For example, building on evidence suggesting that the risk of schizophrenia is increased in offspring exposed to obstetric complications, Harrison et al (22) examined the impact of such complications on the association of urbanicity with schizophrenia and other non-affective psychoses. While these authors did find that obstetric complications were more common in inner-urban areas (22), consistent with Eaton et al (21), no attenuation in the strength of association was observed after adjustment for obstetric complications (22).

Evidence on season of birth, as a proxy for seasonal differences in exposure to infections that may explain the observed increases in incidence in inner-urban areas, remains equivocal. Takei et al (92) reported a significant interaction of urbanicity and season of birth on the multiplicative scale. In this study, the association between urban birth and risk of schizophrenia was stronger in individuals born in winter (92). A similar finding has been reported by Harrison et al (22) for other non-affective psychoses. However, in line with others (17,18,28), these authors found no evidence that season of birth modifies the association between urbanicity and risk of schizophrenia (22,28). Coupled with evidence that, as Pedersen and Mortensen (18) reported, it is urban upbringing rather than birth that increases risk of schizophrenia, these latter findings tentatively suggest that pre- and perinatal exposure to neurodevelopmental insults is likely to be less relevant to the elevated rates of schizophrenia in inner-urban areas.

Another potential explanation of the elevated rates is cannabis use (83). Findings suggest that cannabis use in adolescence is associated with an increased risk of adult psychotic disorder (93,94), and cannabis use has been found to be more common in urban areas (24). Zammit et al (82) reported an attenuation of the association between cannabis use and risk of schizophrenia after adjustment for urban birth (82). In a prospective cohort study, Kuepper et al (83) found evidence of additive interaction between cannabis use and urbanicity in increasing the risk of developing psychotic symptoms: individuals reporting cannabis use and exposed to urban environment were at greater risk than those with either factor alone (83).

Some authors have proposed the physical environment of inner-urban areas as a potential explanatory factor. In a small study by Pedersen et al (84), there was evidence that traffic density is associated with risk of schizophrenia (84). Probing these findings further, Pedersen and Mortensen (35) found no evidence that the association between urbanicity and risk of schizophrenia is modified or confounded by distance from nearest major road. However, this variable was only a very crude proxy for traffic-related exposures such as noise and air pollution. Better measures of exposures in the physical environment are required to elucidate whether these may account for the elevated rates of psychosis in inner-urban areas and to rule out that traffic noise is just a proxy for social adversity and poverty.

Indeed, a number of individual-level markers of social adversity have been suggested to account for the increased incidence of psychosis in urban areas. These include markers of social disadvantage in childhood, such as parental unemployment, poor parental education, growing up in a single-parent household, parent receiving welfare benefits, low parental income, poor housing, and low parental socio-economic status (22,24,39,85). Markers of social disadvantage in adulthood that have been proposed as potential explanatory factors include single or divorced marital status (59), poor education (37,86) and low socio-economic status (87).

While some (limited) attenuation has been reported after adjustment for these factors (37,39,86), in most studies investigating this issue to date, the strength of the association between urbanicity and psychosis remained largely unchanged (22,24,59,87) and statistically significant (22,24,37,39,59,87). In other words, individual-level markers of social adversity in these studies explained only to a limited extent the association between urbanicity and psychosis. However, as for genetic liability (33,95) and cannabis use (83), there is only a limited number of studies investigating whether markers of social adversity interact with urbanicity to increase the risk of psychosis.

One potential research area where urbanicity and social adversity can overlap and interact is the presence of social minorities and migrants in inner cities. Due to relatively low housing prices in certain inner city areas, there is a relatively high proportion of migrants and social minorities living in European and American inner cities, which are often exposed to social exclusion and discrimination, health care services that are unprepared to cater to their needs, and interactions with professionals that fail to take different explanatory models of health and disease into account (96-99). Moreover, minorities and migrants often earn less money than other citizens, suffer from social exclusion at the work place and can be reluctant to report problems with illegal drugs of abuse due to the threat of being deported (100). Unfortunately, studies directly addressing the interaction between social exclusion and discrimination on the one hand and the risk to develop schizophrenia on the other are still lacking to date.

Table 1 Individual- and area-level explanatory factors for geographical variation in incidence of psychosis

Social risk factor	Outcome	Principal finding	Reference
Individual-level factors			
Neurodevelopmental insults			
Obstetric complications	Schizophrenia, non-affective psychosis, affective psychosis	N	Eaton et al (21)
	Schizophrenia, non-affective psychosis	N	Harrison et al (22)
Season of birth	Schizophrenia	I_U	Takei et al (38)
	Schizophrenia	N	Mortensen et al (28)
	Schizophrenia	N	Pedersen et al (17)
	Schizophrenia	N	Pedersen et al (18)
	Schizophrenia	N	Harrison et al (22)
	Non-affective psychosis	I_U	Harrison et al (22)
Cannabis use	Schizophrenia	C	Lewis et al (24)
	Schizophrenia	C	Zammit et al (82)
	Psychotic symptoms	I_U	Kuepper et al (83)
Physical environment			
Traffic density	Schizophrenia	C	Pedersen et al (84)
	Schizophrenia	N	Pedersen and Mortensen (35)
Air pollution	Schizophrenia	C	Pedersen et al (84)
Markers of social disadvantage			
Childhood	Schizophrenia	C	Lewis et al (24)
	Schizophrenia, non-affective psychosis	N	Harrison et al (22)
	Schizophrenia, other psychoses	N	Wicks et al (85)
	Schizophrenia, non-affective psychosis, affective psychosis	C	Zammit et al (39)
Adulthood	Schizophrenia	N	van Os et al (59)
	Psychotic symptoms	N	van Os et al (86)
	Psychotic symptoms	N	Spauwen et al (87)
	Any psychosis	C	Sundquist et al (37)
	Schizophrenia, non-affective psychosis, affective psychosis	C	Zammit et al (39)
Area-level factors			
Social deprivation	Non-affective psychosis	A	Croudace et al (52)
	Schizophrenia	N	Boydell et al (60)
	Schizophrenia	N	Silver et al (88)
	Schizophrenia	A	Allardyce et al (50)
	Schizophrenia	N	Drukker et al (54)
	Schizophrenia, non-affective psychosis	N	Kirkbride et al (56)
	Non-affective psychosis	N	Zammit et al (39)
	Non-affective psychosis	A	Kirkbride et al (67)
Social capital			
Social mobility	Schizophrenia	A	Silver et al (88)
Informal social control	Schizophrenia	N	Drukker et al (54)
Social cohesion/trust	Schizophrenia	N	Drukker et al (54)
	Schizophrenia	A	Kirkbride et al (49)
Social disorganization	Schizophrenia	N	Kirkbride et al (49)

Table 1 Individual- and area-level explanatory factors for geographical variation in incidence of psychosis *(continued)*

Social risk factor	Outcome	Principal finding	Reference
Voter turnout	Schizophrenia, non-affective psychosis	A	Kirkbride et al (56)
	Schizophrenia	A	Lofors and Sundquist (48)
	Non-affective psychosis	N	Kirkbride et al (67)
Social fragmentation	Schizophrenia	A	Allardyce et al (50)
	Non-affective psychosis	A	Zammit et al (39)
	Non-affective psychosis	N	Kirkbride et al (67)
Individual- and area-level factors			
Individual-level ethnicity x area-level ethnic density	Schizophrenia	I_C	Boydell et al (60)
	Schizophrenia	I_C	Kirkbride et al (57)
	Any psychosis	I_C	Veling et al (47)
	Any psychosis	I_C	Schofield et al (89)
	Psychotic experiences	I_C	Das-Munshi et al (90)
Individual- x area-level social fragmentation	Any psychosis	I_C	Zammit et al (39)
Individual- x area-level social deprivation	Any psychosis	I_C	Zammit et al (39)
Individual- x area-level ethnic fragmentation	Any psychosis	I_C	Zammit et al (39)

A – evidence of association (with psychosis); C – evidence of confounding (the association between urbanicity and psychosis); I_U – evidence of interaction (individual-/area-level factor interacts with urbanicity to increase risk of psychosis); I_C – evidence of interaction (individual- and area-level factor interact to increase risk of psychosis); N – no evidence of interaction, confounding, or association

Area-level factors

Already in the early studies carried out in Chicago (9,10), Nottingham (13,14) and Mannheim (15,16), geographical variation in incidence was sought to be explained by adverse social characteristics of areas for which higher rates of disorder had been reported. For example, Faris and Dunham (9) explained their finding of higher rates of schizophrenia in the inner city of Chicago by decreasing levels of social disorganization as the distance from the centre increased. This explanation was not only supported by their own data but also by later investigations in Chicago (6-8) and Mannheim (15,16). Similarly, Giggs (13) reported social and material resources to account for geographical variation in incidence in Nottingham.

However, these earlier studies failed to examine the effects of area-level factors simultaneously with, but independent from, individual-level factors (39), taking into account clustering of individuals within geographic units (i.e., inner-urban areas, neighbourhoods). It is only more recently that appropriate statistical methods such as multilevel modelling have been used to disentangle effects of individual- and area-level factors. Several studies have investigated the role of social deprivation at the area level and found a significant association with the incidence of schizophrenia (50,54,57,60,88) and non-affective psychosis (39,52,57). However, there is consistent evidence from these studies that, after adjustment for potential confounders at both the individual and area level, this association is attenuated (50) and ceases to be statistically significant (39,50,54,57,60). By contrast, in a recent analysis by Kirkbride et al (42), the association between area-level deprivation and non-affective psychosis remained, even after adjustment for other individual- and area-level factors.

The concept of "social capital" remains a frequently proposed explanation of variation in incidence across neighborhoods. Silver et al (88) reported that social mobility (operationalized as the proportion not living at the same address five years earlier and the proportion with rented accommodation) is associated with risk of schizophrenia after adjustment for a number of individual-level factors. Drukker et al (54) distinguished two components of "social capital", informal social control as well as social cohesion and trust, and investigated residential instability as a separate area-level characteristic. While these authors found significant associations of residential instability and social cohesion and trust with risk of schizophrenia, none of these associations held in adjusted analyses. In contrast, Kirkbride et al (49) reported a non-linear association between social cohesion and trust and the incidence of schizophrenia, such that adjusted rates were increased in neighbourhoods with low and high compared with medium levels of social cohesion and trust. However, social disorganization, identified as another component of social capital in this study, was not associated with the incidence of schizophrenia (49). Finally, Lofors and Sundquist (48) used voter turnout as a proxy of "social capital" and, consistent with Kirkbride et al (56), found that lower turnout was associated with an increased incidence of non-affective psychosis.

A related, and potentially overlapping, concept posited to account for geographical variation in incidence across

neighbourhoods is social fragmentation. Allardyce et al (50) reported a dose-response relationship between area-level social fragmentation (operationalized as mobility in the previous year and number of rented households, single-person households, and unmarried persons) and first-admission rates of schizophrenia. Similarly, there is evidence from a Danish register study (39) that the incidence of non-affective psychotic disorders is increased in areas with higher levels of social fragmentation (operationalized as proportion of children who migrated into Sweden, moved into a different municipality between ages 8 and 16 years, or were raised in single-parent households), even after adjusting for potential confounding by a number of individual- and area-level factors. However, no evidence of association between area-level social fragmentation and non-affective psychosis was found by Kirkbride et al (42).

While these findings, taken together, suggest that area-level exposures are likely to be relevant in explaining geographical variation in incidence, they also point to considerable conceptual, operational, and empirical overlap of the environmental exposures investigated to date (101,102). Empirical investigations, informed by social theory (41), are now required to identify underlying categorical or continuous variables of social exclusion and deprivation, social capital, and social fragmentation, using, for example, multilevel latent variable modelling to validate existing operationalizations of these constructs.

Interaction of individual- and area-level factors

More recent studies using multilevel modelling have further investigated how individual- and area-level factors interact with each other to increase risk of psychosis (39). The most prominent and, overall, best replicated finding from these studies is that individuals from migrant and minority ethnic groups are at an increased risk of psychosis in areas with low ethnic density (i.e., areas in which these groups constitute a small proportion of the local population) (47,57,60,89,90). This interaction between individual-level ethnicity and area-level ethnic density has been reported for schizophrenia (60), non-affective psychosis (57), all psychotic disorders (47,89), and psychotic experiences (90). This is particularly interesting as urban areas in which low numbers of migrants live tend to be characterized by rather high levels of average income and general health care.

Becares et al (103) suggested that experiences of discrimination may be buffered by neighbourhood-level ethnic group density. Therefore, it does not seem to be general poverty in an area per se, but rather social support or exclusion that contributes to higher rates of psychosis in migrants living in such (relatively well-off) areas. These considerations are supported by a recent study by Zammit et al (39), reporting an interaction of individual- and area-level social fragmentation, "ethnic" fragmentation, and social deprivation. In accordance with the hypothesis that it is social exclusion in an area that contributes to high psychosis rates, the authors found evidence that risk of any psychosis increases as individual-level deprivation, social and "ethnic" fragmentation increase, and area-level deprivation, social and "ethnic" fragmentation decrease (39). This suggests that risk of psychosis differs in individuals exposed to social adversity depending on the context where they were raised or currently live in.

POTENTIAL MECHANISMS

The above findings, taken together, suggest that there is considerable geographical variation in the incidence of schizophrenia and other non-affective psychoses both across urban-rural areas and across neighbourhoods within inner-urban areas. Since there is evidence on temporality (i.e., urban upbringing rather than current city living) and dose-response gradient (i.e., risk increases in a linear fashion as cumulative exposure to urban environment during upbringing increases), it is unlikely that social drift alone can fully account for this variation.

Current findings further suggest that the impact of adverse social contexts – indexed by area-level exposures such as population density, social fragmentation and deprivation – on risk of psychosis is: a) explained (confounding) or b) modified (interaction) by environmental exposures at the individual level (i.e., cannabis use, ethnic minority group position, social adversity, exclusion and discrimination). This raises the question of which biological and psychological mechanisms may link these (individual- and area-level) environmental exposures and psychosis.

Genetic factors can play a role in individuals exposed to urban environment (4). Since a large proportion of the general population is exposed to urbanicity, development of psychosis in only a few individuals may depend on the degree of familial liability (104). In line with this, two studies have reported a positive interaction on an additive scale between urbanicity and family history of psychosis, suggesting that individuals exposed to urban environment and with familial liability are at significantly greater risk of psychosis than those with either factor alone (33,95). Along similar lines, Weiser et al (105) reported evidence of additive interaction between cognitive and social functioning, as a marker of genetic liability, and population density on risk of schizophrenia. While these findings tentatively suggest that the impact of environmental exposures may depend on genetic risk, to date, there is no evidence of gene x urban environment interaction from studies using direct measure of genes. Moreover, the substantially higher rates of psychosis in migrants from the Caribbean and Africa in London (particularly in areas with low ethnic density), compared with psychosis rates and outcomes in, for instance, the Caribbean, West Africa and India, suggest that there are specific factors related to

migration and associated exposure to social exclusion stress (106-109).

On a neurobiological level, it has been suggested that the risk of developing schizophrenia is associated with a tendency for imprecise information processing potentially based on disturbed cortico-cortical plasticity (110,111), which may also be present in the relatives of schizophrenia patients (112). Therefore, "dysconnectivity" may be a potential biological characteristic of individuals with schizophrenia (113) and with increased genetic risk or an at risk mental state (114,115). It was demonstrated that the dorsolateral prefrontal cortex exerts reduced control over activity in the parietal cortex during working memory (113) and this mechanism may contribute to impairments in habitual recognitions and automatic responding to environmental cues and contexts (116).

In acute psychosis, elevated subcortical dopamine turnover and release (117-119) may then be a secondary phenomenon, which increases the signal-to-noise ratio at the expense of salience attribution to otherwise irrelevant stimuli; these cues may be misinterpreted as indicators of persecution or social threat and thus contribute to delusional mood and delusion formation (67,77,120).

Several authors have proposed social stress as a potential mechanism through which exposure to urban environment may impact on individuals and particularly on dopaminergic neurotransmission to increase risk of psychosis (3,57,77,121). Indeed, animal experiments showed that subcortical dopamine release, particularly in the striatum, is directly affected by social stress factors as well as the intake of drugs of abuse (122,123). The concept of "sensitization" – which denotes an increased sensitivity or "response" of dopamine release and has been used to explain increased dopaminergic neurotransmission following social defeat and other forms of social adversity – was originally developed in the context of drug addiction, where repeated exposure to drugs of abuse can sensitize striatal dopamine release and the associated behavioral responses (2,77,124). Social exclusion stress as well as the consumption of drugs of abuse may thus both sensitize subcortical dopamine release, and stress-associated dopamine dysfunction may further be increased following developmentally early impairment of mesolimbic-prefrontal networks, e.g., following obstetric complications or intra-uterine infections (91).

Animal experiments confirmed that developmentally early temporolimbic dysfunction can impair prefrontal regulation of subcortical dopaminergic neurotransmission, resulting in increased striatal dopamine release following prefrontal catecholamine application to mimic stress exposure (2,125,126). While elevated presynaptic dopamine synthesis is a well-replicated finding in schizophrenia patients (117,127), a recent human positron emission tomography (PET) imaging study in mono- and dizygotic twins demonstrated that non-shared individual-specific environmental factors account for more than 50% of variance in striatal dopamine synthesis and that this effect is even more pronounced in the ventral-limbic striatum (128).

These observations suggest that biological as well as social factors and drug consumption can interact and affect striatal dopamine release as a "final common pathway" in the development of frank psychosis. However, to date studies are missing that directly assess the interaction between social stress factors, individual vulnerability and the risk of developing psychosis in humans.

With respect to urban stress exposure, Lederbogen et al (129) recently investigated whether urban living and upbringing modify neural processing of social evaluative stress. While controlled exposure to social evaluative stress was associated with increased activity in the perigenual anterior cingulate cortex in individuals brought up in an urban environment, amygdala activity was increased in those currently living in urban areas (129). This observation is in line with a potential bias towards threat anticipation (130,131) as a possibly important mechanism in the development of psychotic disorders. However, increased amygdala activation and impaired connectivity between the amygdala and the prefrontal cortex has been reported in non-psychotic affective disorders rather than psychosis per se, and appears to be modulated by serotonin rather than dopamine-related genetic variation (132).

The serotonergic system has indeed been shown to be strongly affected by social isolation stress, and the observed alterations in serotonin turnover and transporter availability were associated with anxiety, aggressiveness and increased drug intake (133,134). The sensitivity to social isolation stress appears to be modified by serotonin transporter genotype, which was also implicated in amygdala activation by aversive stimuli and amygdala-prefrontal coupling (135,136). However, most studies to date reported a predominantly decreased response of the amygdala to affective stimuli in schizophrenia (137-139), so the relevance of the observation of Lederbogen et al (129) in healthy controls for urban psychosis risk remains to be further elucidated.

Interestingly, one recent study in patients suffering from schizophrenia separately assessed the responses of the amygdala to affectively positive and negative stimuli (rather than averaging all responses independent of the valence of the emotional probe) and observed increased responses to affectively negative and decreased activation in response to affectively positive stimuli (140). Together with the observation that dopamine turnover is increased in unmedicated schizophrenia patients (118), and that such an increase in dopamine turnover positively enhances amygdala responses to aversive stimuli in healthy controls (141), these findings may suggest that increases in dopamine production and turnover in acute psychosis can interact with urban upbringing and other chronic stress-associated factors to increase limbic processing of aversive stimuli.

Indeed, studies from our own group and others found that genetic variation in genes regulating the metabolism

and reuptake of monoamines such as dopamine, noradrenaline and serotonin additively affect amygdala responses in healthy controls (142,143). Therefore, further studies are required that simultaneously assess genetic variance as well as social stress factors and their respective interactions in striatal, limbic and prefrontal processing of rewarding and affective stimuli and their potential impairment in psychosis. However, due to the complex nature of these interactions, such studies need to be controlled for overfitting of genetic and potentially also environmental data (144), and independently replicated in separate samples.

CONCLUSIONS

Taken together, the findings reviewed in this paper suggest that urbanicity is associated with an increased risk of schizophrenia and other non-affective psychosis, and that the impact of adverse social contexts – indexed by area-level exposures such as population density, social fragmentation and deprivation – on risk of psychosis is explained (confounding) or modified (interaction) by environmental exposures at the individual level (i.e., cannabis use, social adversity, exclusion and discrimination).

While animal experiments and human studies suggest plausible mechanisms linking social stress and biological alterations found in schizophrenia, specific studies directly testing such mechanisms are lacking to date.

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DOI 10.1002/wps.20056

SPECIAL ARTICLE

Diagnosis and classification of disorders specifically associated with stress: proposals for ICD-11

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The diagnostic concepts of post-traumatic stress disorder (PTSD) and other disorders specifically associated with stress have been intensively discussed among neuro- and social scientists, clinicians, epidemiologists, public health planners and humanitarian aid workers around the world. PTSD and adjustment disorder are among the most widely used diagnoses in mental health care worldwide. This paper describes proposals that aim to maximize clinical utility for the classification and grouping of disorders specifically associated with stress in the forthcoming 11th revision of the International Classification of Diseases (ICD-11). Proposals include a narrower concept for PTSD that does not allow the diagnosis to be made based entirely on non-specific symptoms; a new complex PTSD category that comprises three clusters of intra- and interpersonal symptoms in addition to core PTSD symptoms; a new diagnosis of prolonged grief disorder, used to describe patients that undergo an intensely painful, disabling, and abnormally persistent response to bereavement; a major revision of "adjustment disorder" involving increased specification of symptoms; and a conceptualization of "acute stress reaction" as a normal phenomenon that still may require clinical intervention. These proposals were developed with specific considerations given to clinical utility and global applicability in both low- and high-income countries.

Key words: Classification, mental disorders, ICD, nosology, PTSD, complex PTSD, prolonged grief disorder, cultural appropriateness, DSM

(World Psychiatry 2013;12:198–206)

Disorders specifically associated with stress such as post-traumatic stress disorder (PTSD) and adjustment disorder are among the most widely used diagnoses amongst psychiatrists and psychologists worldwide. For psychiatrists who use the ICD-10, PTSD ranks 14th in their day-to-day clinical practice (1). Among global psychologists who use the ICD-10, it is the eighth most frequently used diagnosis. Among psychologists who use the DSM-IV, PTSD ranks third, following only generalized anxiety disorder and major depressive disorder (2).

Stressful events may be risk factors or precipitants for many mental disorders, including psychotic episodes and depression. However, disorders specifically associated with stress are the only diagnoses that include an exposure to a stressful event in their etiology as a qualifying diagnostic requirement.

These diagnoses are also the subject of continuing controversy (3,4). When the DSM-IV broadened the eligibility for the diagnosis of PTSD to include those people whose exposure was indirect (for example, hearing about a stressful event happening to others, or seeing it on television), some pointed out that such diagnostic expansion both diluted the value of the original construct and medicalized normal stress reactions (3,5).

There has been further debate as to the appropriateness of these diagnoses across cultures. The potential overuse of these diagnostic categories is of particular concern in low resource and humanitarian settings, where their apparent simplicity makes them easily applicable to large numbers of people who may be more appropriately viewed as in the midst of normal reactions to extreme circumstances (6). Another concern in these settings is that an emphasis on traumatic stress results in both misdiagnosis and neglect of those suffering from other common and severe mental disorders.

Significant controversy is also associated with the diagnosis of adjustment disorder, in spite of its frequent use by clinicians (1,2). Adjustment disorder is one of the most ill-defined mental disorders, often described as the "waste-basket" of the psychiatric classification scheme (7,8).

The forthcoming revision of the International Classification of Diseases and Related Health Problems (ICD-11), which is currently planned for approval by the World Health Assembly in 2015, has provided an opportunity for the World Health Organization (WHO) to revisit these issues and devise a classification whose aim is to improve clinical utility and global applicability (9,10). In the context of the overall ICD revision structure, a Working Group on

the Classification of Disorders Specifically Associated with Stress was appointed, reporting to the International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders (9). This Working Group included a diverse and multidisciplinary set of experts from all WHO regions, particularly including low- and middle-income countries.

The primary tasks of the Working Group were: a) to review available scientific evidence related to disorders specifically associated with stress, as well as clinical and policy information on the use and clinical utility of these diagnoses within various health care settings throughout the world, including primary care and specialist settings; b) to review proposals for the DSM-5 in this area and consider how these may or may not be suited for global applications; c) to assemble and prepare specific proposals, including the placement and organization of relevant categories; and d) to provide drafts of the content of these categories for the ICD-11 and its associated products (e.g., definitions, descriptions, diagnostic guidelines). Particular attention was paid to the presentation of the disorders in diverse settings (e.g., health care facilities, humanitarian aid settings) and regions of the world, including low- and middle-income countries. The group's goal was to specify conditions that had distinct clinical presentations and to describe their core elements.

HISTORY

Disorders specifically associated with stress are relative newcomers to psychiatric classification. The predominant attitude in the UK towards acute stress during the Second World War is encapsulated in a 1942 article in *The Lancet* by Dr. Henry Wilson, who described his experience of treating 134 patients in a London emergency department: "They were all told that their reaction was due to fear, that this fear was one they shared with all other patients and the first aid workers, and that it was important that they return to their normal work and resist the temptation to exaggerate the experiences through which they had passed" (11). He identified reactions ranging from acute emotional disturbance to stupor and hysterical paraplegia. All of these patients were discharged within 24 hours and only six of them needed further treatment over the next nine months.

However, this emphasis on normalizing reactions and return to functioning gradually shifted to a greater concern with subtle forms of psychopathology and the introduction of an expanding array of diagnostic categories thought to be etiologically related to stress. The ICD-8, approved by the World Health Assembly in 1965, introduced a "transient situational disturbance" that included adjustment problems, severe stress reactions, and combat neurosis. In the ICD-9, approved in 1975, two such disorders were outlined: acute stress reaction and adjustment reaction. In the ICD-10, approved in 1990, two new disorders appeared as primary diagnoses in addition to acute stress reaction and adjustment disorder: F43.1 Post-traumatic stress disorder (PTSD) and F62.0 "Enduring personality change after catastrophic experiences", which could appear following exposure to stress of an extreme nature (e.g., torture or concentration camp imprisonment).

It is interesting to note that, due to the influence of military psychiatry, acute stress reaction was typically conceptualized as a transient reaction occurring immediately after exposure to a stressor. It was not intended to describe a mental disorder per se, but rather the general distress reactions that people typically experience in the days after exposure to traumatic events. It was expected that these reactions would normally subside within days (12).

THE WORKING GROUP PROCEEDINGS

The Working Group on the Classification of Disorders Specifically Associated with Stress was tasked with examining and improving the classification of a mixed group of conditions, including both "Reaction to severe stress and adjustment disorders" (ICD-10 code F43) and "Enduring personality change after catastrophic experiences" (F62.0). The time frame for its work partly overlapped with the preparation of the DSM-5.

There was a consensus among the Working Group that a specific group of conditions existed – both normative and pathological – requiring the presence of a stressor as a precipitant. These conditions could be distinguished from other disorders such as depression, anxiety, substance abuse or psychosomatic problems, where stress might be a risk factor or precipitant, but which could also occur in its absence.

PROPOSED CLASSIFICATION

The proposed classification of disorders specifically associated with stress in the ICD-11 addresses the full range of severity from normative reactions to pathological conditions (see also 13). One major change is that acute stress reaction is now conceptualized as a normal reaction and thus classified in the chapter corresponding to "Factors influencing health status and contact with services". This category is considered a legitimate focus of clinical intervention, but is not defined as a disorder.

The proposed new grouping of "Disorders specifically associated with stress" includes adjustment disorder, PTSD and complex PTSD. In addition, the ICD-11 will include for the first time a separate diagnosis of prolonged grief disorder. This proposed group of disorders specifically related to stress covers a set of conditions that have distinct psychopathology and require prior exposure to an external stressful event, or adverse experiences of exceptional character or degree (Table 1). Events may range from less severe psychosocial stress ("life events") to loss

Table 1 Proposed ICD-11 categories of disorders specifically associated with stress

Proposed ICD-11 categories	Previous ICD-10 codes	Core diagnostic features
Post-traumatic stress disorder	F43.1	A disorder that develops following exposure to an extremely threatening or horrific event or series of events characterized by: 1) reexperiencing the traumatic event(s) in the present in the form of vivid intrusive memories accompanied by fear or horror, flashbacks, or nightmares; 2) avoidance of thoughts and memories of the event(s), or avoidance of activities or situations reminiscent of the event(s); and 3) a state of perceived current threat in the form of excessive hypervigilance or enhanced startle reactions. The symptoms must last for at least several weeks and cause significant impairment in functioning.
Complex post-traumatic stress disorder	F62.0	A disorder which arises after exposure to a stressor typically of an extreme or prolonged nature and from which escape is difficult or impossible. The disorder is characterized by the core symptoms of PTSD as well as the development of persistent and pervasive impairments in affective, self and relational functioning, including difficulties in emotion regulation, beliefs about oneself as diminished, defeated or worthless, and difficulties in sustaining relationships.
Prolonged grief disorder	New category	A disturbance in which, following the death of a person close to the bereaved, there is persistent and pervasive yearning or longing for the deceased, or a persistent preoccupation with the deceased that extends for an abnormally long period beyond expected social and cultural norms (e.g., at least 6 months, or longer depending on cultural and contextual factors) and that is sufficiently severe to cause significant impairment in the person's functioning. The response can also be characterized by difficulties accepting the death, feeling one has lost a part of one's self, anger about the loss, guilt, or difficulty in engaging with social or other activities.
Adjustment disorder	F43.2	A maladaptive reaction to a stressful event, to ongoing psychosocial difficulties or to a combination of stressful life situations that usually emerges within a month of the stressor and tends to resolve in 6 months unless the stressor persists for a longer duration. The reaction to the stressor is characterized by symptoms of preoccupation like excessive worry, recurrent and distressing thoughts about the stressor or constant rumination about its implications. There is failure to adapt, i.e., the symptoms interfere with everyday functioning, like difficulties concentrating or sleep disturbance resulting in performance problems. The symptoms can also be associated with loss of interest in work, social life, caring for others, leisure activities resulting in impairment in social or occupational functioning (restriction of social network, conflicts in family, absenteeism and so on). If the definitional requirements are met for another disorder, that disorder should be diagnosed instead of adjustment disorder.
Reactive attachment disorder	F94.1	See Rutter and Uher (14)
Disinhibited social engagement disorder	F94.2	See Rutter and Uher (14)
Non-disorder phenomena included under Factors Influencing Health Status and Encounters with Health Services		
Acute stress reaction	F43.0	Refers to the development of transient emotional, cognitive and behavioural symptoms in response to an exceptional stressor such as an overwhelming traumatic experience involving serious harm or threat to the security or physical integrity of the individual or of a loved person(s) (e.g., natural catastrophe, accident, battle, criminal assault, rape), or an unusually sudden and threatening change in the social position and/or network of the individual, such as the loss of one's family in a natural disaster. The symptoms are considered to be within the normal range of reactions given the extreme severity of the stressor. The symptoms usually appear within hours to days of the impact of the stressful stimulus or event, and typically begin to subside within a week after the event or following removal from the threatening situation.

of a close other, to single traumatic events, and repeated or prolonged traumatic stress of exceptional severity. The resulting pathology could be conceptualized as ranging from mild to more severe disorders. The diagnoses in this group require a specific recognizable clinical picture that is distinct from other mental disorders, as well as a demonstrable and continuing functional impairment.

ICD-11 PTSD, complex PTSD, prolonged grief disorder, and adjustment disorder can occur in all age groups, including children and adolescents. In addition, the group includes specific attachment disorders in children that are discussed elsewhere (14).

SPECIFIC DISORDERS

PTSD

PTSD is a well-recognized clinical entity that has distinct psychological correlates. It has been criticized for the broad composition of the symptom clusters, the high levels of comorbidity, and, for the DSM-IV criteria set, the fact that over 10,000 different combinations of the 17 symptoms could result in the diagnosis. Several authors have called for the diagnosis to be refocused on a smaller number of core symptoms (3,15).

Studies have suggested that the threshold for an ICD-10 diagnosis of PTSD is relatively low (e.g., 16,17). A diagnostic requirement for functional impairment has been proposed to help differentiate PTSD from normal reactions to extreme stressors. In addition, evidence-based critiques suggested the removal of the statement that traumatic events are "likely to cause pervasive distress in almost everyone"; the clarification that intrusive memories are not synonymous with re-experiencing in the present; an increased emphasis on the importance of deliberate avoidance; and a more explicit recognition of delayed-onset PTSD (5,18). All these suggestions have been considered in formulating the new proposal.

The proposal also attempts to improve the ease of diagnosis and to reduce comorbidity, by identifying the core elements of PTSD rather than the "typical features" of the disorder. The first core element consists of re-experiencing the traumatic event(s) in the present, as evidenced by vivid intrusive memories accompanied by fear or horror, flashbacks, or nightmares (see Table 1). Flashbacks are defined as vivid intrusive memories in which re-experiencing in the present can vary from a transient sensation to a complete disconnection from the current environment. The second core element is avoidance of these intrusions, as evidenced by marked internal avoidance of thoughts and memories, or external avoidance of activities or situations reminiscent of the traumatic event(s). The third core element is an excessive sense of current threat, as evidenced either by hypervigilance or by exaggerated startle, two arousal symptoms that tend to cluster together (19).

The effect of these changes is to greatly simplify the diagnosis and direct clinicians' attention to the co-occurrence of three core elements all of which should be present, each assessed by two symptoms. PTSD may not be diagnosed if the person also meets criteria for complex PTSD, since the latter is a more encompassing diagnosis that includes all the features of PTSD.

Complex PTSD

Complex PTSD is a new disorder category describing a symptom profile that can arise after exposure to a single traumatic stressor, but that typically follows severe stressors of a prolonged nature or multiple or repeated adverse events from which separation is not possible (e.g., exposure to genocide campaigns, childhood sexual abuse, child soldiering, severe domestic violence, torture, or slavery).

The proposed diagnosis is comprised of the three core features of PTSD in addition to disturbances in the domains of affect, self-concept and relational functioning. These additional domains reflect the presence of stressor-induced disturbances that are enduring, persistent and pervasive in nature and that are not necessarily bound to trauma-related stimuli when appearing. The construct replaces the overlapping ICD-10 category of "enduring personality change after catastrophic experience", which has failed to attract scientific interest and did not include disorders arising from prolonged stress in early childhood. The specific symptoms proposed are based on recent research (20,21) and expert opinion (22).

Problems in the affect domain include a range of symptoms resulting from difficulties in emotion regulation. They can become manifest in heightened emotional reactivity or in a lack of emotions and lapses into dissociative states (23). Behavioural disturbances can include violent outbursts and reckless or self-destructive behaviour (24).

Problems in the self-concept domain refer to persistent negative beliefs about oneself as diminished, defeated or worthless. They can be accompanied by deep and pervasive feelings of shame, guilt, or failure related to, for example, not having overcome adverse circumstances, or not having been able to prevent the suffering of others.

Disturbances in relational functioning may present in a variety of ways, but are exemplified primarily by difficulties in feeling close to others. The person may consistently avoid, deride, or have little interest in relationships and social engagement more generally. Alternatively, the person may occasionally experience close or intense relationships but have difficulties sustaining them.

Complex PTSD can be distinguished from the construct of borderline personality disorder (BPD) by the nature of the constellation of symptoms, by differences in the risk for self-harm, and by the type of treatment required for a good outcome. BPD does not require the presence of a stressor event or the core symptoms of PTSD to be

diagnosed. These are both essential for a diagnosis of complex PTSD. BPD is strongly characterized by fear of abandonment, shifting identity, and frequent suicidal behaviours. In complex PTSD, the fear of abandonment is not a requirement of the disorder, and self-identity is consistently negative rather than shifting (22).

Prolonged grief disorder

Prolonged grief disorder is a new diagnosis being proposed for ICD-11, which describes abnormally persistent and disabling responses to bereavement. It is defined as a severe and enduring symptom pattern of yearning or longing for the deceased or a persistent preoccupation with the deceased. This reaction may be associated with difficulties accepting the death, feelings of loss of a part of oneself, anger about the loss, guilt or blame regarding the death, or difficulties in engaging with new social or other activities due to the loss.

Importantly, prolonged grief disorder can only be diagnosed if symptoms are still apparent after a period of grieving that is normative within the person's cultural context (e.g., 6 months or more after the death), the persistent grief response goes far beyond expected social or cultural norms, and the symptoms markedly interfere with one's capacity to function (see Table 1). If normative grieving in the person's culture goes beyond 6 months, the duration requirement should be extended accordingly.

The introduction of prolonged grief disorder is a response to the increasing evidence of a distinct and debilitating condition that is not adequately described by current ICD diagnoses. Although most people report at least partial remission from the acute pain of grief by around 6 months following bereavement, those who continue experiencing severe grief reactions beyond this time frame are likely to have a significant impairment in their general functioning (25). Many studies from around the world, including both Western and Eastern cultures, have identified a small but significant portion of bereaved people who meet this definition (26).

There are multiple sources of evidence supporting the introduction of prolonged grief disorder. This entity has been validated across a wide range of cultures, including non-Western settings, as well as across the lifespan (26). Factor analyses repeatedly demonstrated that the central component of prolonged grief disorder (yearning for the deceased) is distinct from non-specific symptoms of anxiety and depression. People with prolonged grief disorder experience serious psychosocial and health problems, including other mental health difficulties such as suicidality and substance abuse, harmful health behaviours, or physical disorders such as high blood pressure and elevated rates of cardiovascular disorder (27). Finally, there are distinctive neural dysfunctions and cognitive patterns associated with prolonged grief disorder (26,28).

Concerning treatment, prolonged grief disorder does not respond to antidepressant medication though bereavement-related depressive syndromes do (29). Importantly, psychological therapy that strategically targets the symptoms of prolonged grief disorder has been shown to alleviate their occurrence more effectively than treatments that target depression (30).

The introduction of prolonged grief disorder as a diagnosis has caused debate because of concerns that it could pathologize normal grief responses (31). The Working Group considered this issue thoroughly and emphasized several points. First, the diagnostic requirements have been drawn very carefully to respect the variation of "normal" processes and to pay attention to cultural and contextual factors. Second, the diagnosis only applies to that minority (<10%) of bereaved people who experience persistent impairment. Third, it has been recognized that there is marked cultural variation in the manifestation of grief that has to be taken into account for diagnostic decisions. Fourth, many people will experience fluctuating distressing grief responses beyond 6 months from the death of close persons, but these are not necessarily candidates for a prolonged grief disorder diagnosis due to a lack of persistence and debilitation.

Epidemiological findings show that prolonged grief disorder represents a public health issue. Accurately identifying people with this disorder could reduce the likelihood of inappropriate treatment. Provision of evidence-based interventions directed to prolonged grief disorder symptoms can ease the burden and reinforce the rationale for introducing this diagnosis.

Adjustment disorder

Adjustment disorder has been a poorly defined area of psychopathology, owing to the variety of presenting symptoms that may be involved and the relative absence of distinctive features. It has usually been regarded as consisting of a group of sub-threshold disorders related to a provoking event or situation. Often the identification of such a precipitating event is made *post hoc*. Adjustment disorder has been mostly used as a residual category for patients who do not meet the diagnostic criteria for depressive or anxiety disorders, or as a provisional diagnosis when it is not clear whether or not a post-traumatic or mood disorder will emerge (e.g., 7,8).

The ICD-11 proposal focuses on the notion that an adjustment disorder is a maladaptive reaction to an identifiable psychosocial stressor or life change. It is characterized by preoccupation with the stressor and failure to adapt, as shown by a range of symptoms interfering with everyday functioning, such as difficulties concentrating or sleep disturbance. Symptoms of anxiety or depression, or impulse control/conduct problems are commonly present. The symptoms emerge within a month of the onset of the

stressor(s) and tend to resolve in around 6 months unless the stressor persists for a longer period. The disorder causes significant distress and impairment of social or occupational functioning (32).

Adjustment disorder is viewed as continuous with normal adaptation processes, but distinguished from "normal" by the intensity of distress and resulting impairment. Unlike PTSD, the severity of the stressor is not considered for diagnosis. However, adjustment disorder can result from extreme traumatic distress when symptoms do not meet the full criteria for PTSD.

There is no evidence for the validity or clinical utility of subtypes of adjustment disorder described in the ICD-10, so these have been omitted in the ICD-11. Such subtypes may be misleading through putting the emphasis on the dominant idiom of distress and obscuring the underlying commonality of the disorder. Subtypes are not relevant for treatment selection and are not associated with a specific prognosis (7). The characteristic feature is often a mixture of emotional and behavioural symptoms (8). Although internalizing or externalizing symptoms may predominate, they often coexist.

ACUTE STRESS REACTION AS A NON-DISORDERED RESPONSE

Acute stress reaction as currently defined in ICD-10 is ambiguous. Its name ("reaction") and its diagnostic description suggest its transience, but its position in the ICD-10 chapter on mental and behavioural disorders labels it as pathology. The confusion is compounded by the parallel existence of the "acute stress *disorder*" diagnosis in the DSM-IV and DSM-5.

Acute stress disorder is similar to PTSD in many respects, and sometimes was considered as a precursor to PTSD, but it differs from PTSD in the greater prominence of dissociative symptoms. In the DSM-5 it can only be diagnosed in the first month post-trauma, while PTSD can only be diagnosed after one month. A review of the available literature on acute stress disorder has cast doubt on the notion that it is a good predictor of later PTSD (33). An important reason for inclusion of acute stress disorder in the DSM-5 may be the particular sensitivity to reimbursement concerns in the US, in the context of which the claim is made that treatment would not be provided for non-disorders, even following a severely traumatic experience when basic psychological interventions may be strongly indicated. However, the WHO's position has been that health care financing and reimbursement policy are separate issues from disease definition, and that it is not helpful to the project of reducing global disease burden to conflate them (34). Therefore, reimbursement considerations were not considered a valid reason to define a normal reaction as a disorder.

Moreover, within the ICD-10 and the proposed ICD-11 there is no strict minimal time limit for PTSD; this diagnosis could therefore be used within the first month post-trauma, provided that the symptoms are sufficiently persistent and cause impairment. Therefore, within the ICD-11 there is no need for an acute stress diagnosis along the lines of acute stress disorder in the DSM-5, particularly bearing in mind clinicians' requests for a substantial reduction in the overall number of diagnoses in diagnostic systems (1,2).

At the same time, clinical and public health experience has shown that there is a need for a non-pathological category to define a wide variety of transient emotional, cognitive, behavioural and somatic reactions in the immediate aftermath of an acute stressful event such as a violent attack or a natural disaster. The Working Group has therefore recommended that acute stress reaction be placed in the chapter for conditions that are not considered to be diseases or disorders but which may be reasons for health encounters (the Z chapter in ICD-10). Placement of acute stress reaction in this chapter of the ICD-11 would allow health care workers to be trained to recognize and assist those with such reactions, without the other implications of conceptualizing them as mental disorders. Such reactions often benefit from practical psychosocial interventions rather than psychiatric ones. This includes the approach currently labeled as psychological first aid (35). The ICD-11 conceptualization of acute stress reaction addresses the needs highlighted by commentators who have argued for a less pathologizing means than the DSM-5 acute stress disorder diagnosis to describe and identify acutely distressed people who may need assistance (36).

The proposed ICD-11 description of acute stress reaction does not meet the definitional requirements for a mental disorder, but refers to the development of transient emotional, cognitive, somatic and behavioural symptoms in response to an exceptional stressor involving exposure to an event or situation of an extremely threatening or horrific nature. For example, this might include actual or threatened serious injury or harm to self or a loved one (e.g., natural catastrophe, accident, battle, criminal assault, rape), or an unusually sudden and threatening change in the social position or network of the individual, such as displacement to a different country or refugee camp setting.

Symptoms of acute stress reaction may include being in a daze, a sense of confusion, sadness, anxiety, anger, despair, overactivity, stupor and social withdrawal. Autonomic signs of anxiety (e.g., tachycardia, sweating, flushing) are commonly present and may be the presenting feature. They appear within hours to days of the impact of the stressful stimulus or event and typically begin to subside within about a week after exposure, or following removal from the threatening situation in cases where this is possible. Where the stressor continues or cannot by its nature be reversed, the symptoms may persist, but they are usually greatly attenuated within approximately one month.

This time frame helps to distinguish acute stress reactions from more pathological reactions associated with

more severe disorder. If symptoms do not begin to diminish within about a week after their onset, consideration should be given to a diagnosis of adjustment disorder or PTSD, depending on the presentation. Although acute stress reaction in help-seeking individuals can be accompanied by substantial interference with personal functioning in addition to subjective distress, impairment is not a required feature.

DEVELOPMENTAL PRESENTATIONS

PTSD may occur in individuals of all ages, but responses to traumatic events can differ by developmental stage. The ICD-11 Working Group has included descriptions of age-related symptom presentations for children and adolescents. In children, responses may include disorganization, agitation, temper tantrums, clinging, excessive crying, social withdrawal, separation anxiety, distrust; trauma-specific re-enactments such as in repetitive play or drawings; frightening dreams without clear content or night terrors; sense of foreshortened future, and impulsivity. Self-injurious or risky behaviours are more frequent among adolescents (37,38). Some of these symptoms – such as re-enactments, or repetitive play, or generalized distrust – are also common in prolonged grief disorder among children or adolescents. Complex PTSD symptoms such as emotion dysregulation and interpersonal difficulties may be observed in children in form of regressive and/or aggressive behaviours towards self or others. In adolescence, substance use, risky behaviours (unsafe sex, unsafe driving) and aggressive behaviours may be particularly evident as expressions of emotion dysregulation and interpersonal difficulties (39).

SIMILARITIES AND DIFFERENCES BETWEEN ICD-11 PROPOSAL AND DSM-5

In the DSM-IV, acute stress disorder and PTSD were categorized as anxiety disorders. Both the ICD-11 proposal and DSM-5 have created a separate grouping of disorders related to stress. The ICD Working Group has recommended avoiding the widely used but confusing term "stress-related disorder", given that numerous disorders may be stress-related (e.g., depression, alcohol and substance use disorders), but may also occur in the absence of identifiable stressful or traumatic life events. In an attempt to convey this distinction, the term "disorders specifically associated with stress" for the grouping of conditions described in this article has been proposed for the ICD-11.

Both the ICD-11 proposal and DSM-5 include PTSD and adjustment disorder as part of this grouping. Prolonged grief disorder is represented in the DSM-5 as "prolonged complex bereavement disorder" in the section on disorders requiring further study. Acute stress disorder is retained in this grouping in the DSM-5, but, recognizing the heterogeneity of stress responses, it no longer requires specific symptom clusters and is not intended to predict PTSD.

The new DSM-5 definition of PTSD may be regarded as positioned between the PTSD and complex PTSD diagnoses proposed for ICD-11. The DSM-5 description identifies a new symptom cluster and adds three additional symptoms to the diagnostic criteria, reflecting research evidence of enduring changes in affect and behaviour among PTSD samples. In contrast, the ICD-11 proposal responds to criticisms of complexity and high comorbidity by attempting to define the core features of the disorder and make PTSD more easily distinguishable from other mental disorders. The intention is to enhance clinical utility and prevent unwarranted PTSD diagnoses by focusing more narrowly on a small set of easily identifiable symptoms. At the same time, the marked stress-induced changes that impact on personality, affect regulation, and interpersonal functioning are represented in the separate diagnosis of complex PTSD. It is hoped that using the proposed ICD-11 PTSD and complex PTSD diagnoses in parallel will offer significant gains to clinicians and accelerate the scientific understanding of these disorders.

CONCLUSIONS

The ICD-11 Working Group was given the task of revising the description of disorders specifically associated with stress in the light of the most recent scientific evidence, responding to criticisms levelled at the characterization of these disorders in the ICD-10 and DSM-IV, and maximizing the clinical utility and applicability of the diagnoses. As previously noted, many of these criticisms concerned the symptom structure and the susceptibility of PTSD to overdiagnosis.

In spite of questions raised about the cross-cultural validity of the diagnosis (3,4), recent evidence is consistent with the conclusion of the Working Group that PTSD does have wide cross-cultural validity (40), albeit with some variations in presentation. The Working Group concluded that a universal description of this condition is clinically useful and important for public health. While acknowledging the existence of cultural variations, there was a high degree of consensus on the core features, clinical utility, and applicability of the diagnoses proposed within the ICD-11 grouping of disorders specifically associated with stress.

The proposals of the Working Group include several changes with respect to the ICD-10 that have potential consequences for public health and health care provision. Mental health workers caring for survivors of natural or human-made disasters or conflicts would be encouraged to consider a more normative, non-disorder designation of acute stress reaction instead of immediately diagnosing

initial stress reactions as mental disorders. This change further clarifies the definition of acute stress reaction in the ICD-10 as a transient but essentially non-pathological response, and differentiates it further from the acute stress disorder concept utilized in the DSM-IV and DSM-5.

The proposed changes to the PTSD definition imply a considerable simplification of the diagnosis, especially compared to the many thousands of possible combinations of symptoms qualifying for the diagnosis according to the DSM-IV and DSM-5. It is hoped that this will lead to greater clarity about the syndrome's characteristics, and improved recognition of the disorder in both specialist and primary health care settings. Under the ICD-11 proposals, following a stressful event, clinicians will be guided to pay attention to three clearly distinct types of specific symptoms that, if persistent and causing impairment, could lead to a diagnosis of PTSD. At the same time, the requirement for impaired functioning is intended to set a higher threshold compared to the ICD-10, aiming to focus more clearly on individuals in need of care.

The inclusion of complex PTSD is partly a response to demands from clinicians for a greater recognition of the effects of enduring severity of some post-traumatic reactions. This diagnosis would be given when the core PTSD features are accompanied by persistent and pervasive disturbances in emotion regulation, self-organization, and relationship to the environment. This diagnosis may be particularly valuable in groups exposed to exceptionally high levels of trauma, such as torture survivors or victims of repeated sexual violence and abuse.

The greater specificity now afforded to PTSD and complex PTSD is accompanied in the ICD-11 proposals by additional attention given to alternative diagnoses for those exposed to stress. The revised description of adjustment disorder places now greater emphasis on the presence of impairment, while removing subtypes of the disorder that had not proven practically useful and thus undermined clinical utility. The introduction of prolonged grief disorder is also in response to a perceived clinical need and the recognition that individuals may require a form of treatment directed at this specific pattern of symptoms. As with the other proposed diagnoses, the intention is to strike a balance between retaining continuity with ways of categorizing distress that are already familiar to clinicians, and taking the opportunity to revise, clarify, and differentiate them in the service of clinical utility.

The next steps in the development of ICD-11 proposals for disorders specifically associated with stress will be public review and comment, and field testing.

Review and comment will be by means of the ICD-11 beta platform (http://apps.who.int/classifications/icd11/browse/f/en). Field studies will examine clinician acceptability, clinical utility (e.g., ease of use and goodness of fit), reliability and, to the extent possible, validity of the draft definitions and diagnostic guidelines, particularly in comparison with the ICD-10.

The WHO will use two basic approaches for field-testing of proposals for ICD-11: an Internet-based approach and a clinical settings (clinic-based) approach. Internet-based field testing will be implemented primarily through the Global Clinical Practice Network, a global network currently consisting of more than 7,000 individual mental health and primary care practitioners (www.globalclinicalpractice.net). A field study on disorders specifically associated with stress is already planned. Clinic-based studies will be implemented through the network of collaborating international field study centers appointed by the WHO.

The Working Group looks forward to collaboration with colleagues throughout the world in the testing and further refinement of its proposals of diagnostic descriptions for disorders specifically associated with stress in the ICD-11.

Disclaimer

A. Maercker, C.R. Brewin, R.A. Bryant, M. Cloitre, A. Humayan, L.M. Jones, A. Kagee, C. Rousseau, D.J. Somasundaram, S.C. Wessely and Y. Suzuki are members of the WHO ICD-11 Working Group on the Classification of Disorders Specifically Associated with Stress, reporting to the WHO International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders. G.M. Reed and M. van Ommeren are members of the WHO Secretariat, Department of Mental Health and Substance Abuse. A.E. Llosa, R. Souza, I. Weissbecker and M.B. First are special invitees to Working Group meetings. The views expressed in this article are those of the authors and, except as specifically noted, do not represent the official policies or positions of the International Advisory Group or the WHO.

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DOI 10.1002/wps.20057

Neurobiological advances identify novel antidepressant targets

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It has been over fifty years since the development of monoamine reuptake inhibitor antidepressants, that are widely prescribed and are the medication of choice for the treatment of depressive disorders. Although these agents have been useful, they also have significant limitations, including slow onset of action (weeks to months) and low rates of efficacy (approximately one third of patients respond to initial treatments). Thus, there is a significant unmet need for more effective, rapid-acting agents that have novel mechanisms.

Here we discuss a few selected new areas of drug development and targets that are based on the combination of neurobiological research and clinical findings. This work holds promise for the development of new rapid-acting agents that may enhance the pharmacological armament for the treatment of depression.

TARGETING THE GLUTAMATERGIC SYSTEM: KETAMINE AND RAPID-ACTING ANTIDEPRESSANTS

Pharmacological agents that regulate glutamate, the major excitatory neurotransmitter in the brain, have been under development for the treatment of nearly every major psychiatric disorder, as well as many neurological conditions, for nearly two decades, but only recently have their potential and impact for treating depression been realized.

This is based largely on studies of ketamine, a glutamatergic N-methyl-d-aspartate (NMDA) receptor antagonist which produces rapid (within hours) antidepressant effects in treatment resistant depressed patients (1), representing one of the most significant discoveries in the field of depression since the introduction of the monoamine reuptake inhibitors. This important clinical finding has stimulated subsequent studies of the neurobiological mechanisms underlying the actions of ketamine, which have provided a number of targets for development of new antidepressant medications that are more selective and that have fewer side effects than ketamine.

The most notable ketamine-related targets are found within the glutamate neurotransmitter system (2). Through blockade of NMDA receptors, ketamine causes a rapid, transient increase of extracellular glutamate in the prefrontal cortex (PFC), and its antidepressant actions are blocked by pre-treatment with a glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist (2,3). The "burst" of glutamate caused by ketamine is thought to occur via disinhibition of tonic firing GABAergic interneurons, causing increased glutamate neurotransmission (4). The increase in glutamate activity is accompanied by an increase in the number and function of spine synapses and rapid reversal of the effects of chronic stress (3). Moreover, ketamine stimulates the mammalian target of rapamycin (mTOR), a signaling system that controls the translation of synaptic proteins. Importantly, the synaptogenic and behavioral actions of ketamine are blocked by infusion of a selective inhibitor of mTOR, demonstrating a requirement for this signaling pathway (3). These effects are thought to underlie the antidepressant actions of ketamine by blocking or reversing the synaptic connection deficits caused by stress and depression, thereby reinstating normal control of mood and emotion (2).

Based on these studies of ketamine, several antidepressant targets have been identified within the glutamate system.

First, there is evidence that NR2B is the relevant receptor subtype that mediates the actions of ketamine. Basic research studies demonstrate that the NR2B selective antagonist Ro 25-6981 also produces rapid antidepressant behavioral effects, increases mTOR signaling, and increases synaptic proteins in the PFC (3). There is also preliminary evidence that the NR2B selective antagonist CP-101,606 produces rapid antidepressant effects in depressed subjects, although not as rapidly as ketamine (2).

Second, the presynaptic glutamate autoreceptors, the metabotropic glutamate receptor 2/3 (mGluR2/3) subtypes, are a likely target, as blockade of these receptors controls the release of glutamate. This hypothesis is supported by studies demonstrating that mGluR2/3 antagonists (LY341495 and MGS0039) produce rapid antidepressant actions in behavioral models, including the forced swim test (2). LY341495 also produces a rapid response in a chronic unpredictable stress-anhedonia paradigm, considered one of the best models of depression, and one of the most rigorous for testing rapid-acting agents, as typical antidepressants are only effective after chronic (3 weeks) treatment in this paradigm (5). The possibility that these agents are acting through mechanisms similar to ketamine is supported by evidence that mGluR2/3 antagonist treatment increases mTOR signaling in the PFC, and the antidepressant behavioral effects are blocked by pretreatment with a selective mTOR inhibitor.

Third, based on evidence that ketamine increases glutamate and that the behavioral effects are blocked by an AMPA receptor antagonist, agents that act as AMPA

receptor potentiators could also have antidepressant efficacy. These drugs have been developed for use as cognitive enhancers and are reported to have efficacy in models of depression (2). Further studies are needed to determine if AMPA potentiators, as well as NR2B and mGluR2/3 antagonists, produce a rapid induction of synaptic connections in rodent models, and ultimately to determine their clinical efficacy in depressed patients.

OTHER KETAMINE-RELATED TARGETS

Studies of ketamine and other rapid-acting agents have identified additional targets for drug development.

One is brain derived neurotrophic factor (BDNF), which plays an important role in the survival of neurons in the adult brain, as well as in neuroplasticity and synaptogenic responses in models of learning and memory. Basic research studies demonstrate that the behavioral actions of ketamine are blocked in BDNF mutant mice, including mice which carry a human polymorphism, Val66Met, that blocks the release of BDNF (2). This has resulted in clinical studies reporting that depressed patients with the BDNF Met allele have a significantly reduced response to ketamine. These studies also indicate that a BDNF agonist could produce rapid and efficacious antidepressant actions, although development of small molecule BDNF agonists has not been successful to date.

Another target that has been identified in studies of ketamine is glycogen synthase kinase-3 (GSK-3). This work demonstrates that the antidepressant effects of ketamine do not occur in mice with a GSK-3 mutation that blocks ketamine-induced phosphorylation and inhibition of this kinase (2). This suggests that a GSK-3 inhibitor would produce rapid antidepressant actions in behavioral models, although additional studies to rigorously test this hypothesis in chronic models are needed. In addition, there is new evidence that the combination of a low dose of ketamine and lithium, a GSK-3 inhibitor, produces an additive antidepressant and synaptogenic response, and similar effects are observed with a selective GSK-3 inhibitor (6). These findings indicate that lower and safer doses of ketamine, when combined with lithium, could be used for the rapid and sustained treatment of depression. It is also possible that lithium or another GSK-3 inhibitor could sustain the actions of ketamine, beyond the 1 to 2 weeks typically seen before relapse in depressed patients.

In addition to ketamine, there is evidence that scopolamine, a non-selective muscarinic receptor antagonist, also produces rapid antidepressant actions in depressed patients (7). Basic research studies demonstrate that scopolamine also increases mTOR signaling and synaptogenesis in PFC, and that the behavioral actions of scopolamine are blocked by either an AMPA receptor antagonist or a selective mTOR inhibitor (8). These studies also demonstrate that scopolamine increases extracellular glutamate in PFC. Together with the studies of ketamine, these findings indicate a common pathway for rapid acting antidepressants. Studies are currently underway to identify which of the five muscarinic receptor subtypes mediate the effects of scopolamine, thereby providing a target for development of a selective antagonist with fewer side effects than scopolamine.

INFLAMMASOME AND PRO-INFLAMMATORY CYTOKINES

Another emerging area of interest is inflammation and blockade of pro-inflammatory cytokines. There are consistent reports of elevated levels of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-6 and tumor necrosis factor-alpha (TNF-α), in depressed patients (9). Moreover, basic research studies have begun to elucidate the inflammation processes that underlie the synthesis and release of these cytokines. These studies demonstrate that stress increases the synthesis and release of pro-IL-1β, IL-6, and TNF-α in brain microglia, as well as the processing of pro-IL-1β to the mature form via activation of caspase-1 (9). The latter step involves stimulation of a purinergic receptor, P2X7, located on microglia and macrophages, which leads to activation of the inflammasome and pro-caspase-1.

The potential role of pro-inflammatory cytokines in depression is supported by several lines of evidence from basic research studies (9). First, administration of an IL-1β antagonist or neutralizing antibody produces an antidepressant effect in a chronic stress-induced anhedonia model. Second, administration of a P2X7 receptor antagonist also produces an antidepressant response in the chronic stress model, as well as other standard antidepressant and anxiety paradigms. Third, preliminary studies demonstrate that mice with a mutation of one of the key inflammasome components (NLRP3) are resilient to the effects of chronic stress (9).

The potential impact of this new area of research is further highlighted by the evidence that the inflammasome and pro-inflammatory cytokines are involved in metabolic (diabetes) and cardiovascular diseases that have high rates of comorbidity with depression. These findings suggest that the inflammasome-pro-inflammatory cytokines may represent a common nexus for stress, cardiovascular disease, and metabolic imbalances that underlie or contribute to these comorbid illnesses.

FUTURE DIRECTIONS

The new depression related targets identified by studies of rapid-acting antidepressants and pro-inflammatory cytokines are cause for optimism for new, rapid, and more effective treatments with novel mechanisms. New targets are likely to be revealed by further studies of the neurobiological

mechanisms underlying depression and treatment response. Major advances are being made at a fast pace using a variety of new techniques, such as optogenetic stimulation of neural circuits, and methods for sophisticated tracking of the connectome that underlies mood disorders (10,11).

Together these studies provide elegant approaches to identify the specific subsets of neurons that produce antidepressant effects in rodent models, as well as the extended circuits that underlie these effects. This will lead to further characterization of the neurotransmitter systems and intracellular signaling pathways that regulate these neurons and circuits, and thereby provide new targets for development of antidepressant medications that can normalize these disrupted depression pathways.

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DOI 10.1002/wps.20058

Taking disease seriously in DSM

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One of the most contentious topics in psychiatry is the concept of disease. It might seem odd that a medical specialty should debate the concept of disease, which is so central to medicine itself. Even in the ancient Hippocratic perspective, it was held that the art of medicine had three parts: the doctor, the patient, and the disease. To deny the disease concept would be to deny scientific medicine (1). But for two millennia, most physicians, following Galen, did just that. Galen said there was only one disease: variations of abnormalities of the four humours. One could not be more specific. Further, the one physical disease of the humours differed from person to person since the specific mixes of the four humours that were abnormal could vary infinitely in different persons. Galen "individualized" diagnosis for each person.

Psychiatry today is Galenic, not Hippocratic. The four humours have become a half dozen neurotransmitters, whose rise and fall we speculatively manipulate with drugs. Careful clinical observation and nosology of disease, the hallmark of Hippocratic thinking, have been replaced by penny-in-the-slot drug-for-symptom practice. This pseudoscience is justified on humanistic grounds as being individualized to the patient. We forget that such extremist individualization, which is the opposite of science, produced 2000 years of dehumanizing, harmful bleeding and purging.

It would take the Enlightenment for physicians to begin to rethink this rejection of disease, and return to the central role the idea held in the Hippocratic vision. Morgagni in the 17th century made the classic case for disease as reflecting a pathology of an organ in the body which would be the same in all individuals. Humours were not involved; individual differences need not matter. If you have cirrhosis of the liver, it looks the same in the king as in the pauper, in the male as in the female.

Virchow later codified Morgagni's view in the notion that medical disease involves organ pathology expressed in clinical syndromes. Kraepelin took up this mantle. After a century of detailed French nosology based on clinical symptoms, without much progress in corresponding pathology, Kraepelin made the guess that organ pathology would match better with the clinical course, not symptoms per se.

In the intervening century, under the distorting influence of time, psychiatrists have often reproached Kraepelin unfairly, saying that a century of research has proven him wrong. We have not found the pathology of dementia praecox or manic-depressive insanity, as he defined them, or as redefined later in schizophrenia and bipolar/unipolar illnesses. The reproach is unfair because Kraepelin proved to be correct in two major diseases: Alzheimer's dementia (named after Kraepelin's colleague who worked on those who had a chronic course beginning in old age, unlike dementia praecox, which began in young age), and general paralysis of the insane, which proved to be neurosyphilis in Kraepelin's later years, and was completely cured by penicillin within two decades after his death (2).

It is true that the two other major "disease processes", schizophrenia and manic-depression, have not been definitively proven to be diseases based on clear pathology (as in Alzheimer's dementia) or clear etiology (as in neurosyphilis). We can say, however, that after one hundred more years of research, a huge biological database has been created that confirms a major biological pathogenesis and probable biological etiology to both schizophrenia and manic-depression: ventricular enlargement, white matter abnormalities, amygdalar enlargement, hippocampal atrophy, second-trimester infections, and 80% heritability replicated in dozens of twin studies (3,4). This literature is not small, and it is consistent. We do not have the etiologies, but we do not have them for Alzheimer's dementia or migraine or epilepsies or hypertension or lupus either.

In this sense, I think Kraepelin has been proven correct: there are diseases of the mind, and schizophrenia and manic-depression are among them.

It is important to appreciate that Kraepelin did not classify diseases only; his approach, not unique to him, was to view diagnoses as two basic types: *disease processes* (*Krankheitsprozessen*) and *clinical pictures* (*Zustandsbilden*) (5). If we can scientifically validate a diagnosis – meaning we can delineate it from other diagnoses based on the classic validators of symptoms, course, genetics, biological markers, and/or treatment effects (6) – then we can say there is a *clinical picture*. To take the next step to claim a *disease process*, we would have to do research on that clinical picture and find a large amount of biological pathophysiology or biological etiology or both. This has been done more or less successfully with a few conditions: schizophrenia, manic-depression, obsessive-compulsive disease, autism. They are psychiatric diseases. But many clinical pictures may be scientifically valid, and yet not represent disease processes: they don't have major biological pathophysiology and etiology. These include: substance abuse and alcoholism, hysteria and its variants (post-traumatic stress illness, borderline personality), antisocial personality, neurotic depression and its variants (the many anxiety "disorders" of DSM), simple phobias, attention-deficit/hyperactivity disorder, anorexia/bulimia, grief, and extremes of personality traits (neuroticism, extraversion/introversion, risk-taking) (6). These latter clinical pictures may have a biological component, but they also have

environmental components that are equal if not larger (unlike the psychiatric diseases above) (7,8). Environmental trauma is a prerequisite to post-traumatic stress. The vast majority of persons with borderline personality have sexual trauma as a major etiology, a social cause (9). These clinical pictures are legitimate as clinical pictures, but illegitimate as diseases.

A major problem with contemporary psychiatry is that, after DSM-III in 1980, American nosology refused to distinguish disease processes from clinical pictures. By claiming to be "atheoretical", the term "disorder" was applied to all 300–400 diagnoses, so that clinicians and researchers are unclear as to what is what (10).

Red skies are not red apples; they are different things, despite sharing redness. But bipolar "disorder" is seen as similar to borderline personality "disorder", partly because the word "disorder" puts them at the same ontological plane, ignoring the fact that one condition is almost completely genetic, while the other is less than half genetic, and that one condition has a huge biological pathophysiology and appreciable animal modeling, while the other has a large social etiology, much more limited biological pathophysiology, and zero animal modeling (6).

Red skies are not red apples. The term "disorder" has confused our profession to the point that often we do not call diseases those conditions which are, and we often call diseases those which are not. Or, more commonly, we just reject the concept of disease, and practice as we like, justifying it, if asked, by biopsychosocial eclecticism (11).

DSM-III onward has produced a system that is proudly called "pragmatic" (12) by its leaders, but which reflects in fact an abdication of scientific responsibility. We reject the disease concept, or we apply it indiscriminately. Either way we do not take it seriously. Two generations of mostly failed biological research in etiology, pathogenesis, and pharmacology cannot be laid at the feet of Nature, for creating mental illness to be so complex that we fail to understand it. We should be willing to blame ourselves, for artificially making up "pragmatic" diagnoses without a serious attempt to try to understand Nature, to identify when diseases are present and when they are not. Van Praag warned the profession two decades ago, just before DSM-IV was produced (13). Our prior leaders in DSM-III and DSM-IV did not appear to be aware of this problem (14), and now they simply close their eyes to it.

Pragmatism has led to our current eclecticism, where psychiatrists practice as they wish, based on their personal opinions and dogmas, rather than practicing as scientific knowledge guides them. We cannot obtain that level of scientific knowledge until we take the disease concept seriously in psychiatric diagnosis.

This disease-oriented approach does not mean that we will presume that all psychiatric diagnoses are discrete diseases, as many have criticized Kraepelin for presuming. Van Praag (13) is correct that dimensional definitions may be more appropriate for some conditions, like extremes of personality. But this is an empirical, not a conceptual, matter. Let us do the scientific work and go where the data lead us, sometimes to categorical diseases, sometimes to dimensional extremes of the norm.

It is important not to get nihilistic, as have some biological researchers (13), and some postmodernist-oriented critics of biological psychiatry (15). Critics will point to the tortuous history of psychiatric diagnosis, and conclude that all diagnostic classifications are doomed to fail because mental illness is too complex: it is biopsychosocial (11), or "hybrid" (15), or multidimensional (13). Some psychiatric clinical pictures do not represent simple diseases, certainly, but the claim that none ever does is disproven by history (2,16): neurosyphilis was indistinguishable in many of its phases from what we see today in bipolar illness or schizophrenia. It was complex, polysymptomatic, and variable. And yet it was caused by a single pathogen.

Thus, I would part with Van Praag and with the NIMH Research Domain Criteria (RDoC) approach in the assumption that we should focus on biological or psychopathological dimensions alone (13,17). Progress will be made in that approach, as Wernicke long ago argued (18). But some progress still will require the categorical clinical nosology approach that Kraepelin promoted, and which has been proven valid in so many medical illnesses, dating from Morgagni to Alzheimer and the spirochete.

The key issue is not categories versus dimensions; it is science versus pragmatism (2). Will we continue to deny the primacy of science in favor of the pragmatic utilities of the profession, as the leader of DSM-IV explicitly advocates (12)? Or will we return to the fold of scientific medicine, and base our diagnoses on our best science to date, even if it has limitations or errors?

Scientific truth, after all, is nothing but corrected error. One cannot reach the truth if one is afraid to err.

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DOI 10.1002/wps.20082

The next stage for diagnosis: validity through utility

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Since the advent of descriptive psychiatry over two centuries ago, attempts to validate psychiatric diagnosis have been an ongoing source of controversy and disillusionment. The publication of DSM-III in 1980 certainly represented a watershed in its appropriate bid to enhance reliability, but it is apparent that, despite the huge effort and expense devoted to its successors, we have hit a wall in terms of validity and utility.

A succession of authors have described this failure (e.g., 1,2). The apparently new controversies which flared around the DSM-5 were really at the margins and the more fundamental criticisms were revivals of earlier debates about validity and utility, fueled by a solid dose of ideology, polemic and vested interest.

The field trials for DSM-5 indicate that even acceptable reliability remains elusive in clinical practice; for example, the key diagnosis of major depression achieved a very modest kappa value of 0.28 (3). Many of the growing number of diagnostic categories not only have poor reliability, but more importantly, limited validity. Furthermore, most fail to acknowledge the critical differences in clinical presentations associated with the age of onset of illness, the stage of illness, or its course (2,4).

Most criteria sets reinforce categories that have been derived almost exclusively from observations of people with late stage illness. Inevitably, these categories map poorly onto earlier, often less specific clinical presentations, which means that they hamper efforts to intervene early in the course of illness, where pre-emptive interventions are at a premium. Hence, the problem in most parts of the world is not that milder illnesses are being overtreated or inappropriately medicated (though this admittedly does happen to a proportion of people in some developed countries, such as the USA, where treatment has been reduced by a combination of limitations in mindset and health financing to mere prescribing). Rather, and more seriously, the earlier, and milder, stages of ultimately serious illnesses are routinely locked out of care of any kind until they demonstrate a severity and chronicity that certainly rules out any risk of overtreatment, yet at the same time inevitably and dramatically reduces the chances of response to treatment and recovery.

This conceptually and practically restricts psychiatry to a form of palliative care, which reinforces an unfair and false public perception of relative therapeutic impotence. The neglect and consequent underfunding of mental health care in every country is the key to this, but the lack of a diagnostic approach which allows for the early clinical stages of illness to be recognized and treated as well as the later stages is also to blame. The end result is that mental health has not seen the improvements in mortality and morbidity that have occurred in cancer and cardiovascular medicine in recent decades (5).

New research, only recently possible, is essential to determine the effectiveness and safety of such early treatment. Early treatment, as an antidote to therapeutic nihilism and the "soft bigotry of low expectations" must be carefully studied and debated as in cancer and other areas of health care, free of the polemic that too often plagues mental health from within and without.

Diagnosis is classification with utility (6). Diagnosis aims to characterize clinical phenotypes in a shorthand way that helps to distinguish those who are ill and in need of care from those who are not, and to enhance the selection of treatment and prediction of outcome. Utility in medicine is the ultimate test, but much of current psychiatric diagnosis has low clinical utility. Furthermore, our current classification systems presuppose the existence of multiple, independent and parallel pathways each leading to distinct diagnoses – an assumption that is out of keeping with contemporary family, genetic and neurobiological risk factor studies (7-9). A fundamental change is required.

The mental disorders are not static, sharply defined illnesses with separate etiologies and courses, but rather syndromes that overlap and develop in stages (10). Mental ill-health has to start somewhere. However, as critics are keen to point out, it is difficult prospectively to distinguish this from what passes for "normality" or "the human condition". It is certainly easier to recognize this distinction in retrospect from the vantage point of clear-cut and severe mental illness.

Most people experience the onset of mental health as intensifying and persistent emotional distress linked with problems with relationships and/or achievement. Eaton (11) has described how symptoms arise either from intensification of subjective experiences or behaviours that have been present for some time or from acquisition of new experiences or behaviours, or most commonly a combination of both. Daily human experience involves periodic and sometimes intense and mercurial changes in affect and salience in response to the social environment. When these become more prominent, they can be discerned as subclinical "microphenotypes", which wax and wane, interact sequentially or become confluent, and may mature or stabilize towards pure or hybrid "macrophenotypes" (12).

This process is undeniably fluid and dimensional, and several dimensions of psychopathology can be readily

identified, such as aberrant salience and affective dysregulation (13). While categories could be arbitrarily imposed within these dimensions, the concept of the syndrome, where various symptoms cohere in an increasingly strong and predictable manner, as well as impact on each other over time, is essential to mapping early clinical phenotypes (1,14).

This process is perhaps best considered in young people as they make the transition through adolescence to independent adulthood, since the incidence of mental illness is highest in young people aged between 12 and 25 years, with 75% of all major mental illnesses having their onset before the age of 25 years (15). The onset of mental illness is difficult to distinguish from the transient and normative changes in affect and behaviour that we all experience, especially in young people, where these experiences can be particularly marked (10).

It is now well-recognized that the major psychiatric disorders are typically preceded by prodromes – subthreshold states or microphenotypes – characterized by a varying blend of non-specific symptomatology, most commonly anxiety and depression, often associated with sustained and significant distress and disability. It is here that the failures of our current diagnostic system are most obvious.

While a proportion of these states will resolve with or without treatment, there is nevertheless a need for at least assessment, time-limited support and care for many, and the risk for persistence or progression in a substantial subset is real. This need for care typically precedes the diagnostic clarity demanded by our current late-stage diagnostic concepts, yet it is these that largely set the threshold at which access to care is offered in our underfunded global mental health care system. What is required is a simpler, more flexible hybrid model that accommodates dimensionality, yet provides a graded categorical framework that facilitates early assessment, tolerates ambiguity, minimizes stigma, and has utility for patients, clinicians and researchers.

The clinical staging model, adapted from general medicine, provides such a framework (2,4). This model sets aside the current diagnostic boundaries to include the full spectrum of disorder, including its continuities with psychopathology in the healthy population, to place a strong diagnostic emphasis on where a person sits in the evolution of the clinical phenotype. Stage is determined on the dimensions of severity of symptoms, distress, disturbances in relationships and functioning, and the persistence of these changes, rather than any specific syndromal content, which can add specificity within a matrix model. It is primarily an agnostic, rather than diagnostic, framework, which recognizes that persistent and multiple microphenotypes of disturbance can justify a need for care on their immediate merits as well as on the basis of the risk for progression to more familiar, specific and stable macrophenotypes; while also acknowledging the need for blending dimensional and categorical models, as was originally hoped for DSM-5.

The staging model ultimately holds out the prospect of a more useful framework for clinicians, in that it acknowledges the "grey zone" of ambiguity between what may simply be transient distress and disturbance, and what may prove to be the onset of a more serious mental illness, as well as the substantial cumulative public health burden of what is currently considered as sub-threshold illness. It provides a more appropriate guide for the choice of therapeutic intervention, by ensuring that the treatments selected are proportional to both the clinical need and the risk of illness progression, while minimizing the risk of overtreatment and consequent unnecessary adverse effects, including that of undertreatment. The "soft entry" aspect also has the welcome effect of dispelling stigma.

These elements deal with many of the fears expressed by critics of "diagnostic inflation". Clinical staging in fact represents diagnostic deflation, in proposing a large reduction of the array of syndromal categories, yet makes no apology for extending the boundaries of mental health care to the earliest point from which benefits can flow safely and without stigma and hence outweigh risks. This goal is especially critical in young people, who bear the major burden of the initial incidence of mental disorders, and thus have the most to lose from late or crude treatment in terms of their developmental trajectories and fulfillment of potential.

Twenty-first century health care places an increasing emphasis on personalized medicine, with the goal of tailoring treatment to the individual. Clinical staging aims to bring us closer to other branches of medicine and pave the way for biosignatures to play a stronger role in individual diagnosis and thus for personalized or stratified medicine in psychiatry (2,14). Over the past two decades, research from areas as diverse as genomics, neurobiology and epidemiology has transformed our thinking on the mental disorders, which we now understand to be disorders of the brain and of development.

These advances have put the concept of pre-emptive psychiatry tantalizingly within reach (16). However, pre-emptive psychiatry requires predictive tools that can be integrated into an appropriate diagnostic framework to assess the risk and course of illness, as well as the response to therapy. The clinical staging model, with its explicit recognition of the evolution of mental disorders from relatively undifferentiated phenotypes to clear syndromes, has heuristic potential in facilitating the integration of our growing understanding of the genetic, biochemical and neurobiological biosignatures of mental illness into our diagnostic framework. This would be a major advance, not only in the quest for personalized medicine, but also for validity in psychiatric diagnosis.

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DOI 10.1002/wps.20080

Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies

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Although non-adherence is common across all branches of medicine, psychotic disorders pose additional challenges that increase its risk. Despite the importance of non-adherence, clinicians generally spend too little time on assessing and addressing adherence attitudes and behaviors. Importantly, how adherence is measured significantly impacts the findings, and the most frequently employed methods of asking patients or judging adherence indirectly based on efficacy or tolerability information have poor validity. Novel technologies are being developed that directly assess adherence and that can also be used to both provide real-time feedback to clinicians and serve as an intervention with patients. Several treatments are available that can positively impact adherence. Among psychosocial interventions, those combining multiple approaches and involving multiple domains seem to be most effective. Although long-acting injectable antipsychotics are theoretically a very powerful tool to assure adherence and signal non-adherence, recent results from randomized controlled trials failed to show superiority compared to oral antipsychotics. These data are in contrast to nationwide cohort studies and mirror-image studies, which arguably include more representative patients receiving long-acting antipsychotics in clinical practice. This disconnect suggests that traditional randomized controlled trials are not necessarily the best way to study interventions that are thought to work via reducing non-adherence. Clearly, non-adherence is likely to remain a major public health problem despite treatment advances. However, increasing knowledge about factors affecting adherence and leveraging novel technologies can enhance its early assessment and adequate management, particularly in patients with psychotic disorders.

Key words: Non-adherence, psychosis, schizophrenia, risk factors, assessment, interventions

(World Psychiatry 2013;12:216–226)

Adherence to treatment prescriptions is a critical aspect of health care (1); however, it is often given far less attention in routine clinical practice than necessary. Even though terms such as adherence or compliance are far from ideal in characterizing the interaction of clinicians, patients and medication-taking, they remain in widespread use. We need to develop better methods to de-stigmatize the challenges associated with taking medication as prescribed and create a better enabling environment of education, shared decision-making and responsibility in managing illness. All of this is predicated on the assumption that reaping the expected benefits of efficacious medications (and other treatments) depends upon taking them appropriately.

Medication-taking in the acute care setting is often facilitated by health care professionals, creating a sense of confidence among practitioners that adherence will continue in the post-acute setting. However, the management of many chronic diseases, such as psychotic disorders, suffers from enormous problems in medication adherence, leading to countless avoidable emergency room visits and days in the hospital, as well as suboptimal overall outcomes (2,3). It is estimated that 50% of patients suffering from chronic illness are not taking medication as prescribed after six months (4). The cost of non-adherence in the United States alone could be up to 300 billion dollars per year (5). Both physicians and patients have been shown to overestimate the amount of medication that a patient is taking (6), and physicians in general spend remarkably little time in addressing this issue, which is so critical to the success of their efforts (7,8).

Definitions and measurement strategies in this area vary considerably. In general, the simplest strategies for measuring adherence are likely to be inaccurate, and the most potentially informative strategies are invasive and/or expensive (1). Clearly, there are no specific predictors that are universally reliable and valid. A range of factors influence medication adherence and an individualized approach is important in order to intervene successfully.

In this review, we focus specifically on patients with psychosis, primarily schizophrenia. We discuss issues of definition and measurement, and review data about non-adherence among patients receiving naturalistic treatment for psychosis and those participating in clinical trials. We then discuss factors contributing to non-adherence and strategies to facilitate/enhance adherence.

DEFINITIONS AND MEASUREMENT

Ideally, patients should be taking all of their medications as prescribed. However, adherence is often considered to be "good", or patients are described as "adherent", if they are taking at least 70 or 80% of their medication. Some reports try to break adherence into multiple categories, including fully

adherent, partially adherent and non-adherent (9). However, in some cases, missing 20-30% of one's medication could have clinically significant consequences, while in other cases it might not. The type of medication, formulation, dosage and dosage frequency, along with individual characteristics, such as absorption and metabolism, phase of illness and vulnerability to disease recurrence or progression, will influence the impact of specific levels of non-adherence. Therefore, definitions will and should vary depending upon the context.

Although monitoring of adherence has always been an issue in health care, our ability to accurately determine the degree of adherence among our patients is limited. Methods available for monitoring adherence are generally divided into direct and indirect (1). Every method has its drawbacks and there is no universally accepted "gold standard", as summarized in Table 1.

Table 1 Methods for monitoring medication adherence and their drawbacks

Method	Drawbacks
Patient report	Unreliable (forgetting, hiding)
Patient self-assessment questionnaire	Unreliable (forgetting, hiding)
Patient diary	Unreliable (forgetting, hiding)
Informant report/questionnaire	Unreliable (lack of information, opinion)
Pill count	Somewhat unreliable, pills may not have been ingested
Clinical response/adverse effects	Unreliable, as presence/absence of efficacy and adverse effects is multiply determined
Assessment of physiologic response	Unreliable, as physiologic response is multiply determined
Blister pack	Somewhat unreliable, pills may not have been ingested
MEMS cap	Somewhat unreliable, pills may not have been ingested
Electronic pill trays	Somewhat unreliable, pills may not have been ingested
Pharmacy/prescription refill record	Somewhat unreliable, pills may not have been ingested
Observed ingestion	Highly resource intensive, can lead to conflicts
Measurement of drug in bodily fluid or blood	Only cross-sectional; improved adherence preceding a clinic visit ("white coat compliance")
Measurement of biomarker	Only cross-sectional; requites additive
Hair analysis	Requires long hair, requires a lot of strands, special lab needed
Ingestible event marker/digital health feedback system	Requires accepting a microelectronic chip in the pill and wearing a receiver on a patch on the torso; to date still expensive and not widely available

MEMS – medication event monitoring system

In some situations, patients can be observed swallowing their medication, and liquid preparations or rapidly dissolving formulations could facilitate the process. Measurement of drug concentration in blood or other bodily fluids can give useful information on adherence as well as on individual variability in absorption and metabolism. However, a random blood level may convey an only partial story, unless clinicians have done an observed ingestion and pharmacokinetic study to determine what the blood level "should be", if the patient were fully adherent. A biologic marker could be added to the drug as another method. These approaches could be considered expensive and burdensome to the patients and/or clinician. On the other hand, there are situations where blood level monitoring is a necessary part of treatment, such as with medications that have an established therapeutic window and/or common risk of toxicity (e.g., lithium).

Indirect methods of monitoring include asking the patient (the easiest and often most unreliable method). Measuring physiologic response associated with a particular drug or using clinical therapeutic response as a proxy for adherence are also strategies that are employed, but are fraught with potential problems. The clinical state can be influenced by many factors other than treatment and, for example, some patients with schizophrenia or bipolar disorder may remain asymptomatic for months or even years without medication.

A common method to assess adherence has been pill counts (i.e., counting the number of pills remaining in a medication bottle). However, it is easy for a patient to discard some pills or transfer them to another bottle. Unannounced home visits may get around this problem, but such efforts are clearly expensive and not always welcome. The use of electronic monitoring devices, such as medication event monitoring system (MEMS) pill bottle caps, is also common, but costly (10). The device records the date and time that the bottle was opened. However, this does not confirm that the patient has actually ingested the medication.

Electronic pill trays or boxes are also available, which can record the opening of the box and/or transmit a message to a third party when the box has not been opened (11). Such devices require an initial investment and are by no means foolproof. More recently, a novel technology, referred to as a digital health feedback system (12), has been developed that embeds an "ingestible event marker" in the tablet or capsule, which upon contact with gastric fluid electrolytes emits a unique signal, which is transmitted through bodily tissue to a small receiver worn in a patch on the torso. This device then transmits a signal to a cell phone indicating the time (and date) that the medication has been ingested. The ingestible chip is excreted in the feces and the signal that it emits is similar to that picked up by an electrocardiogram and is not transmitted outside of the person's body. The mobile phone stores the de-identified data and periodically transfers it to a password protected server

Table 2 Studies of non-adherence to medication in patients with major medical conditions (data from 14)

Medical condition	Number of studies	Non-/poor adherence
Diabetes mellitus	23	32.5%
Pulmonary diseases	41	31.2%
Infectious diseases	34	26.0%
End-stage renal disease	20	30.0%
Eye disorders	15	27.4%
Infectious diseases	34	26.0%
Obstetric and gynecological disorders	19	25.2%
Ear, nose, throat and mouth disorders	30	24.9%
Cardiovascular diseases	129	23.4%
Skin disorders	11	23.1%
Genitourinary and sexually transmitted diseases	17	23.0%
Cancer	65	20.9%
Gastrointestinal disorders	42	19.6%
Arthritis	22	18.8%
HIV/AIDS	8	11.7%

using secure encryptions. The adhesive monitor also captures physiologic metrics, including heart rate, body position, skin conductance, physical activity and sleep characteristics.

A major premise underlying this type of approach is that a large proportion of non-adherence, particularly among people with psychiatric/cognitive disorders, is not due to a willful, conscious refusal to take medication, and that any technology which can aid and empower patients and caregivers to play a more informed role in their own health care will offer a way to enhance adherence. Accurate, readily accessible data on patterns of patient medication-taking can facilitate that process. In addition, linking data on adherence patterns to relevant physiologic and behavioral measures, such as sleep and activity, can allow for even greater information sharing regarding health status, treatment targets and specific medication effects.

A pilot study in 28 patients with schizophrenia and bipolar disorder has found this approach to be feasible and acceptable to patients (12). We cite this as an example of a monitoring technique that can also serve as an "intervention" platform to facilitate adherence. In addition, it is likely that further technological innovations will enhance and extend such opportunities.

Prescription refills can also be used as a measure of adherence. Although initially such data were only available in "closed" systems, such as the Department of Veterans Affairs Health Care System, health management organizations, or single service payment systems (e.g., Medicaid/Medicare), broader attempts have been implemented (13). Here too, data are potentially flawed, since filling a prescription by no means insures that the medication was ingested. However, absence of prescription refills is a strong indication of non-adherence. It is particularly important to look at prescription refills over time in order to produce a metric, such as the medicine prescription refill ratio.

EPIDEMIOLOGY

According to a meta-analysis that focused on non-psychiatrist physician prescriptions (including exercise, diet, vaccination etc., as well as medication taking) (14), the average study-defined adherence was highest in HIV disease (88.3%, 95% CI: 78.9-95.2%, 8 studies), followed by arthritis (81.2%, 95% CI: 71.9-89.0%, 22 studies), gastrointestinal disorders (80.4%, 95% CI: 73.9-86.2%, 42 studies) and cancer (79.1%, 95% CI: 75.9-84.2%, 65 studies). The average adherence in other physical diseases ranged between 74 and 77%, including skin disorders (76.9%, 95% CI: 66.5-85.9%, 11 studies); cardiovascular diseases (76.6%, 95% CI: 73.4-79.8%, 129 studies), and infectious diseases (74.0, 95% CI: 67.5-80.0%, 34 studies). Patients with pulmonary diseases (68.8%, 95% CI: 58.5-75.8%, 41 studies) and diabetes mellitus (67.5%, 95% CI: 58.5-75.8%, 23 studies) had the lowest adherence (14) (Table 2).

Most studies in psychotic patients reported high frequencies of non-/poor adherence (Table 3). A study based on Medicaid beneficiaries in San Diego County, California (N=2,801) assessed patients' adherence by utilizing pharmacy records between 1998 and 2000. Using cumulative possession ratio for defining adherence, 24% of all schizophrenia patients were non-adherent (ratio=0.00-0.49), 16% were partially adherent (ratio=0.50-0.79), and 19% were excess fillers (ratio >1.10) (19). Based on Veterans Affairs pharmacy data for patients who received antipsychotic medication between 1998 and 1999 (N=63,214), poor adherence (defined as medication possession ratio <0.8) was seen in 40% of patients (20). Another study (22) also used Veterans Affairs data from the fiscal year 2000-2003 (N=34,128) and the same non-adherence definition, finding that poor adherence was seen in 36.0-37.1% of patients (mean medication possession ratio in patients with poor adherence during the study years: 0.42-0.47). Interestingly, the authors found that adherence fluctuated over time in some patients. Altogether, 61% of patients had adherence difficulties at some point over the 4-year period, and approximately 18% had consistently poor adherence, 43% were inconsistently adherent, and 39% had consistently good adherence (22).

Table 3 Studies of non-adherence to medication in patients with psychotic disorders

Psychotic population	Number of patients	Study type	Measurement method	Non-/poor adherence
Schizophrenia, Norway (15)	280	Naturalistic	Serum concentration	58.4%
Schizophrenia, USA (16)	876	Naturalistic	Self-report	48.4%
Schizophrenia, meta-analysis across 39 studies (17)	40-423 per study	Mixed	Mixed	40.5%
Schizophrenia, Nigeria (18)	313	Naturalistic	Self-report	40.3%
Schizophrenia, Medicaid beneficiaries (19)	2801	Naturalistic	Pharmacy records	40%
Schizophrenia, USA (20)	63,214	Naturalistic	Pharmacy records	40%
Schizophrenia, first episode, 1 year (21)	400	RCT	Discontinuation against medical advice	37.1% (Kaplan-Meier estimate); 28.8% (raw)
Schizophrenia, USA (22)	34,128	Naturalistic	Pharmacy records	36.0-37.1%
Schizophrenia, France (23)	291	Naturalistic	Self-report	30.0%
Psychotic disorders, meta-analysis across 86 studies (24)	23,796; 20-2257 per study	Mixed	Mixed	25.8%
Psychosis, Australia (25)	1825	Naturalistic	Self-report	11.8%
Schizophrenia, first episode, 1 year (26)	498	RCT	Informant and observer report scale	11.6%
Schizophrenia, first episode, 1 year (27)	151	RCT	Dropout from the study due to non-compliance (self-report)	11.3%
Schizophrenia, chronic, within 2 months of exacerbation (28)	300	RCT	Dropout from the study due to non-adherence	8.0%
Schizophrenia, chronic, stable, 1 year (29)	365	RCT	Dropout from the study due to poor compliance	4.1%
Schizophrenia, chronic, stable, 2 years (30)	337	RCT	Dropout from the study due to non-compliance	3.7%
Schizophrenia, chronic, after acute relapse, 1 year (31)	1294	RCT	Dropout from the study due to non-compliance	3.0%
Schizophrenia, first episode, >2 years (32)	555	RCT	Dropout from the study due to non-compliance	2.3%

RCT – randomized controlled trial

Lacro et al (17) reviewed the studies published between 1980 and 2000 which identified risk factors for medication non-adherence in patients with schizophrenia. They included data from 15 cross-sectional, 14 prospective and 10 retrospective studies, with a mean number of 110±80 patients per study (median=80, range=40-423). Across these studies, the unweighted mean non-adherence frequency was 40.5% (median=40%, range=4-72%). Analyzing only the ten studies in which trained personnel measured adherence and in which adherence was defined as "regularly taking medication as prescribed", the weighted mean adherence frequency was 41.2% (median=39%, range=20.0-55.6%). When only the five studies that defined adherence as "taking medications as prescribed at least 75% of the time" were analyzed, the weighted mean adherence frequency was 49.5% (median=47.0%, range=37.7-55.6%) (17). Nosé et al (24) systematically reviewed studies that reported non-adherence with medication and scheduled appointments in community settings. In the 86 studies included (71% prospective, 29% cross-sectional) from the US (44%), Europe (36%) and other areas (20%), involving 23,796 patients (253.8±440.4 per study, median=103, range=20-2257), the overall weighted mean non-adherence by study definition was 25.8% (95% CI: 22.5-29.1%).

Non- or poor adherence in more recent studies was reported to be 48.4% (USA, nationwide, N=876, self-report) (16), 11.8% (Australia, N=1825, self-report) (25), 40.3% (Nigeria, N=313, self-report) (18), 30% (France, N=291, self-report) (23) and 58.4% (Norway, N=280, serum concentration) (15) (Table 3). Thus, non-adherence figures vary widely, presumably reflecting differences in the targeted population, definitions and measurement methods. However, of note, studies using more firm measurement methodology, such as pill count, electronic monitoring, and blood drug level, tend to indicate higher non-adherence (14,15,23,33). In addition, the duration of follow-up certainly also influences the observed frequencies of non-adherence.

Unlike naturalistic studies, controlled trial settings allow us to assess patients'

Table 4 Factors associated with non-adherence

Patient characteristics
Sex, age, race
Education
Socio-economic status
Knowledge
Perceived need for treatment (insight)
Motivation
Beliefs about treatment risks and benefits
Past experiences/"transference"
Past history of adherence
Self-stigma
Illness characteristics
Illness duration (first episode, chronic)
Illness phase (acute, maintenance, etc.)
Symptom type and severity (e.g., negative symptoms, depression, demoralization)
Cognitive function
Lack of insight
Substance use
Comorbidities
Degree of refractoriness
Potential for relatively asymptomatic intervals or "spontaneous remission"
Medication characteristics
Efficacy (consider different domains)
Effectiveness
Adverse effects (of relevance for the patient)
Delivery systems/formulation
Dosage frequency
Cost/access
Provider/system/treatment characteristics
Therapeutic alliance
Frequency and nature of contact with clinicians

Provider/system/treatment characteristics (*continued*)
Duration of treatment (past and expected)
Complexity of administration
Accessibility and cohesion of services
Access to care
Continuity of care
Reimbursement
Ability to monitor adherence
Provision of psychoeducation
Availability of trained psychosocial treatment specialists
Evaluation of obstacles to adherence
Access to alternative formulations (e.g., long-acting injectable antipsychotics)
Complexity of administration
Family/caregiver characteristics
Nature of relationship
Perceived need for treatment (insight)
Beliefs about treatment risks and benefits
Knowledge, beliefs, attribution
Involvement in psychoeducation
Involvement in adherence monitoring
Stigma
Environmental characteristics
Physical environment
Level of supervision
Orderliness
Safety and privacy
Stigma
Extrafamilial support system
Other resource characteristics
Financial
Transportation

adherence in a prospective manner, often with more accurate methods, such as pill counts or blood levels. In addition, since the characteristics of patients (including socio-demographic, diagnostic and biological variables) are known in detail, it is easier to examine potential predictors for non-adherence. However, there is likely to be a selection bias, in that patients recruited in trials are required to undergo consenting procedures, and are therefore likely to be more adherent and to have better cognitive function. Moreover, participation in a controlled trial alters the ecology of treatment delivery and experience. Patients in clinical trials are also prone to receive more and different types of attention than those in routine care, from measures of adherence to reminders to attend clinical/research assessment sessions, or the provision of free medication (1,34,35). Furthermore, adherence is often measured only among patients who continued in the trial, while patients who are non-adherent might be more likely to drop out of the study. Indeed, patients who drop out from the study because of non-adherence are often reported as "withdrew consent" or "patient decision", and the underlying reasons are rarely examined in detail. Thus, for several reasons, it is fair to assume that adherence is much higher in clinical trials than in routine care.

In recent long-term maintenance studies in patients with schizophrenia, the dropout due to non-adherence was as low as 2.3% (N=555, first episode psychosis patients, ≥2 year duration) (32), 3% (N=1294, chronic patients after acute relapse, 1 year duration) (31), 3.7% (N=337, stable patients, oral treatment arm, 2 year duration) (30), 4.1% (N=365, stable chronic illness, 1 year duration) (29), 8% (N=300, unstable patients within 2 months of exacerbation, oral treatment arm, 1 year duration) (28), 11.3% (N=151, first-episode patients, 1 year duration) (27), and 11.6% (N=498, first-episode patients, 1 year duration) (26) (Table 3). However, these figures do not include broader non-adherence.

A randomized controlled trial in first episode psychosis (N=400) reported the number of patients who discontinued treatment against medical advice prior to completing 1 year of treatment (21). The authors regarded these patients as "non-adherent" (raw data: 28.8%, Kaplan-Meier estimate: 37.1%), and this approach might better reflect the occurrence of non-adherence in a more general fashion. In this study, poor treatment response ($p<0.001$) and low medication adherence ($p=0.02$) were independent predictors of discontinuation against medical advice, and ongoing substance abuse, ongoing depression, and treatment response failure significantly predicted poor medication adherence ($p<0.01$) (21).

FACTORS CONTRIBUTING TO NON-ADHERENCE

There are many factors associated with potential non-adherence (17,36), summarized in Table 4. Physicians

usually spend an inadequate amount of time assessing these factors, and patients do not generally communicate their intentions regarding medication-taking to clinicians. There is not a non-adherent personality type, and there is no standardized, universally valid and reliable approach to predicting adherence behavior. Race, sex and socio-economic status are not consistent predictors of poor adherence (1). It is also important to recognize that non-adherence is not necessarily irrational or misguided behavior. Non-adherence is highly influenced by patient knowledge, attitudes towards their illness and the medication, as well as past experiences with their illness and its treatment. In particular, the perceived risks and benefits of the treatment and of the illness (i.e., "illness insight") play a major role in adherence behaviors. Furthermore, lack of support systems and fragmented health care contribute to non-adherence.

In the case of individuals with psychotic disorders, there are a number of unique challenges. Lack of insight or lack of awareness of the illness itself (17,21) is a particular challenge in schizophrenia. In addition, the cognitive impairment frequently seen in psychotic disorders and present to some degree in a majority of individuals with schizophrenia is another important factor (37-39). Although adverse effects of medication are often assumed by clinicians to be a major predictor of non-adherence, the results of patient surveys vary, and some specific adverse effects have more impact than others. In addition, no doubt some patients discontinue medication because of adverse effects that they might not even identify as such. Akinesia, for example, might not be identified by the patient as an adverse effect of medication, as might also be the case with akathisia. Even clinicians can fail to recognize or misdiagnose these phenomena (40).

Although clinicians might underestimate its impact, inadequate response to treatment, even as early as two weeks after initiation of pharmacotherapy (41), is one of the most frequent reasons for discontinuing clinical trials. The complexity of the prescribed regimen has also been shown to influence adherence (17). Although clinicians and pharmaceutical companies are aware of the need to simplify regimens, this remains a problem for many patients.

Patients might also suffer from lack of information as to what to expect from treatment in terms of the risk of specific side effects, time course of response, or degree of impact that a treatment might have in specific domains. The nature and extent of psychoeducation coupled with an optimum therapeutic alliance has been found to be an important predictor of adherence behavior (17,38). Shared decision-making is a concept which incorporates these elements (42).

Cost and overall access remain obstacles in many cases, and the transition from inpatient to outpatient care or the transfer from one provider/payer to another can impact both access and cost to the patient. These problems might be included under the rubric of inadequate discharge planning or inadequate clinical follow-up (17,21,43).

Stigma has also been associated with non-adherence in schizophrenia (44). Although progress has been made in altering perceptions about this illness, the public at large remains poorly informed and stigma remains a major problem.

A particular problem among early phase patients and those who have had a generally good response to treatment is the belief that treatment is no longer necessary. The treatment of asymptomatic disease is always a challenge, but in psychotic disorders this is a particular problem. In addition, among patients in stable remission from symptoms, the time course of relapse is such that medication discontinuation might not result in an exacerbation or relapse for many months (or even years) and this can contribute further to a false sense of security that treatment is no longer necessary.

Some clinicians continue to suggest that those patients who discontinue medication and relapse as a result will be more convinced about the need for continuous treatment. Robinson et al (39) reported on a group of first episode patients who had experienced a relapse due to drug discontinuation, but then went on to discontinue medication yet again after recovering from the prior relapse. A history of significant extrapyramidal side effects during the index admission as well as poorer cognitive function and social educational background were significant predictors of medication discontinuation in this context (39).

It is also important to recognize that adherence can vary across the multiple medications that a patient might be taking. Decisions regarding each medication might be influenced by different factors, such as the awareness of what each specific drug is intended to do. As indicated in Table 4, there are also characteristics of the medication that should be considered. Patients' perception/experience of medication efficacy is an important element. However, in a complex disease such as schizophrenia, medication might be efficacious in one domain (e.g., positive symptoms), but much less so in another domain (e.g., negative symptoms and/or cognitive dysfunction). Patients need to understand what degree of improvement and in which domains they should expect.

Similarly, adverse effects vary from medication to medication and will also be influenced by the phase of illness, with drug-naïve or early phase patients being more sensitive to many side effects. The formulations that are available (e.g., liquid, fast dissolving, long-acting injectable), as well as the number of doses required per day, are also important factors in influencing adherence.

Provider/system characteristics are also to be considered. They include the amount of time devoted to assessing factors that might influence adherence, providing psychoeducation (to both patients and families if appropriate), and creating an atmosphere of shared decision-making and therapeutic alliance. Frequency and continuity of care and the ability of clinicians to monitor adherence using the various

methods discussed previously are also important.

The availability of case managers, health coaches and/or peer counselors can also be valuable in facilitating adherence. Another potentially influential domain is family/caregiver characteristics. The extent to which these parties are involved in helping to manage the illness and the amount of psychoeducation that they have received is also important. Clinicians should attempt to understand and take into consideration their knowledge, beliefs and attitudes as well as the nature of their relationship with the patient and their potential role in facilitating and monitoring medication taking.

THE ROLE OF INTERVENTIONS TO IMPROVE OR MAINTAIN ADHERENCE

Traditionally, psychoeducation has been the main strategy to improve adherence, but new psychosocial approaches have been suggested. Needless to say, optimizing the pharmacotherapy is a critical step towards better adherence. Moreover, new technology may enable us to enhance it further. These psychosocial, pharmacological and technological approaches should supplement each other to maximize their potential effect.

Psychosocial interventions

Various psychosocial interventions have been proposed and studied. Over 50 randomized controlled trials have been reported to date (45). Some examined a specific intervention as monotherapy, some examined the combination of two or more types of interventions (46). The target of the interventions varies and includes the individual, group, family, or community (such as assertive community treatment, ACT) (47). It is difficult to draw clear lines between interventions and to categorize them in specific groups, but the key components include psychoeducation, cognitive-behavioral therapy (CBT), and motivational interviewing.

Psychoeducation aims to teach patients or families to better understand the illness, appropriate medications and potential side effects. It targets individuals or patient groups, sometime families, and involves counseling sessions, and/or use of written/audiovisual materials. It has been the mainstay of strategies to improve adherence for years; however, the results of studies do not appear to be consistently positive. Studies examined psychoeducation without adjunctive components, such as behavioral intervention or family involvement, and showed that it was not efficacious in improving adherence (45-48). Nevertheless, psychoeducation provided together with family involvement seems to have better efficacy than when given to patients alone (48), and psychoeducation becomes more efficacious when other strategies are combined, such as environmental or behavioral interventions (45). A recent meta-analysis (44 trials, N=5142) included randomized controlled trials examining all didactic interventions of psychoeducation, such as programs addressing the illness from a multidimensional viewpoint, including familial, social, biological and pharmacological perspectives (but excluding interventions with elements of behavioral training, such as social skills or life skills training). In this meta-analysis, the incidence of non-adherence was lower in the psychoeducation group (49).

CBT is a psychotherapeutic approach that challenges patients' cognitive processes and maladaptive behaviors through goal-oriented, explicit procedures. In CBT, adherence is conceptualized as a coping behavior based on an individual's perception of the illness and his/her beliefs about medications (46). CBT therapists help patients identify and modify negative automatic thoughts about medications and use guided discovery to strengthen patients' beliefs that taking medication is associated with staying well and achieving goals (36,50).

Motivational interviewing is a semi-directive, client-centered counseling style used to enhance behavior change by helping clients to explore and resolve ambivalence (51). This technique, which was originally developed for treating addiction, has been applied to a broad range of patients in order to assess their level of motivation to adopt medication-adherent behaviors. In motivational interviewing, the clinician tailors the intervention to the patient's current level of motivation. Clinicians try to better understand patient's perspective through expressing empathy, supporting self-efficacy in an unwavering manner, highlighting discrepancies between the patient's current health behaviors and core values, and working with resistance. Patients may then be better able to identify their own solutions to potential barriers to medication adherence. The process includes five phases, consisting of pre-contemplation, contemplation, preparation, action and maintenance (52).

Various interventions combining the components mentioned above have been developed, and their efficacy in improving adherence has been examined. Compliance (adherence) therapy is a form of CBT which incorporates motivational interviewing and psychoeducation to help patients understand the connection between relapse and medication non-adherence (53). Some studies have shown the efficacy of compliance therapy to improve insight, treatment acceptance, and adherence (54-56), but others have not (57,58). Other psychological interventions with positive results include adherence-coping-education (ACE) (59), interpersonal and social rhythm therapy (60), and cognitive adaptation training (CAT) (36). CAT is a strategy that uses individually tailored environmental supports such as signs, checklists and electronic devices to cue adaptive behaviors in the patient's home environment and help compensate for cognitive deficits. CAT significantly improved adherence and reduced relapse compared to treatment as

usual in patients with schizophrenia (36). Such environmental support, needless to say, can help patients to be adherent to the medication, but programmatic interventions, such as ACT and intense case management (ICM), are also reported to be effective. For example, meta-analyses which examined ACT and ICM showed that each intervention was more efficacious in retaining patients in contact with services and preventing hospitalization than standard community care (61,62).

Thus, studies have examined various interventions that are sometimes similar, or that combine multiple approaches. Results are mixed, but interventions specifically designed to improve adherence with a more intensive and focused approach, and interventions combining several strategies, such as CBT, family and community based approaches, have shown more consistently favorable results (45).

Pharmacologic interventions

Drug treatment should always be carried out trying to balance efficacy and adverse effects. Clinicians have to optimize the recommendations by taking into consideration the treatment history, response, comorbidity, side effects, etc. Side effects should be avoided as much as possible by drug choice or dose adjustment, but adding another class of medication, such as anticholinergics for extrapyramidal side effects, can also be an option. Most importantly, patients should be given sufficient information about the medication and be part of the decision making process (63).

Pharmacological strategies which may enhance adherence include switching, dose adjustment, treating side effects, simplifying the treatment regimen, and the use of long-acting injections. Simplifying the medication regimen can be helpful especially for patients with cognitive impairment. A study examined this issue and found that decrease in dosing frequency helped patients to be more adherent. Using a US Veterans Administration data base, Pfeiffer et al (64) examined the medication possession ratio among patients with schizophrenia. Patients who had a decrease in dosing frequency (N=1,370) had a small but significant increase in mean ratio compared with patients (N=2,740) without a dosing frequency change ($p<0.001$). However, patients who were already in simple and stable regimens did not seem to benefit from further simplification. There were no significant differences between those receiving once-daily dosing and those receiving more than once-daily dosing (64).

The development of long-acting injectable (LAI) medication was intended to facilitate the benefits of pharmacological treatment by reducing the all-too-likely variability in ingestion. Major guidelines (36,65-68) recommend the use of LAIs when non-adherence is an issue. LAIs offer not only "guaranteed" medication delivery, but also other potential advantages, such as immediate awareness of non-adherence, no abrupt decline in blood level after a missed injection, freedom from daily medication and reducing concerns about medication adherence as a source of family conflict or tension (69).

Thus, LAIs are intended to facilitate adherence and thereby reduce relapse rates. However, the results from recent, large, randomized controlled trials have been discouraging. Rosenheck et al (70) conducted a federally funded trial and reported that risperidone-LAI was not significantly superior in preventing hospitalization compared to clinicians' choice oral antipsychotics. Similarly, in a study comparing risperidone-LAI with any oral antipsychotic, Schooler et al (71) did not find a significant difference between the two treatment groups. A recent meta-analysis based on 21 randomized controlled studies (including the two studies mentioned above) found that LAIs were not significantly superior to oral antipsychotics (N = 4,950, risk ratio=0.93, 95% CI: 0.80-1.08, $p=0.35$), both in primary analyses and across multiple secondary analyses (35).

However, the results from randomized controlled trials are in strong contrast to some naturalistic studies. For example, Tiihonen et al (72) reported in a nationwide Finnish cohort that the risk of rehospitalization with LAIs was one-third that of oral antipsychotics. Moreover, most LAIs showed significant superiority compared to each oral counterpart regarding all-cause discontinuation.

Mirror-image studies, which compare the periods pre- and post-LAI introduction within subjects, are another way to examine the efficacy of LAIs. In a recent meta-analysis based on 25 mirror-image studies (N=5,940), Kishimoto et al (73) reported that LAIs showed strong superiority over oral medication in preventing hospitalization (16 studies, N=4,066, risk ratio= 0.43, 95% CI: 0.35-0.53, $p<0.001$) and decreasing the number of hospitalizations (15 studies, 6,396 person/years, rate ratio=0.38, 95% CI: 0.28-0.51, $p < 0.001$).

Given such a discrepancy of the results between randomized controlled trials, nationwide cohort studies and mirror-image studies, a question arises as to what is the best way to assess LAI effectiveness in comparison to oral medication. As mentioned before, participants in clinical trials might over-represent patients with better adherence to treatment, lower illness severity, and better cognitive capabilities. Perhaps most importantly, participation in a clinical trial can have a substantial impact on adherence. At the same time, non-randomized, open, naturalistic or mirror-image studies can have their own limitations, such as selection bias, expectation bias, and time effect. Therefore, we need to be thoughtful about how to best use evidence from multiple types of trial design as well as measurement of adherence and non-adherence related outcomes. Generalizability of study results should be a major goal. Studies with a design which is different from randomized controlled trials may more accurately represent the patient population that is most likely to be

prescribed LAIs in clinical practice, i.e., patients with adherence issues.

CONCLUSIONS

Non-adherence is frequent across all domains of medicine. However, patients with psychotic disorders pose additional challenges that increase the risk for and frequency of non-adherence. Although of great importance for treatment outcomes, clinicians generally spend too little time on discussing and addressing adherence attitudes and behaviors. Importantly, the method of adherence measurement significantly impacts the results, and the most frequently employed methods of asking patients or judging adherence indirectly, based on efficacy or tolerability information, have poor validity. Novel technologies are being developed that directly assess adherence and can both provide real-time feedback to clinicians and be used as an intervention with patients.

A number of treatment strategies have already been developed and tested that can positively impact adherence. Among psychosocial interventions, those combining multiple approaches and involving multiple domains seem to yield the best outcomes. Although LAIs are theoretically a very powerful tool to assure adherence and signal non-adherence, recent results from randomized controlled trials have failed to show superiority of LAIs compared to oral antipsychotics. These data are in contrast to nationwide cohort studies and mirror-image studies, which involved real-world patients prescribed LAIs in clinical practice. This disconnect suggests that traditional randomized controlled trials may not necessarily be the best way to study interventions that are thought to work via reducing non-adherence. Rather, we should consider large, simple randomized trials that enroll populations representative of patients who would be eligible for LAI treatment in clinical settings, and that change the ecology of the treatment delivery and patient contact as little as possible compared to usual care conditions.

Clearly, non-adherence is a major public health problem that is likely to continue despite treatment advances. However, more clinical and research emphasis should be put on finding better solutions for the identification and management of treatment non-adherence, particularly in patients with psychotic disorders.

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DOI 10.1002/wps.20060

Progress in compliance research and intervention: a commentary

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Poor compliance or adherence to antipsychotic medication is widely regarded as one of the most important impediments to effective antipsychotic pharmacotherapy and perhaps the one that is most easily remediable.

In their comprehensive review, Kane et al summarize the evidence that, although there is near universal agreement that non-compliance is a major problem in antipsychotic pharmacotherapy, definitions and methods of measurement are quite variable, with some studies suggesting substantially poorer compliance with antipsychotic therapy than with non-psychiatric drug therapies, while others reporting equivalent or even superior compliance for antipsychotic pharmacotherapy.

Much of the variability in the literature on compliance with antipsychotic pharmacotherapy is due to variability and unreliability in methods for measuring compliance, differences in sources of data, and differences in the context in which data is obtained, i.e. whether in carefully managed clinical trials or real-world practice settings.

Perhaps the most remarkable advance presented in Kane et al's review is the recent development of an "ingestible event marker", i.e. a tiny "chip" that is embedded in a capsule of antipsychotic medication and that gives off an electronic signal when the pill comes into contact with stomach acid, a signal that is relayed through a de-identified signal to a remote device that records the exact time of ingestion. This technology would seem to allow, for the first time, precise and completely reliable documentation of oral medication compliance behavior that can be used to assess any and all definitions of "compliance" and to compare them to each other. Perhaps even more remarkably, this technology has been well tolerated by psychotic patients, evidently without triggering delusions of influence, as many might have expected since such patients not uncommonly have delusions that various wires, or chips have been inserted in their bodies by malicious agents. The measurement problem in the compliance field may, thus, at last have been solved and we can look forward to an explosion of high quality research in this area. The technology may currently be too costly for use in general clinical practice, but it has nearly unlimited potential as a research tool and offers the perspective to eventually bring psychiatry into the digital age, an important advance. As costs come down, as they invariably do with sophisticated technology, the "ingestible event marker" may become a useful clinical tool.

The review also describes a similarly diverse set of psychosocial interventions that have been developed to improve compliance, many of which have been tested in randomized trials and found to be effective in achieving this goal. While promising, the impact of these interventions on the ultimate outcomes of treatment (reducing symptoms and improving quality of life and the chance for recovery in psychotic illnesses) has not been demonstrated. In fact, none of the literature cited seems to have examined whether improved compliance mediates improvements in symptom severity or quality of life, and this would seem to be an important area for research using sophisticated statistical methods, like structural equation modeling, that can test the plausibility of hypothesized causal mechanisms. The fact that non-compliance leads to poorer outcomes does not necessarily mean that statistically significant improvements in compliance will improve outcomes. Further research is needed to demonstrate that the potential compliance interventions can have real clinical benefits.

Perhaps the most controversial issue in the study of compliance with antipsychotic pharmacotherapy concerns the effectiveness of long-acting injectable (LAI) antipsychotic medication. There have been six recent relatively large randomized trials that found no benefit of LAI over oral treatment (1-6) and only one that found statistically significant benefits, although the comparator oral treatment, quetiapine, may have been underdosed at a maximum of only 400 mg per day by the study protocol (7). In addition to the meta-analysis cited by Kane et al (8), a second recent meta-analysis also found only small benefits of LAI treatment over placebo and no significant benefit over oral medication, but with significantly *increased* extrapyramidal symptoms (9).

Kane et al balance the lack of evidence of superiority of LAI to oral treatment against two kinds of observational studies. A national study from Finland showed reduced risk of re-hospitalization for patients on LAIs (10), but this observational study could not control for potential selection biases either reflecting severity of illness, reasons for initiating LAIs, or other potentially confounding factors. Kane et al also cite a meta-analysis of mirror-image studies (11) that showed reduced hospitalization risk, but such studies are profoundly flawed by regression to the mean and the lack of equivalent control groups. It is suggested that the observational studies have the

advantage of not selecting stable patients, but at least one of the randomized trials (5) and perhaps others deliberately selected unstable, recently hospitalized, high risk patients and found no benefit for LAIs.

Kane et al acknowledge that "non-randomized, open, naturalistic or mirror-image studies can have their own limitations, such as selection bias, expectation bias, and time effect", but nevertheless suggest that these flaws may be counterbalanced by the fact that they "may more accurately represent the patient population that is most likely to be prescribed LAIs in clinical practice, i.e., patients with adherence issues". However, the use of inopportune study samples in randomized trials of LAIs has not been demonstrated in any study, and is somewhat countered by two studies related to a LAI trial that did evaluate the representativeness of that sample (12,13). Furthermore, the potential for greater representativeness of a sample cannot undo design flaws that preclude demonstration of causal inferences in pre-post studies and that threaten the validity of Tiihonen et al's single impressive but inconclusive national observational study (10).

Many clinicians ardently believe that LAI treatment is superior for non-compliant patients, because it gives them certainty that patients who have received injections are getting exposed to medication, at least in the short run. Perhaps this conviction, based on common sense reaction to increased control over patient medication exposure, explains why there is a widespread readiness to dismiss the results of published clinical trials. But if causal relationships between treatments and outcomes are what we need to know about the medications we use, clinical trials remain the definitive tool for evaluating such relationships. As it happens, the evidence from such trials does not support superiority of LAI over oral treatment, even in selected subgroups of unstable, non-compliant patients (14).

It should also be noted that, while observational studies are limited in determining causal relationships, they are excellent at identifying patterns of real-world service use. Several studies suggest that patients do not stay on LAI treatment for very long, and thus, even if these agents offer benefits while they are used, they may not provide long-term benefits. One study of unstable patients found that only 51% stayed on LAI risperidone for six months (15). A study of thousands of California Medicaid patients found less than 10% completed 6 months of LAI treatment (16). Two large studies of stable LAI risperidone patients found only 51% (17) and 65% (18) completed one year of treatment. According to the US Veterans Affairs administrative data, only 45% of patients stayed on LAI risperidone for 18 months (19). Thus, even if LAI treatment does guarantee access to medicines in the weeks following injection, patients who terminate this treatment derive only short-term benefit. One could argue that even short-term compliance is a meaningful benefit, even if not supported by outcomes in clinical trials, but costs of second generation LAI medications are high and may not be justified by short-term adherence to LAI therapy and lack of randomized trial evidence of benefit.

Kane et al's paper provides a succinct and comprehensive review of issues of compliance in antipsychotic pharmacotherapy. It introduces the use of the computerized "injectable event marker" to a large audience and this, it can be hoped, will spur innovative research on medication adherence that has not previously been possible. It portrays many areas in which our knowledge is incomplete, controversial and needs development – none perhaps more puzzling than the lack of evidence, thus far, of the superiority of LAI to oral medications in randomized trials.

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DOI 10.1002/wps.20062

Managing non-adherence and the 3 Cs: collaboration, cash and coercion

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On disagreements with players, the late maverick English football manager Brian Clough said: "I ask him which way he thinks it should be done … we talk about it for 20 minutes, and then we decide I was right".

The review by Kane et al illustrates eloquently just how much we have learned about adherence and non-adherence to treatment interventions in medicine as a whole as well as psychiatry in particular in the last few decades. In reviewing activity in this field recently myself, I noted that as many as 38 systematic reviews had been published on the topic which had themselves been subject to a systematic review (1). The article also covers many diverse approaches to manage the problem, the results of which are somewhat underwhelming. It is here that I believe we should be focussing our efforts.

There are many relatively commonsense things clinicians can do to improve the uptake of medical treatment arising out of this substantial evidence base, from simplifying prescription regimens and addressing side effects, to the use of reminders and prompts. However, making an impact on chronic, long-term conditions is not so simple and in psychiatry, uniquely, we sometimes have to contend with what might be called clashes of ideology with our patients: when they say there is nothing wrong with them or nothing that the medication can fix. Indeed, as Kane et al suggest, such illness beliefs and lack of insight are the strongest predictors of non-adherence (see 2).

Being alert to side effects of treatment – especially those effects that patients find most obtrusive – is obviously important. However, I think we over-state how much this is really driving non-adherence in psychotic disorders. Patients and clinicians alike may be biased in their perception and attribution of many negative sensations. A person who is sceptical about the value of a particular drug (or drugs in general) is likely to be acutely sensitive to any potentially adverse effect and stop taking it – but the scepticism is the real cause of the non-adherence. The introduction of second-generation antipsychotic drugs was expected to lead to a step change increase in adherence, given their much lower propensity to produce extrapyramidal side effects. This has not happened. Of course, second-generation drugs have their own profile of side effects, with weight gain being noted particularly by female patients in my clinical experience. However, if this were a major driver of non-adherence, we might expect an objective time lag (and gender difference) between initiation of second-generation antipsychotics and serious non adherence – an interesting hypothesis? Actually, it seems that the trajectory of non-adherence is an exponential decay function like the half-life of an isotope. Roughly speaking, after every 6 months on medication, there is a 50% reduction in adherence.

So, turning to adherence enhancement in psychosis, there is again no shortage of well-conducted and thorough reviews on the topic. The first randomized controlled trial (RCT) of an intervention containing elements of motivational interviewing, cognitive-behavioural therapy, education and good clinical practice ("compliance therapy") was published in full in 1998 (3). When delivered to heterogeneous psychosis patients from South East London admitted to the Maudsley Hospital, their adherence and insight improved by the time they were discharged. Surprisingly, improvements in global functioning were maintained over the subsequent 12-18 months and readmission rates significantly reduced. An attempted replication in Dublin (4) was unsuccessful, perhaps due to low statistical power and less expertise in delivery of the intervention. Because the immediate effects of the intervention were not recorded, we do not know if the intervention

brought about useful change which faded by the time of the 1 year outcome, or whether it did not work at all.

Gray et al (5) showed that community psychiatric nurses randomly selected to receive training in the delivery of a medication management package were able to improve their patients' symptoms and adherence compared to patients under the care of control nurses. However, a large Europe wide RCT (N=327) of adherence therapy (closely modelled on compliance therapy), in comparison to a control intervention based on general health promotion, was negative (6). An important difference from the original trial was that it was based on selected outpatients with adherence problems. After 1 year, both groups improved functionally and on adherence measures, but there was no difference between the groups. The most recent study of this kind comes from the Netherlands (7). Outpatients were randomized to the intervention or treatment as usual and raters were blind to treatment allocation. One innovation of this study was the attempt to tailor the intervention called treatment adherence therapy to the more likely causes of poor adherence for each participant – although, in the majority, this was abnormal illness beliefs. The therapists were nurses with 1 week of special training. Immediate and 6 month outcomes showed significant improvements in compliance, but not other general or symptomatic outcomes.

Another approach which has been employed to promote a range of healthy behaviours, including adherence to treatment, has been to offer financial incentives – contingent monetary reinforcement. Such incentivization – when linked to antipsychotic medication in schizophrenia – raises important ethical questions. When does a reasonable incentive become an unreasonable inducement? Does this exploit poor and vulnerable people? And what if they start upping the price? A cluster RCT of a small financial incentive linked to long-acting injection (LAI) of an antipsychotic agent in sub-optimally compliant patients being followed by community mental health teams, led by Priebe in London, has just been completed and will report soon (8). Early results look promising.

LAIs or "depots", as described by Kane et al, have long been seen as a bulwark against non-compliance. But, while making the monitoring of adherence much easier and obviating the need for reliable medication taking in a disorganized patient, LAIs do not in themselves deal with many of the more pressing factors associated with non-adherence as outlined above. While many patients, once established on depots, find them very acceptable (9) or at least as acceptable as tablets, others find them inherently coercive (10). Perhaps this has something to do with cultural expectations and values round injections or formative experiences in the lives of patients. In any event, if we wish to work collaboratively with our patients and make use of LAIs, there is clearly a lot of work to be done with this image problem.

While collaboration and shared decision making is an essential aspiration in health care, psychiatry has, throughout its history, never been able to get away from the need to give treatment involuntarily – albeit now as a last resort and with suitable safeguards. It is therefore unfortunate, in the light of the foregoing discussion of the negative perception of LAIs, that there has been a strong trend to link them with legally mandated coercion. Our experience in England is that the majority of patients placed on the newly introduced supervised community treatment legislation (community treatment orders) – an attempt to have patients spend less time in the restricting environment of the mental hospital – are treated with LAIs (11). Early audit of outcomes suggest low levels of relapse and hospitalization, but caution should be exerted before over-interpreting this kind of observational data.

In sum, our approaches to non-adherence seem to live up to the philosophy of Brian Clough quoted above. Perhaps it is the nature of the challenge of non-adherence that we are as likely to use collaborative approaches as we are to use coercive ones.

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DOI 10.1002/wps.20061

Talking about adherence

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Kane et al are to be commended for advocating an individualized approach to medication adherence. They note that "clinicians generally spend too little time assessing and addressing adherence attitudes and behaviours". That clinicians devote little time to this in routine clinical practice is significant, as the quality of the clinician-patient relationship is known to influence adherence to treatment. A recent meta-analysis found the odds of a patient adhering to treatment to be 2.16 times greater if there is a good doctor-patient relationship (1). This association has also been found in mental health care (2) and specifically in the treatment of psychosis (3). However, to date, interventions to improve adherence have tended not to focus on the prescribing clinician-patient relationship.

The clinician-patient relationship is reflected and negotiated in clinician-patient communication. A central component is shared decision making, which is receiving increased attention in medicine. Its importance is well established in the medical literature, with a small but growing evidence base in the mental health field. In the treatment of schizophrenia, shared decision making has been found to help patients feel more informed about their illness and treatment, improve satisfaction with care (4) and reduce hospitalization (5). However, there are few observational studies of shared decision making in psychosis.

In video recorded outpatient psychiatric visits, there was, on average, one medication decision in every visit, lasting about two minutes (6). Hence, this is a central part of routine reviews, where both the clinician and the patient can negotiate, influence each other's views and come to a decision that is more or less likely to be followed by the patient once he/she leaves the room. That these decisions take only two minutes reflects how little time is spent on this central aspect of care. Patients in these follow-up visits, half of whom had a diagnosis of schizophrenia, were not greatly involved in the decision making process, with a mean score of 12.5% (i.e., 6 out of a total possible score of 48). Although this appears to be higher in first visits (7,8), there is wide variation between psychiatrists in the extent to which they involve their patients in decisions about medication. Further research is warranted to identify what influences such wide variation and how shared decision making can be enhanced in practice.

The challenges to and benefits of improving adherence are well documented. It is also worth pausing to consider the benefits of non-adherence from the patient's perspective. Non-adherence is not always an irrational decision, with evidence suggesting that some patients do quite well without maintenance medication. Increasingly, many people are uneasy about being told that they will be taking antipsychotic medication for the rest of their lives. With an increasing consumer movement, people wish to take more responsibility for their health. They raise concerns about the ongoing unpleasant side effects of medication, how they interfere with their ability to fulfil key social roles and the risks of long-term antipsychotic use to their physical health.

If patients do wish to discuss reducing or discontinuing medication, this can be problematic. In a study of patients coming off antipsychotic medication, 38% of them were not comfortable disclosing this to their doctor and came off medication without telling them (9). More patients were unwilling to disclose that they intended to come off antipsychotics than patients coming off antidepressants. This is a riskier scenario than patients sharing this information and staying in touch with services so their progress can be reviewed. This highlights the importance of joint discussion about the benefits and risks of adherence and non-adherence with each individual and ensuing negotiation about a way forward. Moreover, this discussion needs to be ongoing, as an individual's mental health and personal circumstances vary over time. Depending on the culture of services, this discussion may be more or less difficult for clinicians. There is considerable institutional pressure on psychiatrists to adopt a cautious approach and real dilemmas in facilitating trial periods without medication. For some, it is too risky.

In a study of communication and adherence in the treatment of schizophrenia, patient participation in the form of asking questions and requesting clarification of the psychiatrist's talk was associated with better adherence to medication six months later (10). As with shared decision making, there was considerable variation between psychiatrists in how often their patients requested clarification. Hence, evidence suggests that there is good and poor communicative practice, which impacts on adherence. However, this needs further unpacking, so that specific communication skills can be targeted in training and peer supervision.

Different medications and dosages have different effects on individuals. This is reflected in psychiatrist-patient discussion of the patient's subjective experience of current and past medications, to inform changes in type and dose. Kane et al point to the potential of new technologies, e.g., a digital feedback system recording when medication is taken, along with physiological measures, to directly assess adherence and also act as interventions to enhance adherence. Such technologies also offer other exciting opportunities to use this information to tailor medication type, doses and frequency to an individual patient in order to identify

the most tolerable and therapeutic regimen. Given the adverse side effects of antipsychotics, this would be a welcome advance.

Many factors influence adherence. Many of these factors are impossible to intervene in and change. Clinician-patient communication can be observed, and it is possible to intervene to change communication. However, the focus should be on adherence to joint decisions rather than adherence to medication per se.

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DOI 10.1002/wps.20064

Adherence/compliance: a multifaceted challenge

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Adherence or compliance, whichever term one prefers, presents medicine with a number of challenges, nicely detailed in Kane et al's review. Evident when reading between the lines, although not explicitly stated, is the fact that compliance behaviour is difficult to study. Apart from the prescription of depot antipsychotics, which is really the only way to monitor compliance reliably, there is still no foolproof way to measure adherence. This methodological shortcoming explains why not much progress has been made in the past decades in establishing the foundations of compliance behaviour and the determinants of impaired adherence and, based on the knowledge of both of these, in conducting clinical studies which can shed light on the usefulness of compliance enhancing interventions.

As most of the relevant evidence has been summarized by Kane et al, I am only left to add or underscore a few points. Firstly, with respect to factors jeopardizing compliance, a few thoughts on attitudes towards treatment warrant consideration. Obviously, patients' attitudes impinge significantly on adherence behaviour, but one must also consider the attitudes of the patients' social environment, including relatives, friends and other patients. The latter, for instance, will likely relate their personal experiences with treatment modalities to the patient in question and may thereby shape his/her attitudes and compliance behaviour. Concerned relatives, having studied Internet sources of often dubious reliability, are also likely to interact in this process. Importantly, and this is often overlooked, the involvement of multiprofessional treatment teams poses a specific challenge in the context of compliance behaviour, as team members, if they are not well aligned with regard to treatment means and goals, may undeliberately convey mixed messages to patients, which may contribute to patients' insecurities with regard to treatment priorities. Par example, a social worker will focus on a patient's ability to hold a job, while a psychotherapist will emphasize coping skills and a nurse will make sure that medications are taken regularly. Accordingly, a patient will be confronted with three different intervention priorities and may therefore give undue preference to one over the other. As much as this is depicted in black and white, clinical reality often comes close, and this must be accounted for in team-based approaches.

Patients' attitudes can be influenced by rational or seemingly irrational factors. On the rational side, they can be influenced by previous experience with an antipsychotic or by information acquired via various media. On the irrational side, attitudes can be even influenced, for instance, by the shape or colour of medications or by the assumption that antipsychotics given in doses of 5 or 10 mg/day are "less strong" or "less dangerous" than those prescribed in daily doses of 600 or 800 mg/day.

The conviction to have to take drugs regularly is also driven by the seriousness attributed to one's illness, and schizophrenia patients have been shown to take their illness less seriously than, for instance, people with diabetes or hypertension (1). Furthermore, all antipsychotics block reward dopamine systems, thereby inducing negative reinforcement.

Paradoxically, some side effects may have a compliance improving impact.

For instance, the increased attention given to patients who report adverse events may lead to more and longer contact with the treating clinician, thereby exerting a positive impact on the doctor/patient relationship.

It is key to understand that compliance is a dynamic treatment variable. Adherence behaviour changes over time and is also dependent on treatment circumstances. Therefore, compliance monitoring must be an ongoing treatment measure. As patients quickly learn to give expected and accepted answers to questions like "Do you take your medications regularly?", alternative approaches have been suggested. These include questions like "When you forget your medication, what do you do?" or "Do you think that taking medication over a prolonged period of time is potentially harmful?" (2).

All of the issues described above, together with those reviewed by Kane et al, underscore the key importance of two factors to ensure optimal compliance behaviour. Both are based on communications strategies, namely, a good clinician/patient relationship and the provision of sound information. Both need to be an integral and continuous component of the management of patients suffering from severe mental disorders.

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DOI 10.1002/wps.20063

Practical strategies for improving adherence to medication and outcomes

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Kane et al provide an expert overview that identifies the many causes of the problem of non-adherence, and describes ways of addressing it. However, practitioners and treatment teams may still be uncertain as to how to proceed in the everyday treatment environment. Arguably, every act of prescribing in a shared-decision making dialogue should be accompanied by adherence assessment and often intervention. Non-adherence is not the exception but the rule for long-standing disorders in which medication is taken to prevent the onset or recurrence of symptoms (1). In this commentary, we focus on practical steps that can be taken by administrators, treatment teams and patients to improve adherence and outcomes.

One possible approach involves increasing the use of long-acting injectable (LAI) antipsychotic medications. While pharmacological treatments are not the only approaches to address adherence, there are multiple benefits to using LAIs in the context of shared decision-making. Indeed, practitioners cannot prescribe the right medications at the right doses in an atmosphere of uncertain adherence. A recent study of outpatients with schizophrenia found that, while both home delivered environmental supports or electronic medication support significantly improved adherence, symptoms and outcomes remained essentially unchanged (2). These data have several interpretations, but one that is particularly distressing. Without good data about what our patients are actually doing with their medications, we may be making very poor treatment decisions, including prescribing unnecessary increases in doses, concomitant medications and medication switches. For example, raising a dose may be completely unnecessary if an individual missed 30% of his/her doses in the week prior to the visit.

LAIs can be used to disentangle lack of efficacy from poor adherence when patients appear to be inadequately responsive to medication (3). The value of using LAIs to improve the information on which treatment decisions are based appears to be underestimated, particularly in the US, where prescriptions for LAIs represent less than 10% of those for antipsychotic medications (4). Mirror image studies demonstrate clear improvements in outcomes and decreases in inpatient costs with the use of injectable medications (5). Kane et al's article nicely explains why such dramatic results are unlikely in randomized controlled trials. As we enter a new era in health care focused on value for services, efficient and accountable care, and need to demonstrate improved outcomes, it is likely that there may be a role for mechanisms to increase the appropriate use of LAIs for patients with schizophrenia. Mechanisms might include peer review and clinician or care system incentives for minimizing barriers to LAI access.

There are many reasons for the underutilization of LAIs, but prominent among them is the discomfort on the part of prescribers in making an offer for these medications (6,7). Linguistic analysis of offers of LAIs in community mental health centers demonstrated lack of fluency and other signs of discomfort on the part of practitioners, and a tendency to start an offer by referring to treatment modality

(shot) rather than potential benefit for recovery (7). Training practitioners in how to make appropriate offers of LAIs in a way that strengthens the therapeutic alliance is necessary and would advance shared decision-making. Surveys of practitioners show that many believe LAIs should be used for patients who are poorly adherent. Unfortunately, in mental health centers, only those who refuse medication are clearly identified as poorly adherent. In reality, medication refusers, unwilling to take either oral medications or LAIs, represent a small minority of patients that are fairly easy to identify. Many other patients are willing to take medication, but do not take it regularly due to distraction, forgetfulness, wavering insight and logistical problems. These are the individuals that need to be identified and offered a trial on LAIs. A simple checklist of warning signs that identifies individuals not receiving maximum benefit from their current oral treatments may help prescribers to identify people who may benefit from LAIs. While there are reasons other than poor adherence that could explain poor outcomes, these warning signs should at least get prescribers to consider whether making an offer of LAIs would be appropriate. Such an identification system should be supported by administrators.

Many patients are unaware that LAI medications are a potential treatment and have never been offered these compounds. Patients need to be provided understandable, helpful information regarding the pros and cons of LAIs versus oral medication. Simple decision-aids focused on this issue could be used by case managers or peer counselors. This effort prior to physician visits could support an improved shared decision-making dialogue between the prescriber and patient during visits.

Concerning psychosocial interventions for adherence, among the most promising are the use of environmental supports to prompt the taking of medication and the creation of habit-behaviors around taking oral medication. We have demonstrated improvements in adherence and outcomes in multiple studies with the use of cognitive adaptation training (2,8). This involves weekly home visits to set up individualized alarms, checklists, and organize belongings to assist individuals in taking medications regularly. We have also shown that effective prompts can be delivered with electronic devices, eliminating the need for home visits (2). Pill counts conducted on unannounced home visits correlate very highly with self-report of adherence, as long as the self-report is dose specific ("Did you take your medication just now?"; "Did you take your medication today?"). Simple cell phone applications could be used to check medication adherence each day with very little cost.

In summary, there are simple, practical measures that can be used to identify potential adherence problems, and solutions that can be applied in community mental health settings.

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DOI 10.1002/wps.20065

Non-adherence and its consequences: understanding the nature of relapse

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The article by Kane et al draws attention to the enormous challenge of non-adherence in treating individuals with psychotic disorders and the need to devise better ways of dealing with it.

Non-adherence is common to most chronic medical conditions, with

multiple factors likely contributing simultaneously to its existence in individual patients. Rates of non-adherence are particularly high in those disorders where there may be no immediate consequences of treatment discontinuation (1). For example, one study found that only 50% of patients with hypertension for whom drug treatment is initiated persisted on treatment 1 year later (2). There is a risk that schizophrenia may be considered to fall into this category, as some patients may survive treatment gaps for considerable periods without adverse consequences. However, this is not the case for the majority. Relapse rates are very high after treatment discontinuation, and in many cases recurrences occur within weeks of stopping treatment (3). To make matters worse, there are no reliable early warning signs to assist patients, carers or clinicians in identifying individuals at imminent risk of relapse (4). In fact, when relapses occur, rather than appearing gradually, symptoms typically return abruptly and rapidly reach high levels of severity (5). In other words, an approach of carefully observing patients in whom non-adherence is suspected, with a view to introducing rescue medication at the first sign of recurrence, is unlikely to be effective in real-world settings.

While treatment goals in schizophrenia and other psychotic disorders should include components such as remission and recovery, the need for sustained medication adherence is to a large extent driven by the risks of harm and distress associated with relapse. Although surprisingly few studies have prospectively assessed the consequences of relapse, it is generally recognized that they may be far-reaching. For example, in an international survey conducted by the World Federation of Mental Health, caregivers cited the following consequences of relapse: inability to work (72%), hospitalization (69%), attempted suicide (22%), and imprisonment (20%). Caregivers also reported significant disruption of their own lives (61%), worsening of their own mental health (54%) and worsening of their financial situation (26%) (6). In addition to these psychosocial consequences, there is a risk of biological harm, insofar as disease progression in the form of emergent treatment refractoriness may occur in a subset of patients after each relapse (7,8).

Taken together, all of these factors point to the need for new, more effective strategies for addressing medication non-adherence in psychosis. As pointed out by Kane et al, effectively addressing non-adherence in psychotic disorders poses specific challenges. Two of these challenges demand special attention. The first concerns impairment of insight, which is one of the most prominent manifestations of psychotic disorders (9). The nature of psychotic illness is such that it impairs the individual's ability to recognize the presence of illness and the need for indefinite maintenance treatment – a fact that may not always be sufficiently recognized by clinicians. Therefore, placing the burden of responsibility on patients themselves to maintain sustained medication adherence would be unrealistic. The second consideration concerns the recognition of the very high occurrence of comorbid substance abuse in individuals with psychotic disorders, and the aggravating role it plays in non-adherence (10).

Psychosocial programs addressing adherence should be developed accordingly, taking into account both the impairment of insight and the need to effectively address substance abuse. Similarly, more reliance should be placed on pharmaceutical interventions that improve adherence. More widespread use of depot antipsychotics is indicated, particularly in the early stages of illness when the benefits of continuous treatment are most likely to be observed.

Greater recognition of the extent and impact of non-adherence has not yet translated into widespread changes in clinical practice. In real world clinical settings around the world, few formalized psychosocial interventions addressing adherence exist, and depot antipsychotics are hopelessly underutilized and frequently only considered after many years of illness. In the context of currently available treatments, combining depot antipsychotics with appropriate psychosocial interventions appears to be our best option for effectively addressing non-adherence in psychotic disorders.

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DOI 10.1002/wps.20067

The enduring challenge of antipsychotic non-adherence

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Kane et al provide an excellent review of non-adherence to antipsychotic medication in patients with schizophrenia-spectrum disorders. While stressing the importance of medication adherence, they acknowledge large gaps in what is known, including how best to assess, prevent and manage non-adherence. Nevertheless, they rightly argue for a multi-faceted approach. Medications should be selected as the result of a shared doctor-patient decision in the context of a strong therapeutic alliance and aimed at achieving patient-oriented goals. Simple regimens that are efficacious and have minimal or well-managed side effects are most likely to be taken.

The underlying assumption in the review and much of this commentary is that antipsychotics are effective and therefore adherence is obviously desirable. An important alternative perspective is that antipsychotics are variably effective and sometimes harmful. Thus the choice to avoid antipsychotic medications may be rational. Medication adherence is often helpful in achieving patient-centered goals, but an individual's recovery may also take other paths.

Kane et al review a long list of methods for monitoring medication adherence and conclude that the methods commonly used in clinical practice are unreliable and underestimate non-adherence. An additional approach deserves mention. The Brief Adherence Rating Scale (BARS) is a validated (1) and clinically useful (2) tool that is administered by clinicians to identify and quantify non-adherence. To make a BARS assessment, a clinician first learns about the patient's knowledge of his/her medication by asking about the prescribed regimen. Then the clinician asks about the number of days in the last month that no doses were taken and the number of days of reduced doses. Based on this information, the clinician makes a global rating using a visual-analog scale to produce a score that is equivalent to the estimated percentage of prescribed pills taken in the last month. The BARS is fast and simple enough to use clinically. It can identify people with significant non-adherence and thus most likely to benefit from available interventions.

The 2009 Schizophrenia Patient Outcomes Research Team (PORT) reviewed randomized controlled trials (RCTs) that tested psychosocial approaches to antipsychotic medication non-adherence in people with schizophrenia, and found insufficient evidence to recommend any specific intervention (3). However, the 2009 PORT concluded that behavioral tailoring and environmental supports, such as signs, checklists, and other cues are promising. A 2011 Cochrane review considered a broad range of psychoeducational approaches to schizophrenia, including interventions that did not focus primarily on adherence such as family psychoeducation. These programs were associated with lower levels of treatment non-adherence (4).

Long-acting injectable antipsychotics (LAIs) are often proposed as a solution to non-adherence, but the evidence to support this is weak (5). LAI proponents think that a main reason why RCTs fail to find a benefit is that such studies tend not to include individuals who are most likely to be non-adherent. The fundamental problem with studying LAI effectiveness in RCTs is that the people who enroll must consent to take antipsychotic treatment, thus excluding the people who may be most likely to benefit from LAIs (6). Although it is suggested that a large, simple trial to compare oral to LAI treatments would enhance generalizability and help to clarify LAI benefits, it is not clear how the underlying selection bias inherent in RCTs would be addressed by a large, simple trial.

Adherence falls along a scale from perfect to none. Improving adherence among people at all levels of non-adherence could lead to better clinical outcomes, with the most benefit likely accruing to those with the lowest levels of adherence. Interventions that improve adherence significantly across the scale could have a huge impact on the global burden of psychotic illness and improve the lives of many affected individuals. Different interventions might be appropriate at different points on the adherence scale and according to the reasons for impaired adherence. For example, people who occasionally and unintentionally miss doses due to cognitive or other barriers may benefit from behavioral tailoring involving reminders and cues. Individuals who are poorly adherent and ambivalent about taking medications might benefit from motivational interviewing, LAIs, or a combination of these. People who intentionally do not take medications due either to poor insight or a personal economy of symptoms vs. side effects favoring symptoms may benefit from comprehensive, multifaceted approaches that include motivational interviewing techniques which are tailored to individual goals whose attainment might be aided by medications (7).

While many interventions to improve antipsychotic adherence are explicitly designed to change the behavior of individuals diagnosed with a psychotic disorder, the need for changes in prescriber behavior is implicit. Doctors should remember that the goal of treatment is recovery, not medication adherence. They should be respectful of patient concerns and preferences, and prescribe according to the best available empirical evidence. In addition, doctors need to accept that some medication non-adherence is rational and have the

forbearance to continue to provide support even in the context of non-adherence.

In conclusion, doctors and patients overestimate the extent to which patients adhere to medication regimens. A validated clinician-rated instrument such as the BARS may help identify individuals who are non-adherent and suggest appropriate intervention. Systematic assessment of individuals' goals for treatment may complement such ratings. Currently, individually tailored efforts using combinations of psychoeducation, motivational interviewing, simple and effective regimens, family support, behavioral cuing, and long-acting medications represent the best practice for improved medication adherence. However, successful efforts to improve outcomes of individuals diagnosed with schizophrenia require multi-faceted approaches with a broader focus than adherence alone.

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DOI 10.1002/wps.20079

Should we listen and talk more to our patients?

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We spend a lot of time in researching and discussing the differences between the various antipsychotic drugs, but much less time in addressing the much more relevant problem, arguably the greatest in our everyday practice, of the management of non-adherence in our patients. Between 20 and 40% of our patients are disengaged from services within 12 months, more than 40% stop medication immediately after first hospitalization (1), nearly 20% of first-episode psychosis patients persistently refuse medications and another 50% are non-adherent at least once within 18 months.

Non-adherence is indeed difficult to assess and to manage, due to the numerous factors influencing our patients' attitude and willingness to follow our recommendations: the efficacy and tolerability of the drug, insight (with the need to differentiate between cognitive dysfunction and denial), the experience of the first contact with psychiatry, the influence of partners and caregivers, and many others (2).

Our hope that oral second-generation antipsychotics with less extrapyramidal side effects would lead to markedly increased adherence has not been fulfilled; most data show no clear advantage for these medications with respect to non-adherence rates and time to discontinuation (3). One reason might be that the heterogeneity of these drugs is not fully exploited. The marked differences in their receptor binding and side effect profile would allow a much better individualization of treatment, addressing patients' complaints and problems (which side effects should be avoided by all means, which could be tolerated). An effort to involve the patient in these decisions certainly improves the therapeutic relationship, probably one of the most important factors affecting adherence (2). Another element which may improve the therapeutic alliance is the frequency of contacts, even if needed "only" for safety reasons. The periodic laboratory tests required by clozapine treatment might be one reason for the surprisingly high patients' adherence to treatment with that drug (4). The regular contact with the therapeutic team might also be one major advantage of using a long-acting antipsychotic, in addition to the straightforward identification of non-adherence, if the patient does not come for the injection. The resistance against the use of these preparations seems to be more in the mind of psychiatrists than in their patients (5).

Moreover, questions or evaluations concerning patients' quality of life during treatment with antipsychotic drugs would make explicit our willingness to not only reduce symptoms but also achieve more ambitious therapeutic goals. Not surprisingly, numerous studies indicate a relationship between patients' subjective wellbeing and their willingness to continue antipsychotic treatment (6).

Most randomized controlled trials do not show a superiority of long-acting antipsychotics over oral preparations. However, that is not surprising, since the major advantages of depot treatment cannot be detected in a double blind or similar design, but become obvious only in naturalistic trials (2,7).

Finally, the complexity of the factors influencing adherence, their interaction

and their continuing changes over time underline the need of integrated care treatment systems, targeting people with severe and persistent mental illness and those with the highest risk for service disengagement or medication non-adherence (8). Such systems commonly include intensive care outpatient models such as intensive case management or assertive community treatment (9). Compared to standard care, most such systems have shown lower rates of service disengagement and medication non-adherence (8,10), better multidimensional outcomes (8,10) and lower service costs (8).

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DOI 10.1002/wps.20066

Public health and physician focused strategies to improve medication adherence in psychotic disorders

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Increasing the effectiveness of adherence interventions may have far greater impact on the health of the population than any improvement in specific medical treatments (1). However, literature on treatment adherence in mental health, as is evident in the scholarly review by Kane et al, is focused too narrowly on patient related and therapy factors. The structural barriers to adherence are generally overlooked.

I argue that action is needed to address two important health system related factors: a) providing access to treatment for the estimated 40 million people suffering from schizophrenia living in low and middle income (LAMI) countries, and b) improving adherence through the implementation of evidence-based guidelines for treatment of schizophrenia.

The treatment gap for schizophrenia is estimated to be 70-90% in LAMI countries (2), where the mean duration of untreated psychosis (DUP) in the first episode is 125.0 weeks (3). Endemic poverty in these countries seems to be associated with poor access to treatment and lack of adherence, except perhaps for most acute episode care. In a study that investigated the DUP and its relationship with gross domestic product purchasing power parity (GDPppp), it was shown that in LAMI countries an additional thousand dollars of per capita GDPppp was associated with a decline in mean DUP of ten weeks (3).

Public health strategies which ensure free access to medication have been successfully implemented in other areas of medicine. In tuberculosis, for example, partial treatment adherence is more dangerous than no treatment at all, as partially treated cases result in drug resistance. This means that, once started, treatment must be completed. Therefore, tuberculosis control programmes worldwide have adopted a strategy called DOTS (directly observed treatment, short course). Two essential elements of this strategy are: a) regular uninterrupted supply of all essential anti-tuberculosis drugs backed by governments' commitment, and b) standardized treatment regimen administered under supervision. DOTS programmes have significantly reduced non-adherence to treatment in most developing countries, and are considered to be one of the most cost-effective health interventions (4). Such programmes have not only been implemented for

high mortality disorders like tuberculosis and HIV infection, but also for non-communicable diseases such as diabetes mellitus.

We believe that resources must be mobilized for a global fund to supply free medicines targeting the initial two years in the course of schizophrenia (3,5). This would help to overcome non-adherence to treatment during this "critical period" in the course of illness, which is the strongest predictor of long-term outcome and disability. Such a treatment could be provided in DOTS-like programmes. The key elements of supervision and administration of medication by a close family member have already been adopted for schizophrenia. A proof-of-concept study showed that patients receiving treatment in the Supervised Treatment for Schizophrenia in Outpatients (STOPS) programme had significantly better adherence to medication compared to treatment as usual ($p < 0.02$) and showed significantly better outcomes in terms of symptoms and functioning at 1-year follow-up (6).

Worsening of symptoms in psychotic disorders is often regarded as a consequence of poor treatment adherence, but there is robust evidence that premature treatment discontinuation is frequently due to poor control of symptoms (7). One study reported that treatment discontinuation due to inadequate symptom control was three times as likely as discontinuation due to medication intolerability. Ongoing depression and poor treatment response were found to be independent predictors of poor medication adherence in first episode psychosis patients (8).

Current treatments have well-known limitations in controlling psychotic symptoms. However, evidence shows that the lack of adherence to treatment guidelines by treating physicians may be a major contributory factor to inadequate symptom control even in the best treatment centres. A multisite hospital study involving 508 people in Germany showed that, amongst patients with persistent psychotic symptoms, 73% received insufficient antipsychotic drug management and about 58% of those with depressive symptoms were not treated according to guidelines. Patients with more severe psychotic illness had a higher likelihood of not being treated according to guidelines (9). How much this poor adherence to treatment guidelines contributes to patients' poor compliance to treatment is not known at present. However, physicians may need to develop insight into their prescribing practices as much as the patients are expected to develop concordance with their advice.

Pharmacological development in schizophrenia has been stagnant now for some decades. Optimizing treatment adherence can ensure that the available interventions are used in the most effective way. Taking medicine continuously for years with significant side effect burden in an illness that carries enormous stigma and disability is not easy. A public health approach is required, in which adherence is considered as a problem of the health system and the wider economic context, not just of the individual patient refusing to take medicine due to lack of insight.

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DOI 10.1002/wps.20068

A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls

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A meta-analysis was conducted to explore the risk for cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia and age- and gender- or cohort-matched general population controls. Our literature search generated 203 relevant studies, of which 136 were included. The final dataset comprised 185,606 unique patients with schizophrenia, and 28 studies provided data for age- and gender-matched or cohort-matched general population controls (n=3,898,739). We found that multi-episode patients with schizophrenia were at increased risk for abdominal obesity (OR=4.43; CI=2.52-7.82; p<0.001), hypertension (OR=1.36; CI=1.21-1.53; p<0.001), low high-density lipoprotein cholesterol (OR=2.35; CI=1.78-3.10; p<0.001), hypertriglyceridemia (OR=2.73; CI=1.95-3.83; p<0.001), metabolic syndrome (OR=2.35; CI=1.68-3.29; p<0.001), and diabetes (OR=1.99; CI=1.55-2.54; p<0.001), compared to controls. Multi-episode patients with schizophrenia were also at increased risk, compared to first-episode (p<0.001) and drug-naïve (p<0.001) patients, for the above abnormalities, with the exception of hypertension and diabetes. Our data provide further evidence supporting WPA recommendations on screening, follow-up, health education and lifestyle changes in people with schizophrenia.

Key words: Schizophrenia, cardio-metabolic abnormalities, metabolic syndrome, obesity, hypertension, hyperlipidemia, diabetes, screening, health education, lifestyle changes

(World Psychiatry 2013;12:240–250)

A number of studies have demonstrated that patients with schizophrenia have an excess mortality, measured by a standardized mortality ratio that is two or three times that seen in the general population (1-11). This translates into 13-20 years of shortened life expectancy, a gap that has widened in recent decades (11-13).

It is well known that some of this excess mortality is due to suicide, but the majority is related to natural causes, such as cancer, respiratory diseases and cardiovascular disease (CVD) (13-15). Premature mortality from CVD is commonly attributed to low socio-economic status (e.g., poverty, poor education) (8), behavioural factors (e.g., alcohol and substance abuse, physical inactivity, unhealthy eating patterns) (16-23), and management factors (e.g., side effects of antipsychotic and concomitant medication use, fragmentation of physical and mental health care, disparities in quality of medical care) (24-28).

In order to help clinicians to identify and focus more on patients at increased risk for CVD, the concept of metabolic syndrome (MetS) has been introduced. MetS is defined by a combination of abdominal obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides and hyperglycemia (29-33). In the general population, these clustered risk factors have been associated with the development of CVD (29-33).

Although several definitions have been proposed for MetS, the most often cited are those formulated by the National Cholesterol Education Program (NCEP), i.e., the Adult Treatment Panel III (ATP-III) and adapted ATP-III criteria (ATP-III-A) (34,35), by the International Diabetes Federation (IDF) (36), and by the World Health Organization (WHO) (37). These definitions share similar diagnostic thresholds. However, abdominal obesity is central to the IDF definition, with provision of specific ethnic thresholds for waist circumference (38), while it is not a mandatory NCEP/ATP MetS criterion.

As a prevalent condition and a predictor of CVD across racial, gender and age groups, MetS provides a unique opportunity for identifying high-risk populations and preventing the progression of some of the major causes of morbidity and mortality (29-33).

In a previous meta-analysis (39), we demonstrated that almost one in three of unselected patients with schizophrenia meet criteria for MetS, one in two patients are overweight, one in five appear to have significant hyperglycemia (sufficient for a diagnosis of pre-diabetes) and at least two in five have lipid abnormalities. We also found a significantly lower cardio-metabolic risk in early schizophrenia than in chronic schizophrenia. Both diabetes and pre-diabetes appear uncommon in the early illness stages, particularly in drug naïve patients (40).

To the best of our knowledge, meta-analytic data comparing the cardio-metabolic risk in patients with schizophrenia across different stages (unmedicated, first-episode, multi-episode) versus matched healthy controls are currently lacking. Such data could raise awareness of conditions

that cause a significant burden of morbidity and mortality, and thereby help motivate preventive strategies and adherence to recommended therapies.

The primary aim of the current meta-analysis therefore was to compare the risk for MetS, abdominal obesity, hypertension, hyperlipidemia, and diabetes in unmedicated, first-episode, and multi-episode patients with schizophrenia versus healthy age- and gender- or cohort-matched controls. We also updated comparisons in MetS, abdominal obesity, hypertension, hyperlipidemia, and diabetes risks between unmedicated, first-episode, and multi-episode patients with schizophrenia.

METHODS

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (41). The focus was on patients with schizophrenia, irrespective of age and clinical setting (inpatient, outpatient or mixed).

Inclusion criteria were: a DSM-IV-TR (42) or ICD-10 (43) diagnosis of schizophrenia (with or without related psychoses) and a MetS diagnosis according to non-modified ATP-III (34), ATP-III-A (35), IDF (36) or WHO (37) standards. We included case-control studies, prospective cohort studies, cross-sectional studies, and comparisons of study populations with age standardization. For comparison with healthy controls, only age- and gender-matched or cohort-matched studies were included. In the case of multiple publications from the same study, only the most recent paper with the largest sample was included.

Excluded were studies using non-standardized diagnoses of schizophrenia and/or MetS, limited to patients with known CVD, or limited to children and adolescents.

Two independent reviewers (DV and ADH) searched Medline, PsycINFO, Embase and CINAHL from database inception to March 1, 2013. The key word "schizophrenia" was cross-referenced with the following terms: "metabolic syndrome" OR "obesity" OR "lipids" OR "cholesterol" OR "hypertension" OR "diabetes". Manual searches were conducted using the reference lists from recovered articles. Prevalence rates of MetS, abdominal obesity, hypertension, hyperlipidemia and diabetes for patients and controls were abstracted by the same two independent reviewers. We also contacted authors for additional data and received information from 21 research groups (see Acknowledgements).

To examine the homogeneity of the effect size distribution, a Q-statistic was used (44). When the Q-statistic is rejected, the effect size distribution is not homogeneous, implying that the variability in the prevalence rates of the cardio-metabolic abnormalities between studies is larger than can be expected based on sampling error.

The effect size used for the prevalence rate of all cardio-metabolic abnormalities under research was the proportion, but all analyses were performed converting proportions into logits. Logits are preferred over proportions because the mean proportion across studies underestimates the size of the confidence interval around the mean proportion (due to compression of the standard error as p approaches 0 or 1) and overestimates the degree of heterogeneity across effect sizes. This is especially the case when the observed proportions are <0.2 or >0.8 (45). However, for ease of interpretation, all final results were back converted into proportions. In case of heterogeneity and when information about moderator variables was available, we opted for a mixed effects model. In these analyses, several study characteristics were incorporated, including mean age of the study sample, type of treatment setting (outpatient versus inpatient), medication status (medicated versus drug-naïve), and disease status (first episode versus not first episode). A random effects model was adopted when the Q-statistics indicated that there was heterogeneity and moderator variables were lacking.

Lastly, we pooled data from individual studies to calculate the odds ratio (OR) and used Wald tests to statistically compare the prevalence of cardio-metabolic abnormalities between patients with schizophrenia (unmedicated, first-episode, multi-episode) and age-matched general population control subjects.

RESULTS

Our search generated 203 relevant studies, of which 136 (46-181) were included. Reasons for exclusion are presented in Figure 1.

The final dataset comprised 185,606 unique patients with schizophrenia. Forty-three studies were conducted amongst inpatients (n=12,499; 59.7% male; mean age = 38.9 years), 46 in outpatient settings (n=12,469; 61.0% male; mean age = 38.6 years) and 46 in mixed samples (n=160,638; 62.0% male; mean age = 38.7 years). Twelve studies examined individuals who were in their first episode (n=2,192; 62.0% male; mean age = 28.7 years); 18 studies examined drug-naïve patients (n=1,104; 61.0% male; mean age = 30.7 years).

In 28 studies, age and gender head-to-head or cohort-matched general population control data (n=3,898,739) were available (47,51,55,57,60,61,63,74,78,89,93,94,103, 117,119,122,134,135,138,148,150,152,156,158,165,171, 176). There were, however, insufficient data to compare the prevalence of cardio-metabolic abnormalities of first-episode and/or drug-naïve patients with age and gender head-to-head or cohort-matched general population control data.

The Q-statistic indicated that the distribution of the prevalence of abdominal obesity across individual studies was not homogeneous ($Q(51)=994.4$; $p<0.001$). Compared with multi-episode patients (N=46; n=19,043; mean age = 38.6 years), drug-naïve patients (N=5; n=444; mean age = 28.0 years) had a significantly reduced risk for abdominal obesity: 50.0% (95% CI=46.9%-53.1%) versus 16.6% (95% CI=

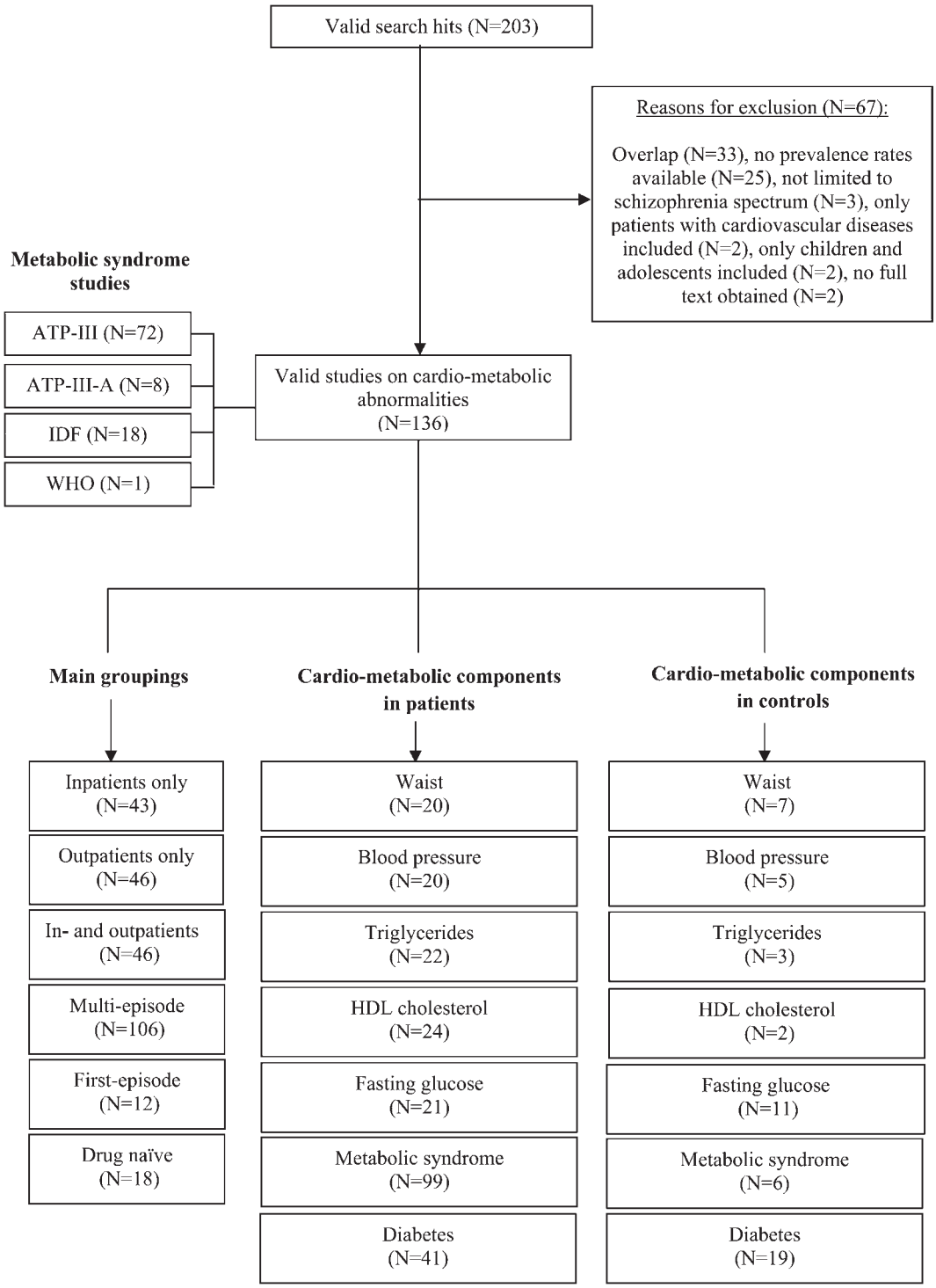

Figure 1 Quality of reporting of meta-analyses (Quorom) search results. ATP-III – Adult Treatment Panel III; ATP-III-A – Adult Treatment Panel III, adapted; IDF – International Diabetes Federation; WHO – World Health Organization; HDL – high-density lipoprotein

11.2%-24.0%) ($p<0.001$). Compared with matched general population control subjects (n=868), multi-episode patients (n=6,632) had a significantly increased risk of abdominal obesity when pooling data of the individual studies (N=5) (OR=4.43; CI=2.52-7.82; $p<0.001$). There were insufficient data to compare first-episode and drug-naïve patients with general population controls.

The Q-statistic indicated that the distribution of the prevalence of hypertension across individual studies was not homogeneous ($Q(56)=12262.5$; $p<0.001$). Fifty-seven

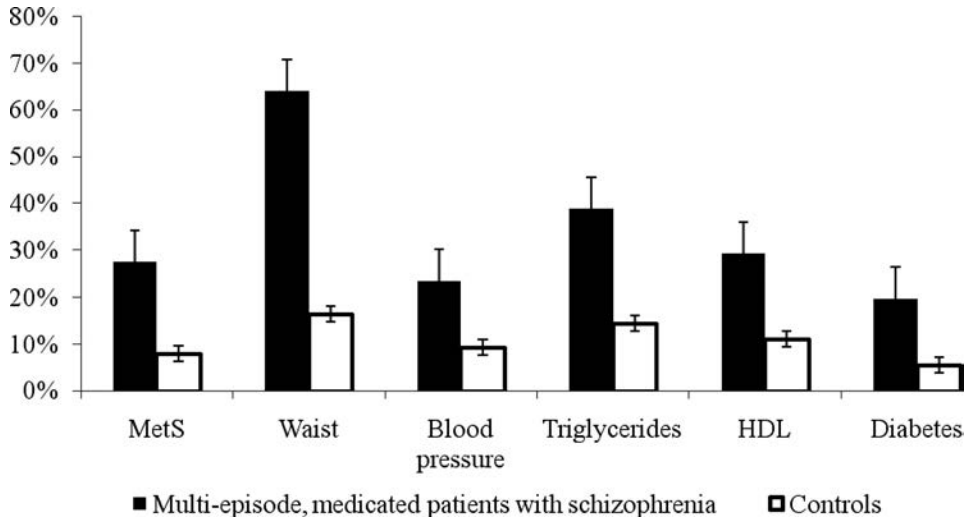

Figure 2 Overview of the prevalence of cardio-metabolic abnormalities in multi-episode medicated patients with schizophrenia versus age- and gender- or cohort-matched controls. MetS – metabolic syndrome; HDL – high-density lipoprotein cholesterol.

studies reported on hypertension (n=113,286; 61.9% male; mean age = 38.8 years). The prevalence of hypertension was 36.3% (95% CI=30.9%-42.1%). Multi-episode patients (37.3%, 95% CI=32.5%-42.3%; N=47; n=112, 167; 62.0% male; mean age = 41.7 years) did not differ (p=0.64) from first-episode (41.1%, 95% CI=20.7%-65.1%; N=1; n=488; 60.0% male; mean age = 26.6 years) and drug-naïve (31.6%, 95% CI=21.3%-44.0%; N=8; n=631; 63.0% male; mean age = 28.3 years) patients. Compared with matched general population control subjects (n=732,965), multi-episode patients (n=2,410) had a significantly increased risk of hypertension when pooling data of the individual studies (N=4) (OR=1.36; CI=1.21-1.53; p<0.001).

The Q-statistic indicated that the distribution of the prevalence of hypertriglyceridemia across individual studies was not homogeneous (Q(57)=1641.2; p<0.001). Fifty-eight studies reported on hypertriglyceridemia (n=20,996; 61.0% male; mean age = 38.5 years). The prevalence of hypertriglyceridemia was 34.5% (95% CI=30.7%-38.5%). There was no significant difference between drug-naïve (N=7; n=538; 60.8% male; mean age = 27.6 years) and first-episode (N=5; n=1,150; 58.0% male; mean age = 30.4 years) patients, with a prevalence of 23.3% (95% CI=15.4%-33.6%) and 10.5% (95% CI=5.8%-18.2%), respectively. In contrast, multi-episode patients (N=46; n=19,152; 61.2% male; mean age = 41.1 years) had a significantly increased prevalence (39.0%, 95% CI=9.9%-44.0%) compared to drug-naïve and to first-episode patients (p<0.001). Compared with matched general population control subjects (n=6,016), multi-episode patients (n=647) had a significantly increased risk of hypertriglyceridemia (OR=2.73; CI=1.95-3.83; p<0.001) (N=2).

The Q-statistic indicated that the distribution of the prevalence of abnormally low HDL cholesterol levels across individual studies was not homogeneous (Q(57)=1118.4; p<0.001). Fifty-eight studies reported on low HDL cholesterol levels (n=20,907; 61.2% male; mean age = 38.6 years). The prevalence rate was 37.5% (95% CI=34.3%-40.8%). There was no significant difference between drug-naïve (N=7; n=538; 61.7% male; mean age = 27.5 years) and first-episode (N=5; n=1,306; 57.2% male; mean age = 28.5 years) patients, with 24.2% (95% CI=17.4%-32.5%) and 16% (95% CI=10.4%-23.9%), respectively. In contrast, multi-episode patients (N=46, n=19,063; 61.5% male; mean age = 41.2 years) had a significantly increased prevalence (41.7%, 95% CI=38.3%-45.2%) compared to drug-naïve and to first-episode patients (p<0.001). Compared with general population control subjects (n=6,016), multi-episode patients (n=647) had a significantly higher risk for low HDL cholesterol levels (OR=2.35; CI=1.78-3.10; p<0.001) (N=2).

The Q-statistic indicated that the distribution of the MetS prevalence across individual studies was not homogeneous (Q(106)=1470.4; p<0.001). One hundred and seven studies reported on MetS (n=28,729; 60.6% male; mean age = 38.8 years). The prevalence was 31.1% (95% CI=28.9%-33.4%). There was no significant difference between drug-naïve (N=11; n=733; 60.0% male; mean age = 29.2 years) and first-episode (N=6; n=1,039; 60.1% male; mean age = 30.1 years) patients, with 10.0% (95% CI=7.0%-14.2%) and 15.9% (95% CI=10.5%-23.3%), respectively. In contrast, multi-episode patients (N=46; n=26,957; 60.6% male; mean age = 38.8 years) had a significantly increased prevalence (34.2%, 95% CI=31.9%-36.6%) compared to drug-naïve and to first-episode patients (p=0.007). Compared with age- and gender- or cohort-matched general population control subjects (n=6,632), multi-episode medicated patients (n=868) had a significantly higher risk for MetS (OR=2.35; CI=1.68-3.29; p<0.001) (N=4).

The Q-statistic indicated that the distribution of the prevalence of diabetes across individual studies was not homogeneous ($Q(42)=3718.8$; $p<0.001$). Forty-one studies reported on diabetes (n=161,886; 61.3% male; mean age=40.1 years). The prevalence was 9.0% (95%CI=7.3%-11.1%). Multi-episode patients (9.5%, 95% CI=7.3%-12.2%; N=29; n=116,751; 60.0% male; mean age = 43.8 years) did not differ ($p=0.56$) from first-episode (8.7%, 95% CI=5.6%-13.3%; N=5; n=1033; 61.0% male; mean age = 32.4 years) and drug-naïve (6.4%, 95% CI=3.2%-12.5%; N=5; n=346; 66.0% male; mean age = 29.2 years) patients. Compared with matched general population control subjects (n=3,891,899), multi-episode patients (n=106,720) had a significantly higher risk for diabetes (OR=1.99; CI=1.55-2.54; $p<0.001$) (N=15).

Figure 2 presents an overview of the mean prevalence for all investigated cardio-metabolic parameters in multi-episode medicated patients with schizophrenia versus healthy controls.

DISCUSSION

To the best of our knowledge, this meta-analysis is the first to demonstrate that medicated multi-episode patients with schizophrenia are at a more than fourfold increased risk for abdominal obesity compared to age- and gender- or cohort-matched general population controls (OR=4.43). The odds ratio of risk for low HDL cholesterol (OR=2.35), MetS (OR=2.35) and hypertriglyceridemia (OR=2.73) was more than double. Compared to general population controls, multi-episode patients with schizophrenia also have almost twice the risk (by odds) for diabetes (OR=1.99), while the odds for hypertension was 1.36. Our data also confirm previous findings (40) that chronic, medicated patients with schizophrenia have a significantly increased risk for developing cardio-metabolic abnormalities compared with first-episode and drug-free patients. No significant differences in blood pressure and diabetes between chronic, medicated, first-episode and drug-free patients were, however, found. A possible reason might be that we were not able to control for use of antihypertensive and glucose lowering drugs.

We wish to acknowledge some limitations in our primary database that should be considered when interpreting the results. First, there was considerable heterogeneity, which could only be partly controlled by stratification for disease stage. Second, there was a very limited number of studies comparing first-episode and unmedicated patients with controls and hence these analyses were not possible. Third, there was marked variation in the sample size of the included studies. Fourth, we were not able to adjust for type and duration of antipsychotic treatment.

Next to a low socio-economic status (8), behavioural factors (16-23), side effects of antipsychotic and concomitantly used medications, and fragmentation of health care (24-28), various inflammatory processes could contribute to the increased cardio-metabolic risk observed in patients with schizophrenia (182). In a recent review, Steiner et al (183) highlighted the alterations in the immune system of patients with schizophrenia. Increased concentrations of interleukin (IL)-1, IL-6, and transforming growth factor-beta appear to be state markers, whereas increased levels of IL-12, interferon-gamma, tumor necrosis factor-alpha, and soluble IL-2 receptor appear to be trait markers of schizophrenia. The mononuclear phagocyte system and microglial activation are also involved in the early course of the disease. The mechanisms whereby inflammatory mediators initiate a wide range of cardio-metabolic abnormalities are being elucidated, but the causes of the vulnerability to chronic low-grade inflammation are still speculative, especially as increased body mass index (BMI) and obesity are in and of themselves associated with increased inflammation (182,183).

Since patients with schizophrenia are a high-risk group for developing cardio-metabolic abnormalities, they should be routinely screened for CVD risk factors at key stages (184,185). This can be achieved by establishing a risk profile based on consideration of cardio-metabolic factors (abdominal obesity, dyslipidemia, hypertension, hyperglycemia), but also through consideration of a patient's personal and family history, covering diabetes, hypertension, CVD (myocardial infarction or cerebrovascular accident, including age at onset) and behavioural factors (e.g., poor diet, smoking and physical inactivity) (186-189). This risk profile should afterwards be used as a basis for ongoing monitoring, treatment selection and management.

Guidelines from the WPA (189) recommend that monitoring should be conducted at the initial presentation and before the first prescription of antipsychotic medication and (for patients with normal baseline tests) repeated at 6 weeks (for blood glucose) and 12 weeks after initiation of treatment, and at least annually thereafter for all parameters. The 6-week blood sugar assessment to rule out precipitous diabetes onset has, however, been recommended in Europe, but not in the US (189). In light of the high rates of metabolic abnormalities observed in all settings, we propose that minimum monitoring should include waist circumference. Optimal monitoring should also include fasting glucose, triglycerides and HDL-cholesterol and hemoglobin A1C (HbA1c). HbA1c has the advantage of not requiring a fasting sample in those taking antipsychotic medication and was recently shown to identify patients with pre-diabetes and diabetes not captured by assessments of fasting glucose (190,191). Moreover, a recent study found that the optimal testing protocol to detect diabetes was a HbA1c threshold $\geq$5.7%, followed by conventional testing with an oral glucose tolerance test (OGTT) and fasting blood glucose in patients who test positive (192).

Psychiatrists should, regardless of the medication prescribed, monitor and chart waist circumference of every patient with schizophrenia at every visit, and should encourage patients to monitor and chart their own weight (189). The WPA (189) states that these physical health monitoring tests

are simple, easy to perform and inexpensive, and therefore can/should be implemented in the health care systems of developed as well as developing countries. In a recent study (193), we demonstrated that the optimal clinical predictors of diabetes in severe mental illness were BMI, waist/hip ratio, height, age, and duration of illness. No single clinical factor was able to accurately rule in a diagnosis of diabetes, but three variables could be used as an initial screening (rule-out) test, namely BMI, waist/hip ratio and height. A BMI <30 had a 92% negative predictive value in ruling out diabetes. Of those not diabetic, 20% had a BMI <30. It is therefore recommended that clinicians use HbA1, fasting glucose and OGTT when testing for diabetes in patients with schizophrenia, especially high risk patients, based on the above clinical factors.

In addition to optimal screening and follow-up, the WPA (189) recommends that psychiatrists, physicians, physical therapists and other members of the multidisciplinary team should help educate and motivate patients with schizophrenia to improve their lifestyle through use of behavioural interventions, including smoking cessation, dietary measures, and exercise. In two recent, multi-centre studies (194,195) we showed that many, although not all, patients with schizophrenia were either unaware of the need to change their lifestyle or did not possess the knowledge and skills required to make appropriate lifestyle changes. Therefore, it is useful that family members and caregivers be offered education regarding the increased cardio-metabolic risk of patients with schizophrenia and ways to mitigate this risk.

Acknowledgements

The authors would like to thank the following researchers for providing additional data: T. Heiskanen and H. Koponen, Kuopio University Hospital, Kuopio, Finland; R. Chengappa, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA; T. Cohn, University of Toronto, Canada; J. Meyer, University of California, San Diego, CA, USA; J. Crilly and J.S. Lamberti, University of Rochester Medical Center, Rochester, NY, USA; P. Mackin, Newcastle University, Newcastle upon Tyne, UK; S. Tirupati, James Fletcher Hospital, Newcastle, New South Wales, Australia; T. Sanchez-Araña Moreno, Psychiatry Hospital de la Merced, Osuna, Spain; P.J. Teixeira, Instituto de Previdência dos Servidores do Estado de Minas Gerais, Belo Horizonte, Brazil; G.J. L'Italien, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA; V. Ellingrod, University of Michigan College of Pharmacy, Ann Arbor, MI, USA; Hung-Wen Chiu, Taipei Medical University, Taipei, Taiwan; D. Cohen, Geestelijke Gezondheidszorg Noord-Holland Noord, The Netherlands; H. Mulder, Utrecht University and Wilhelmina Hospital Assen, The Netherlands; J.K. Patel, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA; K. Taxis, University of Groningen, The Netherlands; B. Vuksan, University Hospital Centre Zagreb, Croatia; R.K. Chadda, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India; L. Pina, Psychiatry, Gregorio Marañon General Universitary Hospital, Madrid, Spain; J. Rabe-Jablonska and T. Pawelczyk, Medical University of Lodz, Poland; D. Fraguas, University Hospital of Albacete, Albacete, Spain.

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DOI 10.1002/wps.20069

Psychotic symptoms are associated with physical health problems independently of a mental disorder diagnosis: results from the WHO World Health Survey

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This study explored whether physical health problems are related to psychotic symptoms independently of a mental disorder diagnosis. A total of 224,254 subjects recruited for the World Health Organization World Health Survey were subdivided into those with both a lifetime diagnosis of psychosis and at least one psychotic symptom in the 12 months prior to the evaluation, those with at least one psychotic symptom in the past 12 months but no lifetime diagnosis of psychosis, and those without psychotic symptoms in the past 12 months and without a lifetime diagnosis of psychosis. The three groups were compared for the presence of medical conditions, health problems, and access to health care. Medical conditions and health problems (angina, asthma, arthritis, tuberculosis, vision or hearing problems, mouth/teeth problems, alcohol consumption, smoking, and accidents), medication consumption, and hospital admissions (but not regular health care visits) were more frequent in individuals with psychotic symptoms but no psychosis diagnosis, compared to those with no symptoms and no diagnosis. The number of medical conditions increased with the number of psychotic symptoms. Given the sample analyzed, this trend seems to be independent from the socio-economic development of the country or the specific health care system.

Key words: Psychotic symptoms, physical health, medical conditions, access to health care, multinational study

(World Psychiatry 2013;12:251–257)

Psychotic disorders have been associated with a mortality rate double that of the general population (1,2) and a shortening of life expectancy by up to 20 years (3). Physical comorbidities are major contributors to morbidity and mortality in people with schizophrenia and other psychotic disorders (1,2,4-8). The impact of cardiovascular and metabolic illnesses has been consistently reported (9-12), and evidence is beginning to accumulate regarding the role of infectious diseases, respiratory illness, and the abuse of different substances, amongst others (1,7,12-16). Lifestyle factors (such as sedentarism, inadequate diet and smoking), treatment with antipsychotics, and unequal access to health care have been suggested as contributors to poorer physical health among people with psychosis (6,17-19). Immune mechanisms and inflammation may also play a role, mediating not only the brain expression of the disorder, but also the concurrent systemic problems (20).

Approximately 3% of the general population have a psychotic disorder (21). However, the prevalence of psychotic symptoms in population-based studies is significantly higher, ranging from 0.7 to 45.8% for the presence of at least one psychotic symptom in a recent world-wide cross-national study (22). The negative impact of psychotic symptoms on functioning seems not to be restricted to individuals with diagnosable psychotic disorders (23,24). Evidence regarding whether medical conditions and other indices of physical health are related to the presence of psychotic symptoms independently of an established mental disorder diagnosis is still preliminary (25). Moreover, nearly all of the available information regarding the larger than expected comorbidity of physical illnesses with schizophrenia and other psychoses comes from studies conducted in industrialized countries, mostly single-country studies (7,26).

In this paper, we present data from the World Health Organization (WHO) World Health Survey (WHS), an international study including countries with different levels of socio-economic development (27). We explored the differential load of physical illnesses and the access to treatment for those illnesses in subjects presenting psychotic symptoms (with or without a psychosis diagnosis) and subjects without psychotic symptoms. We hypothesized that the presence of psychotic symptoms (independent of a psychosis diagnosis) would be related to medical pathology, regardless of each country's socio-economic level.

METHODS

Sample

We included individuals from the 52 countries covered by the WHS: 18 from the African region, 13 from the European region, 7 from the Americas region, 5 from the Asian region, 5 from the South-East Asian region, and 4 from the Eastern Mediterranean region. Fifteen countries were classified in the high or upper-middle economic levels,

according to the World Bank, and 37 in the lower-middle or low levels. All samples were drawn from a current national frame using a multi-stage cluster design enabling each household and individual respondent to be assigned a known non-zero probability of selection. The sampling guidelines and the summary descriptions of the sampling procedures are available from the WHS website (www.who.int/healthinfo/survey/en/index.html).

Informed consent was obtained from all respondents, and the study was cleared by ethical review committees at each site. The individual global response rate was 98.5%, with the final sample comprising 224,254 subjects. All interviews were conducted by specifically trained interviewers. A standard procedure for training and quality control was implemented at all sites and supervised periodically, as per the specified guidelines.

Measures

All respondents were interviewed using the standardized WHS instrument from the WHO. The interview collected data on health status, socio-demographic characteristics, consumption of alcohol and tobacco, lifestyle, household economic status (based on a list of permanent income indicators), and information about functioning, health status and quality of life. Lifetime diagnosis and treatment of psychosis and presence of psychotic symptoms during the last 12 months were assessed. Lifetime diagnosis and symptoms during the last 12 months of asthma, arthritis and angina pectoris were also recorded. Alcohol consumption was coded using two groups and one dummy variable, with lifetime abstainers and occasional drinkers (those who consumed a total of 15 or less units in the previous week, but no more than 4 units on one occasion) being the reference category (87.4%), and occasional heavy drinkers (those who consumed a total of 15 or more units in the previous week, but no more than 4 units on one occasion) and heavy drinkers (those who consumed 5 or more units on at least one occasion) comprising the other category. Smoking was dichotomized as not currently smoking any type of tobacco versus currently smoking tobacco daily (23.8%).

Assessment of psychotic symptoms

Individual questions based on the WHS version of the Composite International Diagnostic Interview (CIDI 3.0) (28) were included to assess the presence of psychotic symptoms, including delusional mood, delusions of reference and persecution, delusions of control, and hallucinations, over the past 12 months. The response format for all the above questions was dichotomous (yes/no). The psychosis module of the CIDI has shown high concordance with clinician ratings (29).

Assessment of specific medical conditions

The diagnosis of angina was based on an algorithm derived from the Rose questionnaire (30). Asthma and arthritis were established according to dichotomous questions (yes/no) about lifetime diagnosis of those illnesses (31). Responders were regarded as having diabetes mellitus if they responded "yes" to the question "Have you ever being diagnosed with diabetes (high blood sugar)?". The diagnosis of tuberculosis was established on the basis of questions about a cough lasting more than three weeks and including blood in cough or phlegm. Lifetime treatment and medication use over the previous 2 weeks were also assessed for all conditions.

The number of comorbid non-psychiatric illnesses, including angina pectoris, asthma, diabetes, arthritis and tuberculosis, was assessed. Results about the association between diabetes and psychotic symptoms in this sample were already reported (32); therefore diabetes was only considered to estimate the global amount of comorbid non-psychiatric illnesses. Information was also included about the self-reported presence (yes/no) of vision problems (and of cataracts during the previous 5 years in people 60 years and over), hearing problems, teeth problems, and road traffic or other injuries in the 12 months before the interview.

Assessment of access to health care

Information about health system use and responsiveness was also collected. Occurrence and length of overnight stays in health centers during the last 5 years, as well as treatment at home or as an outpatient, were included in the analyses, not considering stays potentially attributable to psychiatric reasons. Satisfaction with health systems in the country (from 1, very satisfied, to 5, very unsatisfied), self-reported health dissatisfaction (from 1, very satisfied to 5, very unsatisfied), and perceived lack of health (from 1, very good, to 5, very bad) were also assessed.

Medications being taken at the time of the interview were reported. A total scale of number of medicines being consumed was calculated (range: 0-6), excluding medication for psychiatric problems.

Statistical analysis

We first performed a series of binomial logistic regression analyses comparing subjects with a lifetime diagnosis of psychosis and psychotic symptoms in the last 12 months (N=1,306) and subjects with at least one psychotic symptom in the last 12 months but no psychotic diagnosis (N=27,648) vs. individuals without psychotic symptoms and no lifetime diagnosis of psychosis (N=195,300). In all of these analyses we statistically controlled for age, gender, World Bank category of the country, and country of the individual (including

51 dummy variables as covariates referred to the country of the sample), the last two in order to control for potential differences in the functioning of health services. Independent variables included in those series of analyses were specific medical conditions and access to health care.

Then, to test the global impact of psychotic symptoms and diagnosis on health, we compared the total number of non-psychiatric illnesses (including angina pectoris, arthritis, asthma, diabetes and tuberculosis) and the consumption of medicines prescribed by a medical professional between individuals with lifetime psychotic diagnosis and psychotic symptoms in the last 12 months and individuals with at least one psychotic symptom and no diagnosis vs. individuals without psychotic symptoms and no diagnosis of psychosis.

Comparisons were performed through t-tests for unrelated samples, adjusting the probability level to control for family-wise type I error (Bonferroni's correction). To assess the strength of these associations, effect sizes (Hedge's g) were calculated for associations with continuous variables. Hedge's g with large samples provides values that are very similar to Cohen's d (33), for which the following arbitrary rules of thumb are often used: effect sizes below .20 are regarded as not relevant, between .20 and .50 as low, between .50 and .80 as moderate, and over .80 as high. Also, with the aim of indirectly testing both overall health and health-service responsiveness, the same comparisons were carried out using the total number of medicines currently being taken (excluding those for psychiatric problems) as the dependent variable. Additionally, we analyzed the differences in the number of illnesses and of medicines currently being taken across the continuum of psychotic symptoms (number of symptoms, range: 0-4) through one-way ANOVAs, with the number of symptoms reported as the independent variable and post-hoc comparisons (Scheffé) between specific groups. Patients with a previous diagnosis of psychosis and no psychotic symptoms in the past 12 months were not included in any analysis.

All analyses were carried out with the statistical package STATA, version 11.0 (Stata Corp, 2010). Significance was set at $\alpha=0.05$.

RESULTS

In binary logistic regression analyses, all somatic variables considered had statistically significant ORs ($p<0.001$). Thus, compared with subjects without psychotic symptoms and no psychotic diagnoses, those with at least one psychotic symptom in the last 12 months and no psychotic diagnosis had a higher probability of also reporting angina pectoris, asthma, arthritis, tuberculosis, vision or hearing problems, cataracts (in people with 60 years or over), mouth or teeth problems during the previous year, and high alcohol consumption during the previous week, of being smokers, and of having had more road accidents or other injuries in the previous year (Table 1). The comparison of subjects with psychotic symptoms and a diagnosis of psychosis vs. those with no symptoms and no diagnosis produced very similar results, although suggesting stronger associations. In fact, comparing the two columns in Table 1, almost all 95% CIs did not overlap (the only exceptions were those for cataracts, alcohol consumption and smoking), with a higher range in the case of subjects with a diagnosis of psychosis.

As shown in Table 2, the presence of psychotic symptoms was related to an increased probability of health

Table 1 Physical diseases and health problems in subjects with psychotic symptoms and no psychotic diagnosis and in those with psychotic symptoms plus lifetime psychotic diagnosis vs. subjects without psychotic symptoms or diagnosis

	Psychotic symptoms without psychosis diagnosis OR (95% CI)	Psychotic symptoms plus psychosis diagnosis OR (95% CI)
Angina pectoris	**2.50 (2.38/2.62)**	**3.98 (3.38/4.68)**
Asthma	**1.81 (1.72/1.91)**	**3.71 (3.16/4.75)**
Arthritis	**1.80 (1.73/1.86)**	**2.85 (2.50/3.25)**
Tuberculosis	**2.87 (2.66/3.11)**	**4.72 (3.73/5.97)**
Vision problems	**1.67 (1.59/1.75)**	**2.16 (1.80/2.58)**
Cataracts (people over 60)	1.39 (1.24/1.57)	2.15 (1.28/3.61)
Hearing problems	**1.56 (1.46/1.67)**	**2.27 (1.80/2.85)**
Alcohol consumption (occasionally heavy/heavy)	1.27 (1.24/1.30)	1.14 (1.11/1.17)
Smoking (% currently yes)	1.18 (1.15/1.21)	1.30 (1.14/1.48)
Mouth or teeth problems (last year)	**1.63 (1.58/1.67)**	**2.06 (1.83/2.32)**
Road traffic or other injuries (1 year)	**2.34 (2.23/2.44)**	**3.21 (2.72/3.79)**

All results are significant compared to individuals without diagnosis of psychosis nor psychotic symptoms in the prior 12 months
Values in bold indicate non-overlapping 95% CIs between the two columns

Table 2 Health system care indicators in subjects with psychotic symptoms and no psychotic diagnosis and in those with psychotic symptoms plus lifetime psychotic diagnosis vs. subjects without psychotic symptoms or diagnosis

	Psychotic symptoms without psychosis diagnosis OR (95% CI)	Psychotic symptoms plus psychosis diagnosis OR (95% CI)
Overnight stays (excluding psychiatric)	**1.33 (1.28/1.38)**[a]	**1.91 (1.65/2.22)**
Length of stay (excluding psychiatric)		
3-5 days	1.15 (1.07/1.25)[a]	1.34 (0.99/2.22)
6-14 days	1.22 (1.11/1.34)[a]	1.41 (1.00/1.99)[a]
More than 15 days	1.37 (1.22/1.54)[a]	1.45 (0.94/2.22)
Health care attention, excluding overnight and psychiatric (12 months)	1.79 (0.69/4.62)	0.67 (0.09/4.97)
Health dissatisfaction	**1.28 (1.26/1.29)**[a]	**1.51 (1.44/1.60)**[a]
Self-rated lack of health	**1.42 (1.41/1.44)**[a]	**1.77 (1.69/1.86)**[a]
Dissatisfaction with health care in country	1.12 (1.11/1.13)[a]	1.11 (1.05/1.16)[a]
Prescribed medicines used last two weeks		
Arthritis	1.63 (1.49/1.79)[a]	1.94 (1.36/2.76)[a]
Angina pectoris	**1.30 (1.15/1.47)**[a]	**2.43 (1.65/3.59)**[a]
Asthma	1.20 (1.03/1.39)[a]	1.44 (0.80/2.57)
Tuberculosis	1.86 (1.29/2.69)[a]	3.75 (1.37/10.29)[a]
HIV/AIDS	1.10 (0.66/1.83)	2.95 (0.87/10.03)
Other (non-psychiatric)	1.41 (1.35/1.48)[a]	1.64 (1.36/1.99)[a]
Total medicines (0–6)	**1.31 (1.26/1.35)**[a]	**1.54 (1.36/1.75)**[a]

[a]Significant results using as comparison group individuals without diagnosis of psychosis nor psychotic symptoms in the prior 12 months
Values in bold indicate non-overlapping 95% CIs between the two columns

dissatisfaction, worse self-rated health, higher dissatisfaction with health care in the country, and higher self-reported consumption in the two previous weeks of medicines for most conditions included in the study, except for HIV. There was also a statistically significant positive effect for at least one overnight stay in hospital during the previous five years (excluding psychiatric reasons), and for the length of the stay. Comparing people with psychotic symptoms and a lifetime diagnosis of psychosis vs. those without diagnosis and symptoms, there was also an increased probability of most variables in the former, except for consumption of medicines for HIV or asthma, as well as for the length of the last overnight stay in a hospital for non-psychiatric reasons.

Comparing the two columns in Table 2, there was an overlap in ORs, except for hospital stay in the previous 5 years, consumption of medicines for angina, health dissatisfaction, self-reported lack of health, and total number of medicines currently being taken, for which the presence of diagnosis plus psychotic symptoms in the last 12 months was associated with a higher probability.

The mean number of somatic illnesses was significantly higher ($t=34.0$; $p<0.001$; $g=1.05$, 95% CI: 0.99-1.11) in subjects with a psychotic diagnosis and psychotic symptoms (0.79 ± 0.97) than in those with no psychotic symptoms or diagnosis (0.24 ± 0.52). Similarly, it was significantly higher ($t= 57.8$; $p<0.001$; $g=0.40$, 95% CI: 0.39-0.41) in individuals with at least one psychotic symptom but no psychotic diagnosis (0.46 ± 0.72) than in those without diagnosis or symptoms. Among subjects with psychotic symptoms, the

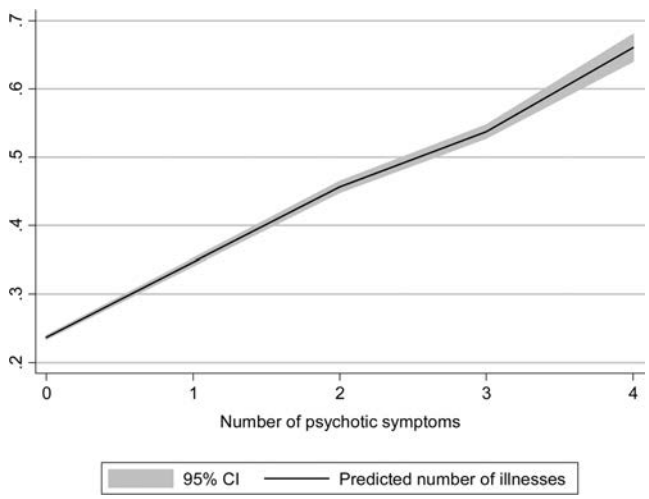

Figure 1 Linear prediction of number of illnesses according to the number of psychotic symptoms, with 95% confidence bands. Illnesses included: angina pectoris, arthritis, asthma, diabetes, and tuberculosis (range 0-5).

association with somatic illnesses was stronger in subjects with a lifetime diagnosis of psychosis than in those without, as shown by the not overlapping CIs in the effect sizes.

As shown in Figure 1, the number of somatic illnesses increased with the number of reported psychotic symptoms ($F=969.3$; $p<0.001$). Post-hoc comparisons (Scheffé) indicated that people reporting four psychotic symptoms had significantly more somatic illnesses (0.68 ± 0.88) than the other groups ($p<0.001$ in all comparisons); people with three symptoms (0.52 ± 0.78) had more illnesses ($p<0.001$) than people with two (0.45 ± 0.71), one (0.40 ± 0.66) or zero (0.24 ± 0.52) symptoms; people with two symptoms had more illnesses ($p<0.001$) than those with one or no symptoms; and people reporting one symptom had more illnesses than those without symptoms and no lifetime diagnosis of psychosis ($p<0.001$).

Individuals with psychotic symptoms in the past 12 months and a lifetime diagnosis of psychosis had consumed more medicines prescribed by a medical professional (excluding psychiatric medications) than persons without psychotic symptoms or diagnosis (0.19 ± 0.48 vs. 0.14 ± 0.41, $t=4.1$; $p<0.001$). Likewise, people with at least one psychotic symptom took more medicines than those without symptoms or diagnosis (0.16 ± 0.43 vs. 0.14 ± 0.41, $t=7.8$, $p<0.001$). When comparing the amount of medicines consumed by subjects with different numbers of reported psychotic symptoms, there was a clear overall omnibus difference ($F=18.1$, $p<0.001$). However, post-hoc comparisons (Scheffé) indicated that differences were only in the direction of a higher consumption for those with one (0.17 ± 0.44; $p=0.012$), or two (0.17 ± 0.44; $p=0.021$) as compared to persons with four psychotic symptoms (0.14 ± 0.40), and with one, two or three symptoms (0.16 ± 0.41; $p<0.001$ in all comparisons) as compared to those without psychotic symptoms (0.14 ± 0.41).

DISCUSSION

The presence of even isolated psychotic symptoms may confer risk for medical comorbidities. Our results indicate that individuals with psychotic symptoms but no psychotic diagnosis, compared to those without psychotic diagnosis or symptoms, present more lifetime medical conditions and health problems, more (and longer) non-psychiatric overnight stays in hospital (with no differences in other health care indicators), and higher consumption of non-psychiatric medicines prescribed by a professional. Most results are replicated, and in most comparisons the effects are higher, when subjects with a diagnosis of psychosis plus psychotic symptoms over the last 12 months are included in the analyses.

Although our results are in line with previous work suggesting that psychotic illnesses are related with worse physical health (4,5,7,8,34) and higher rates of various medical conditions such as angina pectoris or cardiovascular problems (10-12,35), asthma or pulmonary problems (13,35-37) and tuberculosis (38,39), they suggest that this relationship is not dependent on the presence of a psychotic disorder, but that the critical factor is having experienced at least one psychotic symptom. The same applies to the association of psychotic symptoms with other health-related factors, such as presence of accidents, including automobile accidents (40), mouth or teeth problems (7,13,41,42), smoking (4,10-12,18), alcohol abuse (4,5,43) or hearing and vision problems (13,44,45). Although a lower frequency of rheumatoid arthritis has been previously reported for patients with schizophrenia (7,46), this negative association was not replicated in a population-based analysis (47), which also found that the incidence of arthritis in parents of schizophrenia patients was higher than in parents of controls. Unlike most previous studies on psychosis, the term arthritis in this study was not restricted to rheumatoid arthritis. A positive relationship between schizophrenia and rheumatic diseases has also been found previously (47,48).

The use of health care services was higher in persons with psychotic symptoms, particularly in cases with more severe problems needing inpatient attention. Regular visits to health services, however, were not more common among subjects with psychotic symptoms. A possible explanation for this finding could be that patients with psychotic symptoms have worse access to the usual filter systems, given their pathology-driven difficulties in engaging in routine medical care and interpreting illness-related signs (49,50). To be identified by the health system, somatic illnesses in individuals with psychosis may need to be more severe, or to have progressed enough to require treatment in hospital settings (51). Self-rated lack of health and dissatisfaction with health, higher in people with vs. without psychotic symptoms in our sample, also point in that direction.

In all analyses, country of origin, gender, age, and socioeconomic status were statistically controlled for. Therefore, it can be assumed that the results of the present study are globally independent of the country, the socio-economic status or the development level of health systems in each country.

The higher frequency of medical conditions among people with psychoses in this international sample replicates previous results from single countries, but the finding that similar medical complications are present among subjects with isolated psychotic symptoms regardless of their country of origin, has not been, to our knowledge, previously reported, and points to a greater disadvantage of these individuals, even if they are not to develop a full psychotic illness or if they are in the earlier stages of psychotic processes. Our results may be explained by the existence of a physiopathological link based on genetic, inflammatory, immunological and/or metabolic mechanisms, underlying the relationship between psychotic symptoms and physical diseases (20,52-54). The higher frequency of smoking and excessive alcohol consumption, found in our study among subjects with psychotic symptoms, could also mediate the association between those symptoms and physical diseases.

Promoting general physical health and improving screening methods for comorbid medical conditions (55-58) seems to be relevant in persons with psychotic symptoms across countries, even if they do not meet criteria for a psychotic disorder.

The cross-sectional nature of this study does not make it possible to address the direction of the causal link between medical conditions and psychotic symptoms. Likewise, the lack of data on potential determinants of severity or disability associated with psychotic symptoms, such as the number and frequency of episodes, episode length, age at onset, and episode severity, limits the generalization of results to the whole continuum of persons with psychotic symptoms. In addition, the range of psychotic experiences was limited, and not assessed by a clinical interview. Longitudinal studies with more experienced interviewers are needed in order to analyze the natural history of these symptoms in the general population (59).

The strengths of the study include the large sample size and the worldwide scope, including all regions of the world with all levels of development. Most of the research in the domain of psychotic experiences has been conducted in Western countries, and little is known about regions in which multiple economic, cultural or social factors or differences in the health systems can markedly affect the distribution of psychotic symptoms. The present study was performed with nationally representative samples of non-institutionalized persons, avoiding potential problems associated with clinical samples, such as Berkson's bias (60). Notably, country effects, including the categorization of the country's economic status (in addition to individual age and gender), were statistically controlled for.

In conclusion, the present study shows that the presence of at least one psychotic symptom, independent of a psychotic disorder diagnosis, is related to more comorbid medical problems, risky lifestyle behaviours, and an increased use of health services for chronic medical conditions, involving overnight stays in hospitals. Given the sample analyzed, this trend seems to hold worldwide, regardless of the socio-economic development of the country or the specific health care system. Patients with psychotic disorders and even with psychotic symptoms not fulfilling diagnostic criteria for a psychotic disorder should be screened for additional medical problems, and general practitioners should be trained in the identification of patients with these problems, in order to optimize the functioning of health systems and avoid the problems and additional costs associated with comorbid conditions.

Acknowledgements

This work was supported by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III, CIBERSAM, Madrid Regional Government (S2010/BMD-2422 AGES), European Union Structural Funds, Fundación Alicia Koplowitz, Fundación Mutua Madrileña, ERA-NET NEURON (Network of European Funding for Neuroscience Research) and the World Health Organization.

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DOI 10.1002/wps.20070

Parenting and child mental health: a cross-cultural perspective

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In its most general instrumental sense, parenting consists of care of the young in preparing them to manage the tasks of life. Parents provide childhood experiences and populate the environments that guide children's development and so contribute to child mental health. Parenting is expressed in cognitions and practices. However, parents do not parent, and children do not grow up, in isolation, but in multiple contexts, and one notable context of parenting and child mental health is culture. Every culture is characterized, and distinguished from other cultures, by deep-rooted and widely acknowledged ideas about how one needs to feel, think, and act as an adequately functioning member of the culture. Insofar as parents subscribe to particular conventions of a culture, they likely follow prevailing "cultural scripts" in childrearing. Broadening our definition, it is therefore the continuing task of parents also to enculturate children by preparing them for the physical, psychosocial, and educational situations that are characteristic of their specific culture. Cross-cultural comparisons show that virtually all aspects of parenting children are informed by culture: culture influences when and how parents care for children, what parents expect of children, and which behaviors parents appreciate, emphasize and reward or discourage and punish. Thus, cultural norms become manifest in the mental health of children through parenting. Furthermore, variations in what is normative in different cultures challenge our assumptions about what is universal and inform our understanding of how parent-child relationships unfold in ways both culturally universal and specific. This essay concerns the contributions of culture to parenting and child mental health. No study of a single society can address this broad issue. It is possible, however, to learn lessons about parenting and child mental health from the study of different societies.

Key words: Culture, parenting, beliefs, behaviors, methodology, psychiatry, social policy

(World Psychiatry 2013;12:258–265)

Parenting contributes in central ways to the course and outcome of child development (1-3). Parental caregiving plays influential parts in children's mental health because it regulates the majority of child-environment interactions and helps to shape children's adaptation. During early childhood, more than 100 billion neurons develop and connect to configure brain networks through interactions of genetics, environment, and experience (4). Parenting plays key parts in this process and so shapes mental and physical health, behavior and academic skills, and even labor market participation over the life course (5,6). But parenting itself is shaped and afforded meaning by culture (7).

Just as cultural variation clearly dictates the language children eventually speak, cultural variation exerts significant and differential influences over mental, emotional, and social development of children. Every culture is characterized, and distinguished from other cultures, by deep-rooted and widely acknowledged ideas about how one needs to feel, think, and act as a functioning member of the culture. These beliefs and behaviors shape how parents rear their offspring. Culture helps to construct parents and parenting, just as culture helps to define mental health. Culture is also maintained and transmitted by influencing parental cognitions that in turn shape parenting practices (7,8). Whether culturally universal or specific, controls are in place to ensure that each new generation acquires culturally appropriate and normative patterns of beliefs and behaviors.

In this article, I describe the intersection between parenting and culture, and its significance to child mental health.

PARENTING AND CULTURE

In its most general instrumental sense, parenting consists of care of the young in preparing them to manage the tasks of life. Parents provide childhood experiences and populate the environments that guide children's development. Biological parents contribute directly to the genetic makeup of their children, and biological and social parents alike directly construct children's experiences.

In the minds of most observers, mothers are unique, the role of mother universal, and motherhood unequivocally principal to child development (9), even if historically fathers' social and legal claims and responsibilities on children were pre-eminent (10). Cross-cultural surveys attest to the primacy of maternal caregiving (11,12). On average, mothers spend between 65 and 80 percent more time than fathers do in direct one-to-one interaction with young children (13). Fathers may withdraw from their children when they are unhappily married; mothers typically never do (14).

Fathers are neither inept nor uninterested in child caregiving, of course. Mothers and fathers tend to divide the labor of caregiving and engage children emphasizing different types of interactions, mothers providing direct care and fathers serving as playmates and supports (9,15). Research involving both traditional (16) and non-traditional (father primary caregiver) families (17) shows that parental gender exerts a greater influence than parental role or employment status. Western industrialized nations have witnessed increases in the amount of time fathers spend with their children; in reality, however, most fathers are still primarily helpers (18).

Notably, different cultures sometimes distribute the responsibilities of parenting in different ways. In most, mother is the principal caregiver; in others, multiple caregiving may be the norm. Thus, in some cultures children spend much or even most of their time with significant other caregivers, including siblings, non-parental relatives, or non-familial adults. Various modes of child caregiving, like nurturance, social interaction, and didactics, are distributed across diverse members of a group.

Parenting is expressed in cognitions and practices. Parents' beliefs – their ideas, knowledge, values, goals, and attitudes – hold a consistently popular place in the study of parenting and child mental health (19-21). Parental beliefs serve many functions; they generate and shape parental behaviors, mediate the effectiveness of parenting, and help to organize parenting (22,23). More salient in the phenomenology of the child are parents' practices – the actual experiences parents provide children. Most of young children's worldly experience stems directly from interactions they have within the family. Parenting cognitions and attainment of parenting goals are achieved through parenting practices.

Human beings do not grow up, and adults do not parent, in isolation, but in multiple contexts (24), and one notable context of parenting and child mental health is culture. Paradoxically, culture is notoriously difficult to define. Some have considered it a complex of variables (25-27), whereas for others culture constitutes learned meanings and shared information transmitted from one generation to the next, that is "... as set of control mechanisms – plans, recipes, rules, instructions ... – for the governing of behavior" (28). Culture, therefore, consists of distinctive patterns of norms, ideas, values, conventions, behaviors, and symbolic representations about life that are commonly held by a collection of people, persist over time, guide and regulate daily living, and constitute valued competencies that are communicated to new members of the group.

Each society prescribes certain characteristics that its members are expected to possess or act on, and proscribes others they must not do, if they are to function adequately and normally as members of that society. Some prescriptions and proscriptions may be universal and cross cultures; an example might be the requirement for parents (or specified parent surrogates) to nurture and protect children (2). Other standards and values vary greatly from one culture to another; an example might be whether and how to discipline children (29).

Parental caregiving blends intuition and tuition. Parents sometimes act on their intuitions about caregiving. For example, almost everywhere parents speak to their infants even though they know that babies cannot yet understand language. However, parents also acquire understandings of what it is to parent effectively by living in a culture: generational, social, and media images of parenting, children, and family life play significant roles in helping people form their parenting cognitions and guide their parenting practices. Parents in different cultures receive many different kinds of guidance about how to rear children properly, whether in the form of books of advice, suggestions from family and friends, or direct training by example. Insofar as parents belong to a culture and subscribe to particular conventions of that culture, they likely follow prevailing "cultural scripts" in childrearing.

Variations in culture make for subtle as well as manifest, but always impressive and meaningful, differences in patterns of parenting and child mental health. Cross-cultural comparisons show that virtually all aspects of parenting children are informed by culture. For example, mothers in rural Thailand do not know that their newborns can see, and often during the day they swaddle infants on their backs in a fabric hammock that allows the baby only a narrow slit view of ceiling or sky (30). New mothers from Australia and Lebanon living in Australia expect very different timetables of child development, and their culture shapes mothers' expectations much more than other factors, such as experiences observing their own children or directly comparing their children to other children (31).

Culture pervasively influences when and how parents care for children, the extent to which parents permit children freedom to explore, how nurturant or restrictive parents are, which behaviors parents emphasize, and so forth. Japan and the United States maintain reasonably similar levels of modernity and living standards and both are highly child-centered societies, but the two differ in terms of childrearing (32-34). Japanese mothers expect early mastery of emotional maturity, self-control, and social courtesy in their children, whereas American mothers expect early mastery of verbal competence and self-actualization in theirs. American mothers promote autonomy and organize social interactions with their children so as to foster physical and verbal assertiveness and independence. By contrast, Japanese mothers organize social interactions with children so as to consolidate and strengthen closeness and dependency within the dyad, and they tend to indulge young children. These contrasting styles are evident in mother-infant interactions as early as 5 months (35).

Parents normally caregive faithful to indigenous cultural belief systems and prevailing cultural behavior patterns. Indeed, culturally constructed attitudes can be so powerful that parents are known to act on them, setting aside what their senses might tell them about their own children. For example, parents in Samoa think that all young children have an angry and willful character, and, independent of what children might actually say, parents consensually report that their children's first word is "tae" – Samoan for "shit" (36).

Importantly, culture-specific patterns of childrearing can be expected to adapt to each specific society's setting and needs. What parenting is and how it works reflect cultural context. Parenting is a principal reason why individuals in different cultures are who they are and often differ so from one another. Central to a concept of culture, therefore, is

the expectation that different cultural groups possess distinct beliefs and behave in unique ways with respect to their parenting.

Parents in different cultures typically harbor different beliefs about their parenting as well as about children (19,37). In a study in seven cultures (Argentina, Belgium, France, Israel, Italy, Japan, and the United States), mothers evaluated their competence, satisfaction, investment, and role balance in parenting and attributed their successes and failures in parenting to ability, effort, mood, parenting task difficulty, or child behavior (38). Systematic country differences for both self-evaluations and attributions emerged that were interpretable in terms of cultural orientations. For example, Argentine mothers rated themselves relatively low in parental competence and satisfaction and blamed parenting failures on their lack of ability. Their insecurity about mothering appeared to be consistent with the relative lack of social supports, particularly help and advice about childrearing available to them. By contrast, Belgian mothers rated themselves as highly satisfied with their caregiving, which might be expected in light of Belgium's strong childcare supports provided to parents (e.g., periodicals, consultancies, home visits, health care information workshops, and parenting demonstration classes).

Culture-based expectations about developmental norms and milestones (when a child is expected to achieve a particular developmental skill, for example) in turn affect parents' appraisals of their child's development. Hopkins and Westra (39,40) surveyed English, Jamaican, and Indian mothers living in the same city and found that Jamaican mothers expected their children to sit and to walk earlier, whereas Indian mothers expected their children to crawl later. In each case, children's actual attainment of developmental milestones accorded with their mothers' expectations.

Parents' beliefs have power. Parents in most societies speak to babies and rightly see them as comprehending interactive partners long before infants produce language, but parents in some societies think that it is nonsensical to talk to infants before children themselves are capable of speech and so do not speak to them (36). Parents in some societies think of young children as interactive partners and play with them, whereas parents in other societies think that such behavior is pointless (41). Indeed, cultural differences in some parenting beliefs appear to persist even among people born and reared in one culture who then relocate to another culture with different childrearing norms. Pachter and Dworkin (42) asked mothers from minority (Puerto Rican, African American, West Indian/Caribbean) and majority (US European American) cultural groups about normal ages of attainment of typical developmental milestones during the first 3 years of life: differences emerged among ethnic groups for more than one-third of developmental milestones assessed. Cognitions of the majority group are therefore not always readily adopted, and culturally significant parenting beliefs and norms often also resist change (43). In the United States, Japanese immigrant mothers' cognitions tend to be similar to those of Japanese mothers or intermediate between Japanese and US mothers; however, South American immigrant mothers' parenting cognitions more closely resemble those of US European American than South American mothers (44). Different immigrant groups adopt and retain specific cognitions and practices differently (45).

Although much theoretical and empirical emphasis is now placed on cross-cultural differences, many developmental milestones, parenting strategies, and family processes are likely to be similar across cultures. Evolutionary thinking appeals to the species-common genome, and the shared biological heritage of some psychological processes presupposes their universality (46) as do shared historical and economic forces (47). Thus, some demands on parents are common. For example, parents in all societies must nurture and protect their young (2), and at the end of the day all parents must help children meet similar developmental tasks, and all parents (presumably) wish physical health, social adjustment, educational achievement, and economic security for their children, however these successes may be instantiated in a particular culture.

Furthermore, the mechanisms through which parents likely influence children are universal. For example, social learning theorists have identified the pervasive roles that conditioning and modeling play as children acquire associations that subsequently form the basis for their culturally constructed selves. By watching or listening to others who are already embedded in the culture, children come to think and act like them. Attachment theorists propose that children everywhere develop internal working models of social relationships through interactions with their primary caregivers and that these models shape children's future social relationships with others (48). Moreover, social and economic development and information globalization present parents today in different cultural groups with many (increasingly) similar socialization issues and challenges (e.g., Internet safety).

Whether culturally common parenting patterns reflect factors indigenous to children and their biology, biological bases of caregiving, the historical convergence of parenting styles, shared economic or ecological factors, or the increasing prevalence of migration or dissemination via mass media is difficult, if not impossible, to determine. Modernity has witnessed a worldwide pattern of change toward urbanization, media homogeneity, and Westernization that cumulatively contributes to dissolution of traditional cultural patterns. In the end, different peoples (presumably) wish to promote similar general competencies in their young and some do so in qualitatively and quantitatively similar ways.

When different parenting cognitions or practices connote different meanings or serve different functions in different settings, this provides evidence for cultural specificity. For example, mothers in China and India use authoritative

(high warmth, high control) and authoritarian (low warmth, high control) parenting practices, respectively, in ways that relate to differences in their goals of social and emotional development in their children (49). Initiation rites deemed harmless to children in some cultures may be judged abusive in others.

Unsurprisingly, the determinist arguments marshaled by culture-specifists resemble those invoked by culture-universalists. Adults in different cultures could parent differently because of their biological characteristics, for example, their differential threshold sensitivities or attention to child signals. Certain culturally specific biological characteristics of children, such as constitutionally based temperament, could promote culture-specific parental attitudes and/or activities. Finally, ecological or economic conditions specific to a given cultural setting might promote parental beliefs and behaviors indigenous to that culture, ones evolved differentially to optimize adjustment and adaptation of offspring to the circumstances of the local situation.

PARENTING, CULTURE AND CHILD MENTAL HEALTH

In what may be called the "standard model", expectations regarding what is culturally acceptable and what is not shape parents' caregiving cognitions, that in turn shape their childrearing practices and, ultimately, children's experiences and development. Thus, cultural norms become manifest in mentally healthy children through parenting. For example, US European American mothers of 1-year-olds encourage the development of individual child autonomy, whereas Puerto Rican mothers focus on maternal-child interdependence and connectedness (50). These cultural differences are embedded in caregivers' behaviors, with US European American mothers using suggestions and other indirect means of structuring their children's behavior, and Puerto Rican mothers using more direct means of structuring, such as commands, physical positioning, and restraints. Consider child behavioral inhibition, Chinese and Canadian parents' responses to this behavioral constellation, and children's further development. Both cultures have inhibited children, but traditional Chinese mothers have more warm and accepting attitudes, whereas Canadian mothers are more punitive. In school, shy and sensitive Chinese children do better academically and are rated more positively by their teachers and peers, in contrast to shy Canadian children who fare worse (51,52). Of course, beliefs do not always map to behaviors directly, but the two coexist in complex ways, and cultural meaning assigned to each is critical.

It is imperative to learn more about culture and parenting, so that scientists, educators, and practitioners can effectively enhance child mental health. Insofar as (some) systematic relations are established in a culture between how people parent and how children develop, the possibility exists for identifying some "best practices" in how to promote positive parenting and positive child mental health. Some parental practices are perceived as offensive in some cultures, but in others the same behaviors are thought to be benign to children's adjustment. For example, parenting practices in some cultural contexts include folk remedies, which are meant to help children recover from illness, but leave burns or other marks in the process (53,54). These parenting practices become problematic only when parents use them outside of their normative context (e.g., after immigrating to another culture where these behaviors conflict with mainstream cultural definitions of child maltreatment) (55). Legal cases involving such scenarios sometimes invoke cultural evidence (56): one judge dismissed a case in which a mother made small cuts on the cheeks of her two sons to signify that the boys had been initiated into her native tribe (57). Ear piercing illustrates a parenting practice that is normative in one culture (the United States) and that may physically hurt children in the short-term and permanently alter their appearance; nevertheless, parenting that countenances ear piercing is not defined as abusive, and there is no presumption that it has long-term negative effects on children's mental health. Contrariwise, some parenting practices may be detrimental to children even if they are sanctioned by the cultural group. Female circumcision is widely criticized as being abusive and having long-term negative effects on female health, despite its normativeness in certain cultural contexts (57,58). The global community has increasingly taken a stand that children have particular rights regardless of their culture and that it is sometimes necessary to intervene with parents to prevent serious harm. In 1990, the United Nations Convention on the Rights of the Child (CRC) placed the protection of children's rights at the forefront of the international community. The CRC exemplifies how the global community adopts positions that are meant to shape parenting worldwide.

Consistent parenting beliefs and behaviors help to promote children's mental health around culturally acceptable norms. Thematicity (the repetition of the same cultural idea across mechanisms and contexts) has special importance in culture as an organizer of behavior (59). So, for example, in the United States personal choice is closely bound up with how individuals think of themselves and make sense of their lives. Personal choice is built firmly on principles of liberty and freedom and is a persistent and significant psychological construct in the literature on US parenting and child mental health (60).

What is normative in a society matters. For example, the cultural climate in which child discipline occurs is as important as discipline per se in predicting mental health of children (61). In an empirical test of the role of cultural normativeness on parent-child relationships, the moderation link between mothers' use of physical discipline and children's adjustment was studied in six countries (62). Children's more frequently experiencing physical discipline was associated with anxiety, and more frequent use of

corporal punishment related to adult violence and endorsement of violence (63). However, countries differed in their reported normativeness of physical discipline and in the way that physical discipline related to children's adjustment. Children's perceived normativeness of physical discipline moderated the association between experiencing physical discipline and child anxiety and aggression. Children who perceived the use of physical discipline as being culturally normative expressed higher levels of aggression, regardless of whether they personally experienced high or low levels of physical discipline. More frequent use of physical discipline was less strongly associated with adverse child outcomes in contexts of greater perceived cultural normativeness. In short, the association between mothers' use of physical discipline and child mental health was moderated by the cultural normativeness of physical discipline.

US European American parents of adolescents are more likely to engage in authoritative parenting that emphasizes the growth of separation and autonomy within a supportive and responsive relationship, whereas Latin American, African American, and Asian American parents tend to engage in authoritarian parenting, with its greater emphasis on obedience and conformity (64). US American children are encouraged to discuss their own feelings and those of others as a way of increasing their understanding of emotion and ability to regulate it; Chinese families encourage attunement to the feelings of others, but restraint in the expression of own feelings, as key to group harmony (65). Chinese parents remind children of their past transgressions using story-telling, for example, to teach social norms and behavioral standards and to engender a sense of shame over bad behavior. In contrast, American parents avoid stories of transgression so as not to damage their children's self-esteem (66,67).

Some parenting-child mental health relations regularly recur even across very different cultures. When a particular parenting cognition or practice connotes the same meaning and serves the same function in different cultures, it likely constitutes a cultural universal. Parental psychological control of adolescents appears to have negative correlates across a wide variety of cultural contexts. In a study of 11 countries, including at least one each from Africa, Asia, Europe, the Middle East, North America, and South America, virtual unanimity was observed in the direction and significance of associations of parental monitoring with less, and psychological control with more, adolescent antisocial behavior (68).

However, the same parenting cognition or practice can also assume different meanings or functions in different cultural contexts. For example, in some cultures mutual eye contact sets the stage for interpersonal communication and social interaction (69), but in others mutual eye contact signals disrespect and aggression (70,71). Different meanings attached to particular behaviors can cause adjustment problems for children whose parents expect them to behave in one way that is encouraged at home (e.g., avoiding eye contact to show deference and respect) when children find themselves in contexts where adults attach different (sometimes negative) meanings to the same behavior (e.g., appearing disrespectful and unengaged with a teacher at school).

Conversely, different parenting cognitions and practices may connote the same meaning or serve the same function in different cultural contexts. In some cultural groups parents show affection predominately through their tone of voice, whereas in others parents demonstrate affection physically. These different displays serve the same function of making children feel loved, valued, and approved of by parents in their respective cultures. Interrelatedness and autonomy are important in all cultures, but the ways in which parents foster them in children vary as a function of the values and goals that exist in particular cultures (72,73). US American infants use mothers as a secure base from which to explore the world, and Japanese infants enjoy their mothers' indulgence of their needs (74). In essence, wholesome relationships are central in both cultures, but they assume different forms as a function of contrasting cultural emphases on individuation and accommodation. An authoritative parenting style leads to positive mental health outcomes for US European American children, but an authoritarian parenting style leads to positive outcomes for African American children (75).

The specificity and generality of parenting, and relations between parents and their children's mental health, are advantageously assessed through cultural research because neither parenting nor children's development occurs in a vacuum: both emerge and grow in a medium of culture. Variations in what is normative in different cultures challenge our assumptions about what is universal and inform our understanding of how parent-child relationships unfold in ways both culturally universal and specific.

CONCLUSIONS

Culture influences some parenting cognitions and practices and, in turn, child mental health from a very early age, through such pervasive factors as what parents expect of children, when and how parents care for children, and which behaviors parents appreciate, emphasize, and reward. Parents are influenced by conventionalized images of what is and what ought to be proper childrearing, and so they (even unconsciously) seek to implement an agendum derived from concepts that characterize their culture-specific milieu.

It is the continuing task of parents to caregive as well as to enculturate children by preparing them for the physical, psychosocial, and educational situations that are characteristic of their specific culture. For this reason, many social theorists have asserted that the family generally, and the parent-child relationship specifically, constitute the effective crucible for the early (and perhaps eventual) development of the individual and the continuity of culture.

Every culture promotes unique ways of adapting to the stringencies of its requirements, ecology, and environment and has developed traditions to achieve the common goals of childrearing. As a consequence, even in the face of some shared goals, parenting children varies dramatically across cultures. The cultural contexts of parenthood and childhood are therefore of increasing interest to world psychiatry.

That said, after approximately a century of psychological study, with considerable attention paid to parenting and child mental health, still too little is known about the beliefs and behaviors, life circumstances and experiences, of children or their parents in non-Western cultures. In the past, scholars have tended to generalize from person- or situation-specific behaviors to species-general conclusions without paying adequate attention to circumstances and limitations imposed by culture. A pervading critique is that, traditionally, research in this field has tended to describe constructs, structures, functions, and processes in accordance with ideals appropriate to Western, educated, industrialized, rich, and democratic societies (76-78). For example, Patel and Sumathipala (79) surveyed leading psychiatry journals and found that only "6% of the literature [was] published from regions of the world that account for over 90% of global population". A central limitation related to culture has impeded comprehensive understanding of parenting and child mental health. This limitation has led to many critiques of single-culture perspectives and motivated consistent calls for more cross-cultural study (77,79,80). Thus, researchers increasingly recognize the need to expand the scope of parenting inquiry to include more culturally diverse samples. Heeding these calls is important to avoid misperceptions of universality as well as biases of monocultural study.

There is, therefore, definite need and significance for cultural approaches to parenting and child mental health. Descriptively they are invaluable for revealing the full range of human parenting and child mental health. Study across cultures also furnishes a check against ethnocentrism. Acceptance of findings from any one culture as "normative" is too narrow in scope, and ready generalizations from them to parents and children at large are uncritical. Comparison across cultures is also valuable because it augments an understanding of the processes through which biological variables fuse with environmental variables and experiences in development. Awareness of alternative modes of development enhances understanding of the nature of human variation. From early roots in ethnographic work, studies of culture and parenting have grown to occupy an increasingly important position in developmental thinking. We need more detailed and systematic data on cultural beliefs, behaviors, and the settings of parent and child development.

The long-standing issues found at the intersection of parenting, child mental health, and culture are the following. What are the universals of child care and child development in our species? How do parents organize the effective environments of childhood? What are the contributions of culture to parenting, child mental health, and parent-child relationships? No study of a single society can answer these broad questions. It is possible, however, to learn lessons from the study of different societies that may offer partial answers.

Overall, perhaps the most important single thing that a parent does for a child is determine the culture into which that child is born (81). The cultural study of parenting and child mental health is beneficially understood in a framework of necessary versus desirable demands. A necessary demand is that parents and children communicate with one another. Normal interaction and children's wholesome mental health depend on it. Not unexpectedly, communication appears to be a universal aspect of parenting and child development. A desirable demand is that parents and children communicate in certain ways adapted and faithful to their culture.

The cultural perspective reveals the ideals and norms of the society and how they are instantiated; the parental perspective defines beliefs and behaviors that characterize childcare; and the child perspective assesses the impact of culture and caregiving on the development of mental health.

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DOI 10.1002/wps.20071

How to convince politicians that mental health is a priority

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Politicians, especially ministers of health, are crucial to drive national policy and strategy, because they can bring political will to bear on decision making, speed up decision making, and steer decisions in a specific direction. Therefore it is important to persuade politicians that mental health should be a priority.

One of the most helpful things a minister of health can do to make mental health a real priority is to ensure that mental health is well integrated into the national health sector strategic plan at each level (community, primary care, district, provincial and national). This will make it much more likely that community based and primary care health staff will see mental health as an integral part of their work, that district staff will see mental health as an essential part of their support responsibilities to primary care alongside other health priorities, and that provincial level staff will see it as a priority to support the districts within each province to deliver local mental health services. Similarly, it is helpful for the minister to facilitate liaison between health and other relevant sectors (e.g., education, social welfare, criminal justice), so that mental health is appropriately integrated with each of their strategic plans (1,2).

Within the health sector itself, it is likely to be better for population health outcomes to focus on integrating mental health into the general health system rather than seeking a parallel vertical funding and delivery system (3), in the light of growing evidence that other well-funded vertical programmes for communicable diseases have often weakened health systems' capacity to address broader health needs (4).

CHALLENGES TO INFLUENCING POLITICIANS

Politicians are not necessarily health professionals, let alone mental health professionals, and do not have detailed knowledge of mental health issues. They frequently only last a few months to a year or two in one specific ministerial post; at best around three years. There may be tensions between different stakeholders, and careful background dialogue is helpful so that the main stakeholders carry a concerted message.

Politicians usually want to see progress; and they want to have ownership, particularly things they can announce to the public for which they can take political credit. Therefore, it is helpful to establish a steady stream of developments that politicians can announce and take credit for. This is often a good way of briefing politicians, as they will need their speeches to be drafted and these can be used to set out the arguments for priority status.

WHAT ARGUMENTS CAN BE USED?

The general arguments used to try and persuade politicians are that mental illness is common, disabling, accompanied by significant physical illness and mortality (5-8), that effective interventions are available, and that it is important to address the human rights of people with mental illness. If these arguments were enough to persuade politicians, mental health would have long been a major priority in all countries, as the evidence has been available for several decades (9). Therefore mental illness also needs to be placed in the context of critical concerns for politicians, which include overall improvement of national economic productivity; achievement of economic, health, education, social and environmental targets, including those set in the Millennium Development Goals; and the issues that trouble their constituents, families and friends.

PLACING THE ARGUMENTS WITHIN THE POLITICAL CONTEXT

Politicians are concerned with the whole functioning of government: not just health, but also the other sectors of the economy, employment, education, social welfare, housing, criminal justice, as well as defence. Within the health system itself, the politicians are concerned with the overall structure and financing of the general health system, and the way in which it may deliver improved health outcomes for child health, reproductive health, and communicable as well as non-communicable diseases. It therefore helps to place the arguments within the political context in which the politician is functioning, so he/she can see how mental health matters to his/her other political concerns, and how it will assist achievement of the goals of other health targets and non-health sector goals.

TAKING ACCOUNT OF OTHERS WHO ARE ADVISING THE POLITICIANS

The politicians are influenced by government economists and external economic advisors. There are also government

information technology experts who influence the data which is collected by governments, and this data collection influences the information available to governments on which decisions may be based. It is often particularly difficult to establish appropriate mental health data collection at community and primary care levels in low- and middle-income countries (10), resulting in a dearth of information for planning purposes.

Politicians are, of course, also operating within the context of daily bombardment by the media about current topics of concern, and sometimes by daily advice from close political advisors about the likely electoral impact of any decision. Politicians may make the crucial decisions, but their implementation is undertaken by civil servants and professionals in the relevant sectors, who also need to be persuaded of the need to make mental health a priority, if implementation is to proceed successfully with serious impact. Political life spans are generally too short to rely on the support of a politician without also engaging the support of his/her civil servants.

WHAT POLITICIANS NEED TO KNOW TO MAKE CONSIDERED JUDGEMENTS ABOUT MENTAL HEALTH ISSUES

It is helpful for politicians to be briefed about the wider picture of mental health in their country, if they are to consider it a priority. Therefore, some understanding is required of the broad concepts of positive mental health, mental illness, disability, premature physical mortality, and suicide; of the different broad categories of illness and how common they are; of risk and protective factors; of impact on other illnesses; of wider impact on education, employment, productivity of individuals and countries; of the levels of health care relevant to mental health including household and community, primary care, secondary care, and tertiary care; and of the intersectoral aspects of mental health, including education, social welfare, employment and criminal justice. Without such a multilevel multisectoral understanding, political solutions to meeting population needs for mental health are likely to be insufficient.

WHERE CAN POLITICIANS BE INFLUENCED?

Politicians can be found and influenced in a variety of places, such as within their ministry, at public events, when invited to a health care setting, in dialogue in the media, at social gatherings and chance encounters. The core principles for oral encounters in each setting are similar, namely to be brief, unambiguous, balanced, memorable and clearly related to context. The length of the conversation will have to be tailored to the setting and situation, and any oral briefing needs to be accompanied by a written note. It is not always clear how long one will have with the minister, so it is often best to start with a summary and then expand further if time permits. It is helpful to link the briefing to current media and political concerns, to the special interests and concerns of the minister, to overall government strategy, and to overall resource availability.

Crises should be used as an opportunity, not just to solve the immediate problems, but also to promote the long-term agenda for mental health, to explain complex issues, and to instigate the next research steps.

As well as oral briefings and written briefings by a single person or organization to a single politician, there can also be major cross-government commissioned reviews which influence politicians. For example, the Foresight Report on Mental Capital and Wellbeing commissioned by the UK Government Chief Scientist in 2006, reported to the whole of government in 2008 (11), directly encouraged action across government departments since then (12), and the US Institute of Medicine Report on Neurological, Psychiatric and Developmental Disorders (13) resulted in increased prioritization and research investment in mental health by major international donors.

NEVER TO GIVE UP

The final point, but perhaps the most important, is never to give up. Progress inevitably tends to ebb and flow, but as long as the dialogue with and pressure on politicians is maintained, overall progress over ten to twenty year time spans is generally significant. Too many psychiatrists become discouraged when politicians change post, instead of seeing each new incumbent as a new opportunity. The briefing given to the previous one about the conceptual framework and importance of mental health will never be wasted, as it will have relevance whatever the future post held, so that mental health can be considered in all policy making.

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DOI 10.1002/wps.20073

Beyond dichotomies: confronting the complexity of how and why individuals come or do not come to mental health care

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With up to 50% of individuals in the "developed" world and up to 85% in the "developing" world assessed to have mental health problems but receiving no treatment (1), inevitable questions arise about the reasons for the gap. There are standard explanations – issues of access, cost and manpower; issues of mental health literacy or lack thereof; and of course, the large set of issues of prejudice and discrimination that we call stigma. But the now extensive list of research correlates that have been documented across hundreds of studies have yet to unravel the subtleties that underlie the dilemma of unmet need.

Here, a slightly different approach takes some liberties with classic and cutting-edge findings to set a foundation for a holistic, cross-cultural understanding of how person-related and service-related factors come together to influence how individuals respond to the onset of mental health problems. These general principles are writ large, embracing the notion that people, places and professions matter in all times and in all places, even as they play out differently in different societies.

SERVICE UTILIZATION RESEARCH: A BRIEF ORIENTATION

At least since the middle of the last century, utilization theories from diverse disciplines developed, placing primacy on different explanations of entry into treatment. Somewhat crudely put, medicine and psychiatry look to etiologically-based practices and professionals; anthropologists and psychologists look to cultural beliefs and individual motivations respectively; and economists and sociologists look to fiscal availability and organizational arrangements of services, including larger structures of inequality that facilitate or hinder access.

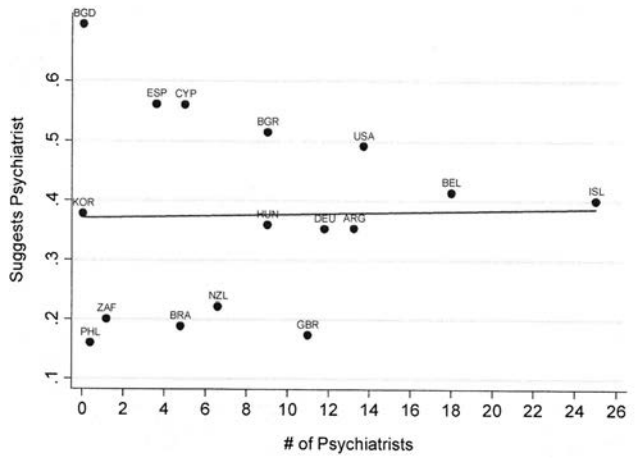
Over time, disciplinary perspectives have taken each other into account, resulting in a proliferation of revised models, hybrid models, and a nearly endless stream of diagrams or frames that purport to be new theoretical models. Yet, we still do not have a simple and clear answer about unmet need. Perhaps the dichotomous conceptualizations we tend to use in both research and practice stand in the way: either people see a physician or they don't; either people see a psychiatrist or a general practitioner; either it is their beliefs or their lack of insurance that matters; or either people belong to a majority group and think this way or they are part of an ethnic/racial/geographic minority and they do not. The list of paired comparisons is lengthy.

What is clear is that the messy realities of confronting the onset of mental health problems in every society challenge traditional ways of thinking. Perhaps *each* major approach brings a unique wisdom to the understanding of how individuals get, or fail to get, to services. If we are to understand the factors or forces, from local to global, that affect whether individuals with mental health problems end up receiving care, perhaps only a mosaic of the empirically validated, central points of each perspective can fully represent the complexity of the public response to the onset of mental illness (2).

FINDING 1: MULTIPLE PATHWAYS TO CARE EXIST IN EVERY SOCIETY ARISING, AT LEAST IN PART, FROM INDIVIDUALS' ATTEMPT TO USE THEIR OWN "COMMON SENSE" VISION (3)

Even individuals who end up in the same mental health treatment center are likely to have traveled very different pathways to get there. There are different, but regular and routine, pathways to care, molded to time and place. In the US, for example, just under half of those who had their first major contact with the public mental health system made any kind of decision to do so. Over a quarter ended up in the mental health system through a coercive pathway, whether brought in by social control authorities (e.g., police, jail/prison system, judicial discretion) or seriously pressured by their families. Even more curiously, over a third of individuals reported they "muddled through", traveling a pathway that was neither one they designed or was designed for them against their will (4).

All societies hold a reservoir of different kinds of lay and professional "advisors" that are likely to have been involved in the pathway to care. These "gateway providers" (5) determine crucial trajectories that shape outcomes. While we may be comforted by the finding that those who have the most serious mental health problems almost always get to treatment, this should be offset by the early and recent research which reveals that pathways, even for the most severe cases, tend to be lengthy in terms of time and numerous in terms of options sought (6-8).



ARG – Argentina; BEL – Belgium; BGD – Bangladesh; BGR – Bulgaria; BRA – Brazil; CYP – Cyprus; DEU – Germany; ESP – Spain; GBR – Great Britain; HUN – Hungary; ISL – Iceland; KOR – Korea; NZL – New Zealand; PHL – Philippines; USA – United States; ZAF – South Africa

Figure 1 The relationship between suggesting psychiatrist for schizophrenia and number of psychiatrists (r = .03, ns) (adapted from 13)

Thus, the implication of these findings is that not all utilization is "help-seeking", at least not necessarily by the individual affected; and, pathways are not efficient, even for the most serious cases. Thinking of service use under typical assumptions only interferes with our ability to understand the realities of responding to onset and the challenges of unmet need. The basic meaning of the response onset for individuals may be best captured by Anderson et al's "containment" (9), that is, the interpretation of changes in body and mind reflects social and cultural circumstances and experiences that tend to normalize the situation and respond with minimal changes in routines.

FINDING 2: THE USE OF SERVICES IS NOT A SOLITARY PROCESS NOR AN IDEOLOGICALLY-FOCUSED JOURNEY TO FORMAL TREATMENT

This is, of course, in some ways a corollary of the first set of findings. Yet, implicit in many theories of health services use is the image of a decision-maker, a rational individual weighing the costs and benefits of seeking care. Some approaches add in the influence of those around them (e.g., as "norms") as one more contingency in the calculus. Yet this view clashes with a now substantial body of research that onset, recognition and response are embedded in social networks. Illness behaviors are not just what individuals "do" (visit a clinic, pray, take over-the-counter medications, self-medicate with drugs and alcohol, exercise) but include those "individual consultations", sometimes wanted, sometimes forced (e.g., employers, teachers, parents), that are activating forces.

Social influence plays a big part of what happens in unmet need, by suggestion or substitution. Throwing out or clinging to the idea of "agency", that every instance of illness behavior is planned, thought out, and decided, is naïve. Individuals are neither lone, individualistic actors nor are they puppets of others or of the place and times in which they live. As described above, individuals may be proactive, they may go along, or they may resist. And, they may change their stance along the way. But they are always accompanied by what Antonucci (10) calls their "social convoy". Whether their social ties to others are extensive or decimated matters, and whether their networks hold informational and emotional resources or not shape use.

FINDING 3: CULTURE MATTERS AT THE INDIVIDUAL, THE LOCAL AND THE NATIONAL LEVELS

Again, these findings link and build on each other. If the structure of social networks matter, their counterpart in molding pathways is culture. Local ideas, beliefs, meanings and attitudes are embedded in and transmitted through the set of human ties in everyday life. As Mojtabai (11) recently demonstrated, even the larger, national context of stigma is associated with whether individuals support treatment use or not.

Culture also impacts treatment directly. Provider beliefs about what their patients *believe* turns out to be a poor substitute for specific knowledge that can be gained in the interaction itself. Individuals do not have to ideologically align themselves with one or another tradition of healing, one or another way of thinking about the etiology of mental illness. While providers may hold an ideological stand inculcated through professional training or apprenticeship, individuals do not. They can simultaneously hold beliefs about genetic causation and about "god's will" as part of the underlying etiology. These layers of beliefs allow for a practical and flexible response which translates into pathways to care when problems are not resolved. Culture may determine where that pathway starts, an individual's "cultural toolbox" may shape next steps, but whether relief is found will determine the pathway's endpoint.

FINDING 4: A SOCIETY'S ORGANIZATIONAL ARRANGEMENTS FOR CARE SET THE LIMITS AND THE POSSIBILITIES OF PATHWAYS TO CARE

Andersen (12), pioneering the role of access, famously noted that even individuals who hold the right beliefs and have great need can only use services if those can be acted upon because of geographical and financial availability. But again, findings do not line up with simple expectation. Figure 1 shows data from 15 countries in our Stigma in Global Context Study (13), a theoretically

and methodologically-synced, nationally representative study of public understanding and response to mental illness. When asked the open-ended question, "What should [name] do, if anything?", immediately after being read a case scenario of a person meeting DSM/ICD criteria for schizophrenia, there is little correspondence between availability of psychiatrists and the spontaneous mention of this option. Individuals in some countries with a moderate number of psychiatrists per capita (e.g., Great Britain) do not mention psychiatry, while many who have little hope of ever seeing a psychiatrist (e.g., Bangladesh) do. Of course, these findings are curious and bear more analysis and interpretation than possible here. The point here is, again, to show that what we "know" and what "we think we know" can be two different things, requiring us to recast our ideas given the wealth of data and a new era of science.

CONCLUSIONS

Mental illness lies in the area of complex diseases. How the public understands and reacts, and how that is linked to their illness behavior, represents a complex response. In the end, the public only seeks to be better – better than before the severe symptoms of many mental health problems diminished their well-being and, for many, created a critical turning point in their life trajectory. If, like other areas of science, we are poised at a new era of understanding which demands that our research embrace delays, missteps and pathways, our models and findings may provide a more useful foundation for improvements in clinical and community practices. If we assume complexity – that large interacting systems shape what people, including providers, do – we will synthesize rather than separate; ask rather than assume; and conceptualize messy reality rather than strive for false parsimony.

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DOI 10.1002/wps.20072

Teenage depression: some navigational points for parents and professionals

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Adolescence is an expected time of turbulence, with most showing mood shifts. Key dilemmas for parents include whether any "depression" is "normal" or of concern, how to raise the possibility of any depressive disorder with their adolescent and, if assistance is required, how to access appropriate assessment. Dilemmas for professionals include judging whether they have the relevant expertise for assessing and managing, how to structure a diagnostic interview, how to "relate" to the adolescent, and awareness of diagnostic and management nuances, especially prescription of psychotropic medications.

While there have been several previous monographs and papers on this topic (e.g., 1-3), as well as meta-analytic reviews of treatment options (e.g., 4), this paper overviews our personal clinical approaches.

"NORMAL" VERSUS "CLINICAL" DEPRESSION?

There are no absolute boundaries distinguishing clinical depression from "normal" depression in adults. Clinical mood disorders are broadly more severe, persistent, impairing and more likely to be associated with gravid symptoms such as suicidal ideation. While the same holds for adolescents, differentiation is confounded further by the turbulence of adolescence itself, non-specificity of some symptoms and the extent to which the adolescent lacks psychologically mindedness and "openness" to assessment.

While weighting the same parameters adopted in adult assessments, there are some useful "signals", particularly if the adolescent is resistive to interview. For example, distinct asocial behaviour (e.g., not mixing with friends, not replying to text messages, remaining in their room) or loss of "light in the eyes" suggests a more severe condition. Predicting suicidal risk in adolescents is as difficult and imprecise as for adults, but more complicated by the reality that their suicidal messages may simply reflect low-risk adolescent existential despair or be a high-risk warning. Professionals should not be concerned about risking "false positive" judgments (that is a fact of professional life) and, if in doubt, weight their management to a "worst case" scenario.

RAISING THE POSSIBILITY OF A MOOD DISORDER

It is right and appropriate for parents to directly raise their concerns with their adolescent child or, if the parent-child communication lines are poor, another family member (e.g., sibling, grandparent) or a close friend of the adolescent might accept enquiring gently. The aim should be to have concerns raised, to indicate the signs that have generated concern and to encourage a "conversation" with the adolescent to determine if professional assessment is warranted and by whom – ideally obtaining some agreement about each issue.

Assessment options range from generic support service (e.g., school counsellor) to general health services (e.g., primary practitioner) to specialist mental health service (e.g., psychiatrist). Coercing an adolescent to have an assessment or "tricking" the adolescent (e.g., not explaining that they are consulting a psychiatrist until at the professional's rooms) is counter-productive.

PROFESSIONAL ASSESSMENT

The optimal assessment model is for the health practitioner to start by explaining that he/she is undertaking a confidential interview, and that, while he/she may then wish to interview parents, the adolescent will be invited to nominate issues not to be raised.

The interviewer should relate as authoritatively and warmly to the adolescent as he/she would to a young adult interviewee and reject any attempt at a "parity" model (e.g., adopting an adolescent argot of "cool, groovy"). The secondary interview of the parents ideally occurs with the adolescent in the room, and with the interviewer first seeking to obtain the parents' impressions of their child over time (both for salient information and to reduce any tension) before inquiring into their recent concerns. As managing most people with mood disorders (particularly adolescents) is a "team game", I favour the clinician *then* providing all parties with his/her views on diagnostic probabilities, a formulation and management recommendations, followed by a discussion clarifying and detailing each relevant component. Obviously it may be inappropriate for a particular parent to be involved in the process (e.g., if there is an issue of sexual abuse), while delicacy rather than demanding absolute open communication may be required when parents are uncomfortable about discussing some of their observations (e.g., suicidal messages, psychotic features) in front of the adolescent.

Review visits should focus on the adolescent's and parents' judgement about progress. Confidentiality is of key importance at each stage and the managing clinician should state the "rules" to all family members. The clinician

should appreciate feedback about progress from parents – whether at the clinic or, at times, independently. In latter instances, the clinician should state that, while he/she is able to be a "receiver" of information, to respect their child's confidentiality, he/she is unable to be a "transmitter" in offline conversations. If an adolescent is at very high risk of killing themself, such rules of confidentiality are outweighed by the risks, and the parents should be alerted and brought into selection of immediate management options.

DIAGNOSING THE MOOD DISORDER

The dominant diagnostic model underpinning psychiatric classification and the evidence base of treatments is the dimensional DSM model, which effectively contrasts major versus minor depressions, but also categorizes bipolar I and bipolar II conditions. In the trials of different drug and non-drug interventions for major depression in adults, all treatments appear similarly effective (5), a non-specific result reflecting "major depression" itself being a non-specific "domain" subsuming multiple depressive disorders.

Our contrasting preference (5) is a sub-typing model which positions some categorical conditions (e.g., psychotic and melancholic depression; bipolar I and II disorders) and a set of heterogeneous "non-melancholic" depressive conditions.

Unipolar psychotic depression is quite rare, while unipolar melancholic depression is somewhat uncommon in adolescents. In adults, a distinctive feature of those conditions is overt psychomotor disturbance (e.g., distinctly observable retardation and/or agitation). In adolescents, signs of psychomotor disturbance are less common and best assessed as symptoms. Students experiencing melancholia will report (like adults) concentration difficulties, finding study difficult and acknowledging that their brain feels "foggy". There will be less light in their eyes and anergia (they just lie in bed in the morning) and diurnal variation of mood and energy (being generally worse in the morning).

While bipolar I disorder is also rare in adolescence, bipolar II disorder most commonly commences in mid to late adolescence and is seemingly becoming more prevalent – whether reflecting a true increase or greater awareness, better detection or improved screening. All adolescents being assessed for a mood disorder should be screened for a bipolar II condition.

Our approach to clinical identification of bipolar II disorder is to ask depressed adolescents if they have times when – neither depressed nor euthymic – they feel "energized and wired". If acknowledged, we ask whether, at such times, they are more talkative and loud, spend money excessively and feel shame later, become verbally or non-verbally indiscreet, need less sleep without feeling tired, observe a disappearance of any general anxiety, feel invulnerable, become more creative and take risks. While DSM imposes a minimum duration of four days, many adolescents report hypomanic episodes lasting hours to days. Their depressive episodes tend to be melancholic, albeit with "atypical features" of hypersomnia and hyperphagia over-represented.

The non-melancholic depressive conditions reflect the impact of significant life event stresses on certain attributional and personality styles, a model akin to adult disorders but with differing condition prevalences and some phenotypic variations. The personality styles of relevance include: a) anxious worrying (such adolescents are highly susceptible to depression before final school examinations); b) perfectionism (often again being vulnerable to exam stressors); c) social avoidance or severe shyness (the behaviourally inhibited teenager may become seriously depressed as a consequence of being bullied and "walked over"); d) rejection sensitivity (the adolescent is hypersensitive to judgement – praise or rejection – by others, and develops food cravings and hypersomnia when depressed); e) an intrinsically low self-esteem often due to emotional neglect in childhood, and f) a "self-focussed" style of poor impulse control and anger, which can risk aggressive and self-harming explosive behaviour during a depressed period.

In terms of stressors, as for adults, we can distinguish between "distal" and "proximal", and between "acute" and "chronic" stressors, again showing some commonality with events experienced by adults, but also some being adolescent-weighted. "Distal" stresses include having an uncaring, violent or abusive (verbally or sexually) parent, while "proximal" stresses include any event compromising the individual's sense of self-esteem or self-worth (e.g., humiliated by a peer, bullying and increasingly cyberbullying being key exemplars). Many of the non-melancholic depressive disorders in adolescence reflect an amalgam of acute and chronic life events. For example, having had a depressed mother and an indifferent father, being bullied at school for being "dumb" or "fat", having the only supportive family member (e.g., grandmother) die or a school friend commit suicide.

TREATMENT GUIDELINES

General priorities are to identify the type of depression and assess the adolescent's background and suicide risk, with a formulation shaping management, which in extreme high-risk scenarios may include hospitalization.

Most treatment guidelines are predicated on a dimensional (DSM or ICD) model differentiating depressive conditions by severity. A representative document was prepared by the Australian organization named *beyondblue* (6). In essence, it recommends: a) monitoring, support and possibly cognitive behaviour therapy (CBT) or interpersonal psychotherapy (IPT) for dysthymia or "mild" to "moderate" major depressive disorder, and b) CBT/IPT or fluoxetine (if necessary) for both "severe" major depression and treatment-resistant depression.

Our approach (5,7) prioritizes: a) combination of antidepressant and antipsychotic drugs for psychotic depression; b) an antidepressant drug – initially a selective serotonin reuptake inhibitor (SSRI) and, if ineffective, a broader-action antidepressant – for melancholic depression; c) a mood stabilizer (and possibly a low-dose antipsychotic drug initially) for bipolar I disorder and d) a mood stabilizer (preferably lamotrigine) or, on occasions, an SSRI for bipolar II disorder. For such "biological" conditions we also recommend 1000 mg of fish oil daily.

For the non-melancholic depressive conditions, we generally regard psychotherapy or counseling as the primary modality, with therapeutic choice weighted to the identified background (e.g., assertiveness training for the socially avoidant adolescent; IPT or counseling for a stress-induced depression; CBT for those with a low self-esteem or "atypical depression"). For adolescents with anxiety-weighted personality styles (e.g., anxious worrying, interpersonal rejection sensitivity), adding an SSRI may also assist by muting the "emotional dysregulation".

Most current guidelines, including the *beyondblue* ones, note the risk of increased suicidal thinking and behaviours in adolescents exposed to antidepressants. While multiple explanations are possible, an antidepressant-induced serotonergic reaction appears a common linking factor (with its prevalence seemingly higher in adolescents than in adults). Thus, all antidepressants should be introduced at low dose and the adolescent (and family) warned about such a possibility and to taper and cease the medication if such symptoms develop.

CONCLUSIONS

Managing adolescent depressive disorders is somewhat more demanding than for adults, reflecting the concerns brought by adolescents to any psychiatric assessment and treatment, their experiencing the "impact phase" of the condition, and their intrinsic preference to deny or minimize their condition. Establishing a therapeutic alliance will usually take longer. Adolescents who commit to managing their condition and "stay" with the therapist generally do very well (whatever their mood condition) and are highly appreciative of therapeutic attention.

Acknowledgements

Thanks are due to Karlyn Greenshields and Stacey McCraw for assistance with manuscript preparation and the National Health and Medical Research Council (Grant number 1037196) for funding support.

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DOI 10.1002/wps.20059

Priority issues in women's mental health

As mental health professionals update their training and practices to accommodate the new paradigms (integration of mental health in primary care, mainstreaming of gender perspective, increasing attention to evidence-based interventions), they will encounter several challenges in the field of women's mental health, as outlined previously in the International Consensus Statement on Women's Mental Health (1).

Violence against women and children and its consequences for mental health is probably the most pressing issue. We have now a solid body of knowledge about this scourge: data on the magnitude and the geographic variations in prevalence (2,3); the recognition of the dire consequences of exposure to violence, which damages the capacity of the individual to deal with stress and predisposes to mental and physical ailments (4,5); both qualitative and quantitative research to support the ecological model of multiple levels of causality (6), as well as evidence that the perpetuation of traditional submissive roles of women is a very important factor, particularly in settings were patriarchal attitudes have not been challenged. The pressing task now is to design interventions and subject them to good quality research to determine their effectiveness. The conversion of successful pilot interventions into region- or state-wide programs cannot be delayed further.

The impact of social determinants on women's mental health is progressively better understood (7). Stress at work, inequity in access to health care, the multiple roles and burdens of women (as professionals, spouses or partners, mothers, caregivers, role models) and the demands of globalization all may have an impact in determining how much a woman realizes her right to health.

The evaluation and management of mental disorders in women across the life cycle extends beyond perinatal care, to include the need to advance in our knowledge of dementias and other conditions that affect older women (8). The management of affective disorders during pregnancy and puerperium is an exciting area of interest mostly for medical professionals, while women's mental health encompasses the whole array of concerns of women along the entire life cycle and across the different areas of development.

In the field of perinatal mental health, the wide recognition of the impact of functional impairment in women affected by common mental disorders on children's health and survival has determined advances in research and clinical practice. Remarkably, the role and place of medication is better understood, with recommendations to use drugs only in moderate to severe depression (9). The role of primary health care has been studied in several sites and the results are promising, with an emphasis on the usefulness of community support and non-pharmacological interventions (10,11). More research is needed in this promising area.

The demands of professional careers and the unrealistic expectations of beauty, success and perfection placed on women by the media may pose special dangers to young women, unless societies can collectively build environments where the distribution of opportunities and rewards is not determined by criteria such as conforming to a bodily stereotype or belonging to a certain class or gender.

The normative developments that have been adopted by most countries as a result of international covenants and some international pressure have not been accompanied by changes in attitudes and cultural mores. The result is the lack of implementation of laws about gender based violence and the persistence of discrimination in political, economic and academic advancement of women.

During the recent 5th World Congress on Women's Mental Health (Lima, March 4-7, 2013), it was recommended that:

- educational and attitudinal changes have to catch up with what we know and what international and national laws say about equality and protection of women from violence and exclusion;
- academics must advance the conceptualization and expansion of our understanding of the mechanisms that turn experience into changes in the way women – and men – feel, think and behave;
- states need to enforce and monitor the law and policies to advance equality and autonomy of women;
- civil society and professional advocates must use the globalized flow and intercultural exchange of information to shape the global agenda in order to advance gender equity and the right to live free of violence for all women.

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DOI 10.1002/wps.20074

My Voice, My Life: a measure based on the consumer model of recovery

We note the Forum on "Consumer models of recovery: issues and perspectives" in the October 2012 issue of *World Psychiatry*, which comments on the paucity of robust, psychometrically sound measures of recovery. We wish to highlight such a measure, "My Voice, My Life", formulated using a systematic psychometric process of scale development (1), as advocated by Bellack and Drapalski (2), while based on the consumer model of recovery and utilizing the consumer-led model of development promoted by Rose et al (3), as advocated by Callard (4).

The process of development of the measure began with a deliberately over-inclusive preliminary version consisting of 127 items, based on 12 presumptive domains derived from the recovery literature and consumer consultation, which was piloted with 504 mental health consumers. The participant data set was randomly split into two discrete sets, one for the initial exploratory factor analysis and the other for the subsequent independent confirmatory factor analysis and reliability estimation. These analyses identified and confirmed (using the separate data sets) a robust factor structure, with 11 distinct and relatively independent factors (relationships; day-to-day life; culture; physical health; quality of life; mental health; recovery; hope and empowerment; spirituality; resources; and satisfaction with services) underlying one substantial principal construct (that we refer to as "consumer recovery"). The measure was then refined to 65 items, between three and ten items for each of the 11 domains, with uniformly high reliabilities (1).

These 11 psychometrically discrete domains may be seen as a significant verification of the consumer-driven theory of recovery, based on, and informed by, first-hand experience. Such results provide empirical support for the theoretical validity of the consumer recovery construct in its own right, rather than as a derivative of a social cognitive model developed within an earlier construct of mental illness, as proposed by Bellack and Drapalski (2).

At 65 items, the measure is longer than many routinely used "outcome" measures. However, if it is to adequately measure the 11 factors identified and confirmed in the factor analysis, this is perhaps inevitable. Maintaining domain coverage was considered crucial by our consumer reference group and it was this, as much as the psychometric issues, that determined our decision not to condense the measure at this stage. The fact that our process of scale development was consumer led ensured that matters of significance to consumers generally were prioritized.

Development processes which commence with and/or insist on a small number of domains and items, such as the Maryland Assessment of Recovery in People with Serious Mental Illness (MARS, 2), run the risk of neglecting constructs and consequently being criticized for applying a reductionist form of science (5). Our empirical work suggests that the MARS may not be measuring the full range of recovery domains and/or is encapsulating multiple constructs within individual domains.

If these measures are to influence services in a manner consistent with the consumer recovery paradigm, they must reflect all its distinct and independent domains. Failure to do this will distort how "recovery" services are developed, risking some key domains being ignored or at least undervalued.

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DOI 10.1002/wps.20055

WPA Scientific Sections

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WPA Secretary for Sections

WPA Sections (current number is 68) are the scientific backbone of the WPA. They promote and disseminate scientific knowledge, covering practically every aspect of psychiatry and enjoying a great degree of independence within the framework of the WPA Statutes and By-Laws. Over the years, with able leadership of their officers, the Sections have provided valuable and exceptional additions to the scientific knowledge in psychiatry and allied fields.

More specifically, the purposes of the Sections, in accordance with the existing WPA By-Laws, are the collection, analysis, presentation and dissemination of information concerning services, research and training in the various fields of psychiatry and mental health and the advancement of scientific knowledge in these fields.

The Sections achieve these purposes by: a) establishment of working relations with national and international organizations with a view to achieving better coordination of activities of interest to the Section and the WPA; b) organization of scientific meetings and symposia on topics of specialized interest to the Section; c) organization of educational activities dealing with the Section's specialty at different WPA meetings; d) development of educational programs, guidelines, publications and proposals for adoption as WPA consensus and position statements; e) promotion and conduction of international collaborative research.

The Sections hold elections every three years to elect their office bearers. Clustering of Sections, on the basis of common interests and activities, is encouraged with an objective to promote collaboration, produce consensus or position statements, organize joint scientific activities within WPA and other scientific organizations. The activity and productivity of each Section (e.g., symposia, publications, educational programs and consensus statements) are regularly evaluated by the Secretary for Sections and the Executive Committee. The section work is supported by an Operational Committee, which includes experienced members of WPA offering valuable guidance (C.R. Soldatos, M. Amering, S. Harvey and T.E. Schlaepfer).

Following the current triennium action plan, all Sections have continued with their excellent work and promising contributions in many areas of mental health. During 2012, 16 WPA co-sponsored meetings were organized by different Sections, and from January to June 2013, 12 meetings have already taken place. There has been an increased interest in joint working and, in addition to Sections organizing their own sessions, joint sessions are proposed at scientific meetings (28 sessions at the Prague International Congress in 2012; 8 sessions at the Athens Thematic Conference in 2012; 9 sessions at the Athens meeting and 6 sessions at the Bucharest meeting in 2013). Organization of intersectional forums is the new addition to promote collaboration among Sections' work. Topics like education, stigma and suicide were chosen for these forums, that have been held at WPA conferences.

Various Sections (e.g., Dual Diagnosis, HIV Psychiatry, and Education in Psychiatry) have also produced documents and recommendations in their respective fields. Sections on Addiction and Public Policy have recently set up a joint group for the establishment of an Intersectional Initiative (ISI) for Addiction and Concurrent Disorders among Vulnerable Urban Populations.

WPA Sections are actively participating in the development of the chapter on mental disorders of the 11th edition of the International Classification of Diseases (see 1-3) and WPA Section officers are providing a variety of contributions to *World Psychiatry* (e.g., 4-10).

It is hoped that the current enthusiasm in Section work will lead further contributions to the quality of scientific knowledge and development of innovative approaches in psychiatric care for our patients. This is indeed a promising trend that brings specialized expertise to the WPA membership and updates their knowledge and understanding of current professional needs.

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DOI 10.1002/wps.20076

WPA publications: opportunities to improve psychiatric research and inform clinical care and education

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WPA Secretary for Scientific Publications

The WPA publications program has a long tradition of distributing and disseminating information regarding psychiatric research, evidence-based clinical care, and education and training to psychiatrists and other mental health clinicians throughout the world; promoting psychiatric services and research in low and middle income countries; and improving the capacity and capabilities of the publishing infrastructure of WPA.

The WPA has a scientific publications operational committee and an executive committee to help guide its publications agenda. There is also a WPA assembly comprised of member societies and groups where the goals, objectives and performance of the scientific publications program are presented and reviewed on a triennial basis.

Since 2002, a major contribution of the publications effort has been the official journal of the Association, *World Psychiatry*, edited by Professor Mario Maj, a highly recognized journal whose impact factor has been continuously increasing (1) and is now 8.974. The journal is translated from English into six languages (Spanish, Chinese, Russian, French, Arabic and Turkish), indexed in PubMed, and now published by Wiley-Blackwell, and serves to present and disseminate cutting-edge scientific work that is read across the world by clinicians, educators and researchers.

In addition, the scientific publications group helps to organize and promote successful book series, such as *Depression and Heart Disease* (2), *Depression and Diabetes* (3) and *Depression and Cancer* (4). These books are highly useful and have been recently translated into Spanish.

The very active Scientific Sections of the WPA are increasingly interested in developing their publications portfolios. Several of the Sections have their own newsletters or journals and are actively publishing books that address the various topics studied and researched by the Section members. The books often present an international focus, and include authors from many countries, working in a wide distribution of psychiatric sites and types of clinical and research settings.

One of the more important areas of work is how to best disseminate information and research to low and middle income countries. The WPA, under the leadership of President Pedro Ruiz, has tried to provide books, at no cost to WPA members, with distribution at WPA and other psychiatric meetings. These programs have been viewed as very successful and helpful. President Elect Dinesh Bhugra is actively developing a platform for further writing and dissemination of work for low and middle income countries and ways to help inform those clinicians who live in remote or rural areas of the world.

We are also much focused on helping to promote the next generation of psychiatric researchers and educators and continuously are looking for ways to promote dissemination and opportunities for publications for medical students, psychiatry residents and junior faculty. Symposia and workshop sessions are held at local, regional and international WPA meetings to help educate and train junior colleagues as to how to bring their work to scientific publication.

Other opportunities for publications within the WPA include the *WPA Depression Bulletin*, edited by Driss Moussaoui, and small articles in the *WPA Newsletter*, as well as particular projects that evolve from some of the educational efforts and WPA meetings held throughout the world. Examples are the WPA guidances, educational modules and recommendations (e.g., 5-10), available on the WPA website (www.wpanet.org).

In conclusion, the WPA scientific publications program is robust and looks to partnering with individuals and groups to provide information and materials that help support the vast needs and public health efforts of psychiatric research, clinical care and research throughout the world.

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DOI 10.1002/wps.20077

The new impact factor of *World Psychiatry*

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The new impact factor of *World Psychiatry*, based on citations in the year 2012 to papers published in the journal in the years 2010 and 2011, is 8.974. The impact factor of the journal was 3.896 in 2009, 4.375 in 2010, 5.562 in 2011, and 6.233 last year.

The journal is now in the top 5 of psychiatric journals, preceded only by *Molecular Psychiatry*, the *American Journal of Psychiatry*, the *Archives of General Psychiatry* and *Biological Psychiatry*.

The papers that received the highest number of citations during the period considered in the calculation of the new impact factor are the two pieces by De Hert et al on physical illness in patients with severe mental disorders (1,2); the special articles on resilience under conditions of extreme stress (3), prediction and prevention of schizophrenia (4) and long-term costs of traumatic stress (5); the research reports on self-experience in the early phases of schizophrenia (6), income-related inequalities in the prevalence of depression and suicidal behaviour following the economic crisis (7), and a randomized controlled trial of supported employment in England (8); the articles related to the development of the ICD-11 (9-12); the WPA guidance papers and recommendations (13-18); and the forums on psychiatrists as an endangered species (19), broadening the diagnosis of bipolar disorder (20), personality and psychopathology (21), and pathophysiology of schizophrenia (22-25).

The journal editorial staff is grateful to the authors, the referees and the many colleagues worldwide who made this accomplishment possible.

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DOI 10.1002/wps.20078

Acknowledgement
This publication has been partially supported by an unrestricted educational grant from Otsuka Pharmaceutical Italy S.r.l., which is hereby gratefully acknowledged.