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## The World Psychiatric Association (WPA)

The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 135, spanning 118 different countries and representing more than 180,000 psychiatrists.

The WPA organizes the World Congress of Psychiatry every three years. It also organizes international and regional congresses and meetings, and thematic conferences. It has 65 scientific sections, aimed to disseminate information and promote collaborative work in specific domains of psychiatry. It has produced several educational programmes and series of books. It has developed ethical guidelines for psychiatric practice, including the Madrid Declaration (1996).

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



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## World Psychiatry

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*EDITORIAL*

# The WPA Action Plan 2008-2011

**Mario Maj**

President, World Psychiatric Association

The activity of the WPA during the triennium of my presidency will be guided by an Action Plan, which has been approved by the WPA General Assembly during the World Congress of Psychiatry held in Prague last September. This Action Plan consists of ten institutional goals and a series of initiatives by which these goals will be pursued. I am sharing here these goals and some of the relevant initiatives with the readers of *World Psychiatry*, including now almost 33,000 psychiatrists in 121 countries.

The first institutional goal of the WPA during the triennium 2008-2011 will be to enhance the image of psychiatry worldwide among the general public, health professionals and policy makers. Unfortunately, the image of our profession is currently not very brilliant, and this has an obvious negative impact on the motivation of persons with mental disorders and their families to seek for our advice and help and to adhere to our therapeutic interventions, as well as on the motivation of medical students to choose psychiatry as a career.

The image of psychiatry as a modern medical specialty, that deals with a vast range of mental disorders, some of which are very common in the general population, and that delivers a variety of therapeutic interventions, some of which are among the most effective that medicine has at its disposal, is currently unfamiliar to the general public in most countries of the world.

On the contrary, the limitations of our diagnostic tools and our treatments often receive a great emphasis in the lay press, with messages which are frequently biased by ideological prejudice. The source of this biased information is sometimes represented by psychiatrists themselves. Antipsychiatry within psychiatry is still a reality in several countries, and our profession is unique among medical specialties in its ability to generate auto-antibodies.

We aim to pursue the goal to enhance the image of psychiatry worldwide by: a) giving visibility to successful experiences in the mental health field, through regular press releases and reports in a section of the WPA website intended for the general public; b) funding three projects on improving the public image of psychiatry, selected on the basis of an international call for proposals; c) producing a set of guidelines on how to combat stigmatization of psychiatry and psychiatrists, to be posted on the WPA website and translated in several languages; d) establishing a regular track at World and International Congresses and a special section in *World Psychiatry* focusing on successful experiences of mental health care in the various regions of the world; e) launching an international programme aiming to raise the awareness of the prevalence and prognostic implications of depression in persons with physical diseases, in collaboration with other international and national medical associations and with organizations of users and families.

Our second institutional goal will be to partner with our Member Societies in their efforts to improve the quality of mental health care, education and research in their countries and regions, and in their attempts to upgrade their own structure, governance and organizational capacity. More specifically, we will join and assist Member Societies, upon their request: a) in their interactions with national and regional institutions concerning policy matters; b) in the production and implementation of guidelines, ethical codes and research protocols; c) in promoting the refinement of curricula for graduate and post-graduate psychiatric and public mental health education; d) in the development and implementation of programmes for continuing education of psychiatrists, other mental health professionals and primary care practitioners; e) in refining their structure and organization. We will produce a template for graduate and post-graduate psychiatric education to be posted on the WPA website and translated in several languages. We will organize a series of seminars at World and International Congresses in which leaders of selected Member Societies will illustrate the structure and activities of their associations to representatives of other Member Societies, answer their questions and provide advice on specific issues.

Our third institutional goal will be to promote the dissemination of information on recent clinical, service and research developments in such a way that it can be assimilated by psychiatrists of all regions of the world, including those who are not able to read English. This goal will be pursued by: a) the implementation of high-quality itinerant educational workshops, to be replicated in the four WPA Regions (the Americas, Europe, Africa and the Middle East, Asia/Australasia); b) the development of a CME online programme; c) the production of a series of guidelines on issues of great practical relevance, translated into several languages; d) an increased dissemination of *World Psychiatry* and the promotion of the translation of entire issues or selected articles in several languages, making them available on the WPA website and on the websites of relevant Member Societies; e) activities aimed to support the development of selected national psychiatric journals.

Our fourth institutional goal will be to promote the professional development of young psychiatrists worldwide. This goal will be pursued by: a) launching, in collaboration with a network of centers of excellence, a programme of one-year fellowships for young psychiatrists from low-income countries, who will commit themselves to apply in their country

of origin what they have learnt; b) organizing a series of workshops on leadership and professional skills for young psychiatrists; c) facilitating the participation of young psychiatrists in WPA Congresses and other worthwhile scientific meetings; d) stimulating the participation of young psychiatrists in the activities of WPA Scientific Sections; e) joining and assisting Member Societies in the development and implementation of programmes for young psychiatrists.

Our fifth institutional goal will be to contribute to the integration of mental health care into primary care in low-income countries. We will develop a "training the trainers" programme, targeting nurses and clinical officers working in dispensaries and health centers, to be implemented in selected low-income countries, among which the first will be Nigeria.

Our sixth institutional goal will be to foster the participation of psychiatrists from all regions of the world in the international dialogue on clinical, service and research issues, by ensuring an adequate representation of colleagues from all regions in WPA programmes, scientific meetings and publications, and in the activities of WPA Scientific Sections.

Our seventh institutional goal will be to promote the highest ethical standards in psychiatric practice and to advocate for the rights of persons with mental disorders in all regions of the world. This goal will be pursued by: a) launching an international programme on the protection and promotion of physical health in persons with severe mental disorders, in collaboration with other international and national medical associations and with organizations of users and families; b) supporting international and national programmes aiming to protect the human rights of persons with mental disorders; to promote the meaningful involvement of these persons in the planning and implementation of mental health services; to encourage the assessment and development of these persons' talents, strengths and aspirations; and to promote equity in the access to mental health services for persons of different age, gender, race/ethnicity, religion and socioeconomic status.

Our eighth institutional goal will be to promote the establishment of networks of scientists conducting collaborative research in the mental health field. We will fund at least two high-quality international research projects conducted by WPA Scientific Sections, and will facilitate the involvement of the most prominent scientists in the activities of these Sections.

Our ninth institutional goal will be to increase the visibility and credibility of the WPA, by ensuring that the initiatives and products of the Association are of the highest possible quality level, with a fully effective utilization of available human resources.

Our tenth institutional goal will be to build up a long-term, solid and transparent partnership with potential donors. A consortium of donors has been created, which will partially fund the above-mentioned activities.

Readers of *World Psychiatry* who are interested to be informed or wish to contribute to the above initiatives are welcome to contact the WPA Secretariat (wpasecretariat@wpanet.org).

# Diagnosing and treating attention-deficit/hyperactivity disorder in adults

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*Adult attention deficit/hyperactivity disorder (ADHD) is a valid and impairing psychiatric disorder. In this article, we review the diagnosis of ADHD in adults, focusing on symptom presentation differences between pediatric and adult ADHD as well as the importance of assessing functional impairments. Differentiating ADHD from other clinical disorders is often the most difficult part of making an ADHD diagnosis in adults. Psychiatric comorbidities are also described and discussed as potential impact factors upon not only diagnosing ADHD but also treatment of adult ADHD. Especially in those adults with psychiatric comorbidities, treatments need to be multimodal and include both pharmacotherapy and psychosocial interventions.*

**Key words:** Attention-deficit/hyperactivity disorder, adult, comorbidity, stimulant medications, psychosocial interventions

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Over the past thirty years, there has been increasing recognition of the persistence of attention-deficit/hyperactivity disorder (ADHD) into adulthood. Once perceived to be exclusively a childhood disorder, it is now well accepted that about 4% of the adult population has ADHD (1-3). ADHD does not initially appear in adulthood. All valid diagnoses of adult ADHD have a clear developmental history of impairing symptoms dating back to childhood. However, it is possible that an individual may be initially *diagnosed* as having ADHD in adulthood (4). It is not uncommon to find adults self-referring themselves for an ADHD evaluation without having been diagnosed in childhood, and some data suggest that only 25% of adult ADHD cases had been diagnosed in childhood or adolescence (5).

This article provides an overview of the diagnosis, epidemiology and management of ADHD in adults.

## DIAGNOSING ADHD IN ADULTS

Several sources of evidence show that ADHD can be diagnosed in a reliable and valid manner. Psychometric studies find clinician-administered ADHD rating scales to have high internal consistency and inter-rater reliability (6-8), and ADHD symptoms in adults are associated with clear signs of functional impairment (9-12). For screening purposes, a psychometrically validated self-report measure of adult ADHD is also available (8).

Despite substantial evidence for the validity of DSM diagnoses of ADHD, some questions remain regarding how the criteria are implemented when diagnosing adults, which requires a two stage process: a) determining that the adult met criteria for ADHD in childhood and b) determining that the adult currently meets criteria for the disorder. We will base our discussion on the DSM-IV-TR (13), which is the gold standard and most commonly applied method for diagnosing ADHD across the lifespan in the United States and is widely used in ADHD research around the world.

### Diagnosing childhood onset ADHD in adults

When making the diagnosis of ADHD in adults, clinicians must establish that diagnostic criteria for the disorder were met in childhood. Because the passage of time may make symptoms difficult to recall, it is possible that the threshold for caseness should be lowered when making these retrospective diagnoses. But, as shown by Faraone and Biederman (6) in a population survey of 966 adults, lowering symptom thresholds can increase the risk for false positive diagnoses. They estimated a prevalence of 2.9% for narrow ADHD (meeting DSM-IV criteria in both childhood and adulthood) and 16.4% for broad ADHD (adding to that definition those meeting subtreshold criteria).

In a series of papers, Faraone et al (4,14,15) examined the validity of diagnosing ADHD in patients having impairing symptoms of ADHD which never exceeded DSM-IV's threshold for diagnosis (subthreshold ADHD). They evaluated the validity of these atypical diagnoses based on Robins and Guze's (16) criteria for the validity of psychiatric diagnoses, including clinical correlates, family history, treatment response, laboratory studies, course and outcome. They found that subthreshold ADHD had less psychiatric comorbidity, less neuropsychological dysfunction, and fewer substance use problems compared with full threshold ADHD. Moreover, the pattern of familial transmission for subthreshold ADHD differed from full threshold ADHD. These data suggested that cases of subthreshold ADHD should be viewed cautiously. Some might be a milder form of true ADHD, but others may be false positive diagnoses.

Several studies of youth have challenged the validity of the age at onset criterion (AOC) established by the DSM-IV for the diagnosis of ADHD (onset prior to age 7). One study comparing teenagers with onset before or after age 13 found no link between age at onset and severity of symptoms, types of adjustment difficulties, or the persistence of the disorder (17). Rohde et al (18) compared clinical features between adolescents meeting full criteria for ADHD and those meet-

ing all criteria except the AOC. Because these two groups had similar profiles of clinical features, the authors concluded that DSM-IV's age at onset criterion should be revised. In an epidemiologically ascertained sample of adolescents, Willoughby et al (19) found that adolescents meeting full criteria for combined type ADHD had worse clinical outcomes than those failing to meet the AOC, but found no differences attributable to the AOC for the inattentive subtype of ADHD. In the DSM-IV field trials, requiring an AOC of 7 reduced the accuracy of identifying currently impaired cases of ADHD and reduced agreement with clinician judgments (20). Hesslinger et al (21) found that adults with late onset ADHD had the same pattern of psychiatric comorbidity as adults whose ADHD onset met DSM-IV's criterion. In contrast, in an epidemiologic sample of 9 to 16 year old children, Willoughby et al (19) did not find late onset ADHD to be associated with oppositional defiant, conduct or anxiety disorders, while it was associated with depression among inattentive ADHD cases. In the series of papers by Faraone et al (4,14,15), late onset and full ADHD subjects had similar patterns of psychiatric comorbidity, neuropsychological impairment, substance use disorders and familial transmission. All of their late onset cases had onset in adolescence.

Taken together, studies of late onset ADHD suggest that the DSM's AOC is too low. Although these studies do not provide definitive evidence for a specific threshold, they clearly suggest that moving the AOC into adolescence (e.g., to 12 or 13) would be valid.

### Diagnosing persistent ADHD in adults

After determining that the patient meets diagnostic criteria for ADHD in childhood, clinicians must determine if some of these symptoms have persisted into adulthood. When doing so, it is important to remember that the DSM-IV-TR criteria for ADHD allow the diagnoses to be made in adolescents and adults when only residual, impairing, symptoms of the disorder are evident. As Faraone et al's (22) review of longitudinal studies showed, about two-thirds of ADHD children will continue to have some impairing symptoms of ADHD in adulthood.

Barkley (23) has suggested that the DSM symptoms and symptom thresholds for ADHD are overly restrictive for diagnosing the disorder in adults. For example, he studied DSM symptom thresholds in two longitudinal samples followed into adulthood. As adults, 98% of their control participants endorsed three or fewer symptoms of inattention and 100% endorsed three or fewer of hyperactive impulsive behavior. In contrast, 100% of the ADHD group endorsed three or more inattention symptoms and 72% endorsed three or more hyperactive symptoms (23). These data suggest that six symptoms of inattention or hyperactivity (as required by the current DSM) is too high a threshold when diagnosing the current presence of ADHD in adults. However, when making a retrospective diagnosis about the occurrence of ADHD in childhood, the DSM threshold of six symptoms should be used (4,14,15).

In regards to symptom specificity and differentiating ADHD from other forms of psychopathology (e.g., mood disorders), Barkley (23) reported that symptoms of difficulty organizing tasks, having difficulty staying seated and talking excessively were equally prevalent in ADHD adults and adults with mood disorders or anxiety disorders. Three DSM-IV-TR inattentive symptoms correctly classified 87% of the ADHD group and 44% of the clinical control group: failing to give close attention to details; difficulty sustaining attention to tasks; failing to follow through on instructions. Three hyperactive/impulsive symptoms accurately classified 76% of ADHD cases and 49% of clinical control cases: fidgeting with hands/feet or squirms in seat; difficulty engaging in leisure quietly; interrupting or intruding on others.

Differentiating ADHD from other clinical disorders is often the most difficult part of making an ADHD diagnosis in adults, given the high comorbidity between ADHD and other psychiatric disorders (15). To further guide this differential diagnosis, Barkley (23) developed symptoms based upon his executive functioning theory of ADHD (24). The symptoms which best discriminated ADHD cases from those adults with other forms of psychopathology were: making decisions impulsively; having difficulty stopping activities or behavior when should do so; starting projects or tasks without reading or listening to directions carefully; poor follow through on promises; trouble doing things in their proper order; driving with excessive speed. These six items correctly classified ADHD with 85% accuracy (23). Making decisions impulsively and having difficulty stopping activities or behavior when one should were the best at discriminating adults with ADHD from adults with other forms of psychopathology. It is interesting that hyperactivity in adults may not distinguish adults with ADHD from normal adults or adults with other clinical disorders (23). As it is conceptualized now, however, hyperactivity is a core aspect of DSM-IV ADHD.

### Assessing impairment in ADHD adults

While the relationship between symptoms and impairment in children with ADHD is modest ($r$ = .3) (25), it may be more robust in adults ($r$ = .7) (23). The DSM-IV-TR criterion C, which requires impairment in two or more settings, is central to the diagnosis of ADHD. It is essential that the diagnostic interview ask questions such as how is he/she doing at work, school, parenting, child-rearing, managing finances, driving, leisure time, and maintaining fulfilling relationships. The focus on functional impairments is central to the diagnosis of ADHD, most especially in an adult who does not have an ADHD diagnosis from childhood. Barkley's longitudinal data suggest that, in rank order from most to least impairing, educational impairments, home responsibilities, and occupational domains are the three most functionally impaired domains in adults with ADHD (23).

Unlike childhood disorders, in which the parents' and teachers' reports are frequently used, adult ADHD is often diagnosed with considerable or sole emphasis on self-report, because other informants are often not available. However, information from spouses, parents or other informants can be useful for several reasons, including the possibility of malingering symptoms for secondary gain (26). Similarly, given the positive illusory bias which has been documented in both children (27,28) and adults (29) with ADHD, it may be that adults with ADHD are not the best reporters of their own functioning. However, gaining collateral report from spouses, employers, coworkers, friends, etc. may be either difficult to obtain or clinically contraindicated. Nonetheless, we believe it should be obtained in a sensitive fashion whenever possible.

### Diagnosing ADHD: primary care vs. psychiatry

Primary care physicians are increasingly being asked to make ADHD diagnoses. In a medical record review of 854 adults with persistent childhood-onset ADHD, Faraone et al (5) examined the diagnostic practices of primary care physicians and psychiatrists. They found that primary care physicians were less likely than psychiatrists to make an initial diagnosis of ADHD in adults if no pediatric ADHD diagnosis had been made. Primary care physicians were also more likely than psychiatrists to seek outside consultation before making an ADHD diagnosis in adults, with 15% of primary care physicians making a referral to another provider, most often a psychologist. Psychiatrists were also more likely to diagnose a comorbid psychiatric condition than primary care physicians (44% vs. 20% respectively).

## EPIDEMIOLOGY OF ADHD IN ADULTS

### National Comorbidity Survey Replication (NCS-R)

As discussed above, Faraone et al (6) computed a population prevalence of 2.9% for adult ADHD. Another estimate of population prevalence comes from the National Comorbidity Survey Replication (NCS-R) (3), an epidemiologic study of 9,200 adults ages 18-44. In this sample, the prevalence of adult ADHD was estimated to be 4.4%. Additional results indicated that adults with ADHD had lower educational levels, were less likely to be employed and were more likely to be separated/divorced than those without ADHD. ADHD was also less commonly reported in African-Americans and Latinos compared to Caucasians (3).

Fayyad et al (30) conducted an epidemiological study of adult ADHD in ten countries in the Americas, Europe and the Middle East. Their prevalence estimates ranged from 1.2 to 7.3%, with an average of 3.4%. The prevalence was lower in lower income (1.9%) compared with higher income countries (4.2%). Consistent with other studies, ADHD was associated with psychiatric comorbidity and functional impairment.

In children, ADHD is more commonly diagnosed in males (31).The NCS-R data suggest that sex differences are less pronounced in adult ADHD (3), which is consistent with data from clinical samples (4,32). The relative equal sex ratio in adult ADHD may indicate that ADHD in females is more persistent. It is also possible that this finding is due to referral biases in childhood: boys with ADHD are more likely to have conduct disorder and be referred for treatment (31). By being able to refer themselves, adults with ADHD may be less likely to have this referral bias.

### Psychiatric comorbidity

Comorbid anxiety, mood and substance use disorders are commonly reported in adult ADHD (3,23,33-38). These comorbidity rates do not differ as a function of gender (3,39). The NCS-R data suggest that 43% of people with ADHD between 18 and 29 years of age experienced a psychiatric comorbidity, compared to 56% of those between 30 and 44 years of age.

In clinic-referred populations, histories of conduct disorder and oppositional defiant disorder occur in approximately 24-35% of adults with ADHD (1,35). This is lower than the rates often reported in pediatric ADHD (50-60%) (40). Alcohol use disorders are also common in clinic-referred adults with ADHD; alcohol dependence or abuse disorders lifetime prevalence rates range from 21 to 53% (1,15,35,41). Cannabis and cocaine use disorders are both also relatively common in adults with ADHD (42,43). Cigarette smoking has also been demonstrated to be more prevalent in adult ADHD (44). Comorbid conduct or bipolar disorder increases the risk for substance use disorders (45,46); however, ADHD is an independent risk factor for later substance use disorders (43,47). Those with comorbid ADHD and substance use disorders have been reported to have earlier onset of substance abuse relative to adults with substance abuse yet without ADHD (48) and a greater severity of substance abuse/dependence (49,50).

Mood disorders such as major depressive disorder occur in children with ADHD, especially those with conduct disorder (51). Between 16 and 31% of adults with ADHD have current comorbid major depressive disorder (1,3,23,35,41), with lifetime rates as high as 45% (3).

About 25% of children with ADHD have a comorbid anxiety disorder (40); rates of anxiety disorders in adult ADHD appear similar. For example, 25-43% of adults with ADHD meet criteria for generalized anxiety disorder (1,3,35,38,41), with lifetime rates as high as 59% (3). Panic disorder, obsessive compulsive disorder and social phobia are less common, yet can be comorbid conditions (3,38,52).

## TREATING ADHD IN ADULTS

Despite the relatively high prevalence rate, the overwhelm-

ing majority of adults with ADHD are untreated; the NCS-R (3) demonstrated that only 11% of adults with ADHD are treated.

### Pharmacotherapy

Stimulant medications, especially extended release formulations, are a front-line management strategy in both pediatric and adult ADHD (53,54). Approximately 3 of every 4 adults with ADHD will have a positive response to a stimulant medication. Two stimulants are FDA approved for use in ADHD adults: extended release mixed amphetamine salts and lisdexamfetamine dimesylate. Atomoxetine is a nonstimulant that is FDA approved for managing adult ADHD and may be particularly effective for adults with ADHD and comorbid depression (55) or for those with a comorbid substance use disorder addictive potential (56). Both the stimulants and atomoxetine improve core symptoms of hyperactivity, inattention and impulsivity (54,57,58). Secondary to psychiatric comorbidity, polypharmacy may be more likely in adult ADHD than pediatric ADHD (59).

Adherence to stimulant medications in ADHD wanes as a function of age (60), and efforts should be instituted to attempt to avert poor adherence. Stimulant misuse and/or diversion is another clinical reality in ADHD pharmacotherapy (61). Those with comorbid conduct disorder or substance abuse diagnoses are most at risk for stimulant misuse and/or diversion (61,62).

### Psychosocial treatments

Substance use disorders may also require interventions, many of which may be independent of the ADHD interventions. Some have suggested that ADHD interventions should be initiated first to determine the extent to which ADHD is contributing to substance use disorders (23). The rationale for this is that the presence of ADHD appears to potentiate the substance use disorder, resulting in a more severe disorder (63) and poorer outcomes (64). However, because it can be very difficult to treat ADHD patients who are actively abusing alcohol or drugs, one must often treat the substance use disorder first. Given the potential for abuse or misuse of stimulant medications (65), in patients with a history of substance use disorders, one should use either long-acting stimulants (because their formulations make them less abusable) or a nonstimulant. The long-acting, prodrug stimulant, lisdexamfetamine dimesylate, is of particular interest given its lower abuse-related liking scores compared with equipotent doses of immediate-release d-amphetamine (58).

Similar to pediatric ADHD, a psychosocial treatment component is typically recommended in adult ADHD (66). What constitutes the psychosocial component, however, is different in adult ADHD relative to pediatric ADHD. For example, neither cognitive behavioral therapy (CBT) nor cognitive therapy is effective for pediatric ADHD (67-71). In contrast, there are some data to suggest that CBT is efficacious for adults with ADHD. For example, in the adult ADHD literature, there is some evidence that CBT reduces functional impairments in adults concurrently treated with stimulants (72,73).

### Treating ADHD: primary care vs. psychiatry

Psychiatrists are more likely than primary care physicians to prescribe a medication for adult ADHD (91% vs. 78% respectively) (5). While both psychiatrists and primary care physicians most often prescribed a stimulant (84%) or an antidepressant (12%), psychiatrists were more likely to prescribe dextroamphetamine, generic methylphenidate hydrochloride, mixed amphetamine salts, and oral osmotic controlled-release methylphenidate. Psychiatrists were less likely than primary care physicians to prescribe immediate release methylphenidate (5). Drug holidays were prescribed in approximately 20% of adults with ADHD, yet were more often prescribed by psychiatrists (24% vs. 17% respectively).

## CONCLUSIONS

Within the last 30 years, the persistence of ADHD into adulthood has become increasingly well accepted, to the point that it is now considered a valid and impairing disorder. This suggests that the number of adults seeking clinical services for ADHD will likely continue to increase. Those working with adult populations need to be aware of the symptom presentation differences between pediatric and adult ADHD and the importance of assessing the functional impairments caused by ADHD symptoms.

Significant functional impairment and psychiatric comorbidity are the hallmark of adult ADHD. Especially in those adults with psychiatric comorbidities, treatments need to be multimodal and include both pharmacotherapy and psychosocial interventions.

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# The unique challenges of managing depression in mid-life women

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*Throughout most of their lives, women are at a greater risk of becoming depressed than men. Some evidence suggests that this heightened risk is associated with increased sensitivity to the hormonal changes that occur across the female reproductive lifecycle. For some women, the peri-menopause and early post-menopausal years may constitute a "window of vulnerability" during which challenging physical and emotional discomforts could result in significant impairment in functioning and poorer quality of life. A number of biological and environmental factors are independent predictors for depression in this population, including the presence of hot flashes, sleep disturbance, history of severe premenstrual syndrome or postpartum blues, ethnicity, history of stressful live events, past history of depression, body mass index and socioeconomic status. This paper explores the current knowledge on the complex associations between mood changes and aging in women. More specifically, the biological aspects of reproductive aging and their impact on mood, psychosocial factors, lifestyle, and overall health are reviewed. In addition, evidence-based hormonal and non-hormonal therapies for the management of depression and other complaints in midlife women are discussed. Ultimately, this article should help clinicians and health professionals to address a challenging clinical scenario: a preventive and effective strategy for the management of depression in the context of the menopausal transition and beyond.*

**Key words:** Depression, menopause, symptoms, hormones

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Depression in mid-life women is a significant cause of morbidity and disability (1). The unique manifestations and multifactorial etiology of mid-life depression makes it difficult to recognize and treat (2). In addition, symptoms of depression may overlap with those associated with menopause, presenting a clinical dilemma for psychiatrists and other health professionals in women's health (3). As the baby-boomer generation of women approaches and passes menopause, mid-life depression has become a serious public health issue and the subject of interest of a growing number of epidemiological and clinical studies.

This paper examines the evidence for and the nature of relationships between mood symptoms and aging in women, including chronological and reproductive aging, and between mood symptoms and other psychosocial, lifestyle, and health factors. In addition, the biological basis for development of depressive symptoms in mid-life women, and the potential for hormonal and non-hormonal therapies to provide relief, are discussed.

## MOOD, MID-LIFE AND MENOPAUSE

Mid-life women may seek medical advice due to such symptoms as hot flashes, aches and stiff joints, trouble sleeping, and lack of energy. In the Melbourne Women's Mid-Life Health Project (4), some of these symptoms were experienced at baseline by more than 40% of the 438 women surveyed in the late stages of the menopausal transition. Of particular interest, nervous tension and feelings of downheartedness and sadness were among the six most common complaints.

The causal relationships between depressive symptoms and menopause, however, are unclear; a particular controversy has been established around the question whether depressed mood is caused by psychological factors related to aging or whether ovarian hormonal changes may play a significant role in its occurrence.

Research on the relationship between menopause and depressive symptoms has provided contradictory results. Several studies revealed no relationship (5-7), while others found that mood symptoms decreased with increasing age (8), or that there was an increase in depression among women in the menopausal transition (9). Controlling for the presence of vasomotor symptoms reduced the correlations between depression and menopause in some reports (10). A strong relationship was found between hysterectomy and depressed mood (11).

Longitudinal studies that followed subjects through the transition from regular menstruation to the post-menopausal period have provided contradictory results as well. Different methodologies and the confounding effect of chronological aging make the results of these studies difficult to compare. In addition, correlations between changes in ovarian hormones and mood are not clear, because few studies measured these parameters. Some longitudinal studies have shown no relationship between depression and menopause (10,12). Other studies demonstrated an increased risk of depression during the transitional phase from peri-menopause to post-menopause (13,14); in particular, women entering this transitional phase earlier had a significant risk of developing new-onset depression (15). Dennerstein et al (12) found both an improvement in mood during mid-life and a decrease in negative mood as menopausal symptoms improved.

Reproductive aging in women has been divided into stages by the Stages of Reproductive Aging Workshop (STRAW) consensus (16). A recent restaging study (17) has used data to provide clinicians with practical definitions of the stages of the menopausal transition. Irregular menses, defined as more than 7 days difference persistently occurring between the length of cycles, is characteristic of the early menopausal transition, which begins at about age 35. The late menopausal transition begins when there have been at least two missed menstrual periods, and the post-menopause is the period which begins after the last menstrual period. The Melbourne Women's Mid-Life Health Project study showed that estradiol levels varied widely early in the menopausal transition, with a dramatic decrease in the late menopausal transition period, while follicle-stimulating hormone (FSH) increased (18). After the final menstrual period, estradiol levels continued to fall and FSH continued to rise.

The occurrence of physical and mental symptoms in women during menopausal transition stages was documented in the Women's International Study of Health and Sexuality (WISHeS), a large cross-sectional survey of women aged 20 to 70 years in France, Germany, Italy, the United Kingdom, and the United States. Subgroups of women at several stages were prospectively defined, and symptoms in physical, vasomotor, psychosocial and sexual domains were evaluated (19). Regularly menstruating women aged 20 to 49 were compared with post-menopausal women aged 50 to 70 and also with women who had surgical menopause before and after age 50. Subjects with surgical menopause were of interest because oophorectomy removes approximately half of circulating androgens, as well as estradiol, and the effects are more severe and sudden than naturally occurring menopause (20).

This important study showed that some symptoms experienced by mid-life women were clearly related to declining estradiol, including vasomotor symptoms, poor memory, trouble sleeping, aches in the neck/head/shoulder area, vaginal dryness, and difficulty with sexual arousal. These symptoms reached a maximum prevalence at age 50 and occurred earlier in women who had early (before age 50) surgical menopause. There was a curvilinear effect of age, and there were no differences between women from different countries and no effect of body mass index on the prevalence of this group of symptoms (19).

In contrast, psychological symptoms, such as mood swings, and breast pain showed a curvilinear pattern that peaked much earlier at age 35 to 40 years, or during the early menopausal transition period. After age 35 to 40 years, mood symptoms decreased with age through menopause and into the post-menopausal period and were increased in the presence of other physical or mental health problems. Interestingly, significant differences were found between women from different countries in the prevalence of this group of symptoms (19).

A third cluster of symptoms was also observed that did exhibit a linear effect of age with no maximum prevalence at age 50. These symptoms, such as decreasing physical strength and lack of energy, are the expected effects of increasing age and were also affected by the country of origin, body mass index, and other physical and mental problems (19).

Similar results were found in the Melbourne Women's Mid-Life Health Project, in which positive and negative moods, as well as hormone levels, were followed in a longitudinal fashion. Depressed mood declined significantly with aging. The results also showed that being in the menopausal transition phase amplified the negative mood effects of other major life events, such as poor health or job loss (12).

These observations suggest that the menopausal transition may be considered a "window of vulnerability" during which women are at high risk for depressive symptoms. This vulnerability period is similar in nature to other well-known vulnerability phases, such as the premenstrual period and the immediate post-partum period. The Melbourne Women's Mid-Life Health Project investigators found several risk factors associated with depression during the menopausal transition. A previous history of depression or premenstrual tension, negative attitudes about menopause, as well as lifestyle and psychosocial variables, were important risk factors for depressive symptoms (12). In addition, a follow-up study 11 years later of women aged 57 to 67 found that depression was highest for those who had surgical menopause and for those who were still menstruating (11).

In another substudy, happiness scores during and after the menopausal transition were followed and found to be significantly related to happiness scores recorded before the transition began. Before and after the menopausal transition, happiness scores were the effect of intrinsic personality factors and extrinsic factors, such as marital status, work satisfaction, and life events (21). In general, well-being increased over time as women passed through the menopausal transition, and no direct effect of hormone levels could be ascertained (22).

Another area of interest was the effect of the "empty nest syndrome" on mood symptoms for women in the menopausal transition. This substudy of the Melbourne Women's Mid-Life Health Project showed decreases in depressed mood and daily hassles with increases in positive mood and well-being associated with the "last exit event", when the last child left home. Interestingly, the return of children to home during the menopausal transition resulted in reductions of positive mood and decline in the frequency of sexual activity for women (23).

The consequences of physical, emotional, or sexual violence on mood in mid-life women were also evaluated. This substudy of the Melbourne Women's Mid-Life Health Project showed that intimate partner violence predicted depressed mood, divorce or separation, low sexual functioning, and use of psychotropic drugs (24). Among the overall population, 22% had used psychotropic drugs, most often antidepressants. Four percent had had psychiatric hospital admissions and 7% had had counseling. Psychotropic drug use was associated with interpersonal stress, poor self-ratings of health, and premenstrual depression (25).

Structural equation modeling has been used to show the relationships between changing estradiol levels and the symptoms specifically associated with declining estradiol levels. Women's sleep and perception of health are affected by vasomotor symptoms. Poor lifestyle choices, daily hassles, and stressors also affect mood. Also, decreases in estradiol compromise mood by affecting sexual functioning and women's feelings for partners (26).

## IS TREATMENT FOR DEPRESSION DIFFERENT IN MID-LIFE WOMEN?

Chaotic changes in hormone levels during the menopausal transition may be one of the major factors in increased risk of depression (27-29). Clinicians have an opportunity to provide a targeted therapy in the form of a stable hormonal milieu, which may exert a prophylactic and/or neuroprotective effect to prevent depression, as well as a therapeutic effect (29,30).

An ongoing longitudinal study, the Harvard Study of Moods and Cycles, reported on the long-term, prospective evaluation of 1000 women who were pre-menopausal (36 to 44 years of age) at the time of enrollment. They received periodic hormonal, psychiatric, and quality of life assessments, and the results were controlled for factors that are commonly investigated in depression, such as body mass index, smoking, marital status, and occupational status. The data from this study indicate that peri-menopausal women were two times more likely than premenstrual women to develop new-onset severe depression. In addition, the risk was exacerbated in those who developed vasomotor symptoms during peri-menopause (15).

This study indicates that peri-menopause and vasomotor symptoms, caused by estrogen fluctuations, may have a common biochemical pathway with depressive symptoms. The history of estrogen research provides ample evidence to support a strong role for estrogen in regulating brain function. Neuroprotective effects and a role in preserving memory and cognition are well documented, as are thermoregulatory and antidepressant effects in animal and clinical studies. The brain regions most likely to be affected by estrogen are those more likely to be related to monoaminergic systems, including the serotonergic and norepinephrine systems (31), and other evidence supports the role of estrogens in synthesis, release, and receptor activity of serotonin and norepinephrine (32,33). Consequently, it is intuitive to believe that the absence or intense fluctuation of estrogen could result in mood and behavioral changes, as well as vasomotor and other menopausal symptoms.

Several controlled clinical studies examined whether estrogen therapy may have an antidepressant effect in perimenopausal and post-menopausal women with major depressive disorder (30,34-37). An important finding of these studies was that estrogen was not efficacious for depression in post-menopausal women, suggesting that fluctuating estrogen levels, rather than absolute estrogen levels, may be more important for the antidepressant effects of estrogen. Another interesting aspect of these studies was that positive results were associated with use of transdermal rather than oral estrogen. This finding may be due to the heightened bioavailability of estradiol with transdermal administration, which could be advantageous for the interaction with estrogen receptors in brain areas that regulate mood and behavior.

Another point for consideration in treatment of depression in mid-life women is the efficacy of antidepressant therapies for relief of physical symptoms of menopause, such as hot flashes. A set of prescription data collected by McIntyre et al (38), before and after publication of negative results concerning the use of hormone replacement therapy from the Women's Health Initiative in July 2002 (39), may be relevant to this question. The initial reports of the Women's Health Initiative study suggested no protective effect against (actually, a slightly increased risk for) cardiovascular events (e.g., stroke, myocardial infarction) among post-menopausal women using hormone therapies. As a result, physicians became more reluctant in prescribing estrogen, even for younger, symptomatic women. The study by McIntyre et al (38) demonstrated that hormone replacement therapy prescriptions decreased in the year following the Women's Health Initiative results; interestingly, the number of prescriptions for antidepressants significantly increased, suggesting either that women developed psychological symptoms (e.g., depressive symptoms, anxiety) as they stopped using estrogen or that antidepressants were being used to treat menopause-related symptoms. Limited comparisons of estrogen and antidepressant therapies for treatment of depression in women with menopausal symptoms have indicated similar efficacy of escitalopram (40) and hormone therapies for relief of menopausal symptoms and improvement in menopause-related quality of life measures. Duloxetine (41) and citalopram (42) open trials also suggest that antidepressants may have a positive impact on menopausal symptoms, an important treatment consideration for women who cannot or will not take estrogen.

Other point of interest is whether age and menopausal status of mid-life women could affect the efficacy of some antidepressant therapies. Several clinical trials have shown differences between the responses to antidepressants of pre- vs. post-menopausal women (43) and younger vs. older women (44-47). In a pooled analysis, responses to selective serotonin reuptake inhibitors (SSRIs) appear to be affected by age (i.e., higher in women younger than 50 years of age than in women older than 50 years), whereas responses to venlafaxine, a serotonin-norepinephrine uptake inhibitor (SNRI) were similar across age groups (48).

The question of whether estrogen plays a role in this difference in efficacy was investigated in a pooled analysis of data from women over 50 years of age who were or were not receiving concomitant estrogen therapy during treatment with SSRIs or venlafaxine in eight studies. This study showed higher response rates to venlafaxine than SSRIs in both

groups. However, the gap in efficacy between SSRIs and venlafaxine was significantly larger in women who did not receive estrogen therapy, and SSRIs were significantly more effective than placebo only in the women who received estrogen (48). These data support previous evidence that estrogen might modulate or prime binding affinity/response to SSRIs (49).

The emergence of vasomotor symptoms in mid-life women is hypothesized to be the result of disturbed thermoregulatory function, a complex, hypothalamus-based process. As estrogen levels fluctuate, the so-called thermoneutral zone becomes significantly narrowed, leading to frequent sweating or shivering in response to normal changes in body temperature and producing the characteristic heat dissipation of menopause (50). Thus, the treatment for hot flashes aims to restore/expand the thermoneutral zone and consequently keep the changes in body temperature within that zone.

Although estrogen remains the gold standard for treatment of vasomotor symptoms, several alternative therapies, including many natural remedies, have been investigated. These include psychoactive medications, such as antidepressants, mood stabilizers, anticonvulsant medications, and anti-anxiety therapies (51-58). It should be pointed out that two of the most popular natural remedies for vasomotor symptoms, soy and black cohosh, have been found to have very little impact on these symptoms when compared with placebo in controlled trials (59) and that women may still be exposed to adverse events and side effects through their use.

Another strategy for women with significant nocturnal vasomotor symptoms (night sweats) would be to improve sleep patterns. A trial of the sleep agent eszopiclone for menopausal women with insomnia and awakenings due to hot flashes was recently shown to have a positive effect on these symptoms. The treatment also promoted improvement of mood and quality of life, possibly due to improved sleep patterns (60).

## CONCLUSIONS

Epidemiological and clinical studies demonstrate that mood changes and depressive symptoms may occur in some women during the menopausal transition. This period of fluctuating hormone levels constitutes a "window of vulnerability" for depression, especially for women with a previous history of depression or for those with concomitant, severe menopausal symptoms. Estrogen fluctuations may affect mood changes indirectly, through mediation of menopause-related physical symptoms, particularly sleep and sexual disturbances. In addition, estrogen may affect both vasomotor and depressive disturbances through common biochemical pathways and receptor-mediated actions on brain function.

Estrogen therapy has been shown to improve both mood and vasomotor symptoms and remains a viable option for symptomatic mid-life women. Recent concerns involving the long-term safety of estrogen therapy have led clinicians to pursue non-hormonal treatment strategies. Low-dose antidepressant therapy has been shown to improve vasomotor symptoms as well as depression and may be the preferred alternative for women with depression who cannot receive estrogen. Clinical evidence also supports use of some anticonvulsant and anti-anxiety therapies, as well as sleep agents, for treatment of hot flashes. Natural remedies in general have not shown a positive impact on vasomotor symptoms.

We conclude that, although depression in mid-life women presents unique challenges due to the added complexity associated with the menopausal transition, the "window of vulnerability" for depression also constitutes an opportunity to provide targeted and effective therapies that address both physical and mood symptoms in mid-life women.


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SPECIAL ARTICLE

# Deficit schizophrenia: an update

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*The criteria for deficit schizophrenia were designed to define a group of patients with enduring, primary (or idiopathic) negative symptoms. In 2001, a review of the literature suggested that deficit schizophrenia constitutes a disease separate from nondeficit forms of schizophrenia. Here we provide a review of new studies, not included in that paper, in which patients with deficit schizophrenia and those with nondeficit schizophrenia were compared on dimensions typically used to distinguish diseases: signs and symptoms, course of illness, pathophysiological correlates, risk and etiological factors, and treatment response. Replicated findings and new evidence of double dissociation supporting the separate disease hypothesis are highlighted. Weaknesses in research and treatment options for these patients are also emphasized.*

**Key words:** Deficit schizophrenia, heterogeneity, negative symptoms, apathy, double dissociation

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Deficit schizophrenia is a syndrome defined by the following criteria: a) presence of at least two out of six negative symptoms: restricted affect (referring to observed behaviours rather than to the patient's subjective experience); diminished emotional range (i.e., reduced range of the patient's subjective emotional experience); poverty of speech; curbing of interests; diminished sense of purpose; diminished social drive; b) some combination of two or more of the above symptoms have been present for the preceding 12 months and were always present during periods of clinical stability; c) the above symptoms are primary or idiopathic, i.e., not secondary to factors such as anxiety, drug effect, psychotic symptoms, mental retardation, depression; d) the patient meets DSM criteria for schizophrenia (1-3).

In 2001, a review of the literature suggested that deficit schizophrenia is a disease separate from other, nondeficit forms of schizophrenia (3). The proposal of a separate disease was based on the evidence that deficit and nondeficit schizophrenia differ on five dimensions typically used to distinguish diseases: signs and symptoms, course of illness, pathophysiological correlates, risk and etiological factors, and treatment response. The deficit group has a poorer quality of life and level of function, so one potential interpretation of the above evidence is that the deficit group simply has a more severe form of the same illness as nondeficit schizophrenia. However, in some studies, the deficit group was closer to healthy controls than the nondeficit group with respect to some variables (e.g., the volume of some brain regions), while in other studies the two groups were simply different from each other, as well as from control subjects (e.g., with respect to season of birth) (3).

In the years following the publication of that review, there have been a number of other studies focused on deficit schizophrenia, as defined by the above criteria. These have advanced our understanding of this group of patients, but have also clarified the remaining weaknesses in this research area (4). Here we will focus on those studies comparing patients with deficit vs. nondeficit schizophrenia.

## RISK AND ETIOLOGICAL FACTORS

### Family history

Kirkpatrick et al (3) reviewed studies showing that the deficit/nondeficit categorization has a significant concordance within families and that family members of deficit probands, compared with relatives of nondeficit probands, have more severe social withdrawal and an increased risk of schizophrenia.

Since that time, another study found an increased prevalence of subclinical negative symptoms in the relatives of deficit compared to nondeficit probands (5). In an unpublished study, we have also replicated the finding of a significant concordance within families: in families with more than one affected member, the deficit/nondeficit categorization of one member predicted the categorization of the other family member at a rate greater than chance.

### Genetics

A few studies have examined the genetics of deficit and nondeficit schizophrenia, but the results have been disappointing. Hong et al (6) reported that the dihydropyrimidinase-related protein 2 (DRP-2) gene was associated with risk for both deficit and nondeficit schizophrenia; however, after correcting for multiple comparisons, the association with nondeficit schizophrenia was not significant, and for deficit schizophrenia the association was present only for Caucasian but not African-American subjects.

Galderisi et al (7), in a sample of 56 deficit and 50 nondeficit patients, found that the Val(158)Met polymorphism of catechol-O-methyl transferase (COMT) influenced neuromotor performance in the deficit but not the nondeficit group. Wonodi et al (8) did not find an association between COMT polymorphism and the deficit/nondeficit categorization, but the total number of deficit and nondeficit subjects

was 86. Limitations in sample size undermine the value of all of these studies, and replications to date are lacking.

### Other risk factors

An association between schizophrenia and *winter* birth has been replicated by several studies, especially in the Northern hemisphere. The effect size is small, with a 5% to 8% excess of births (9). This association applies to schizophrenia as a whole, that is, without regard to deficit vs. nondeficit categorization. The 2001 review (3) cited studies that had found an association between deficit (but not nondeficit) schizophrenia and *summer* birth in the Northern hemisphere, with the deficit group differing from both nondeficit schizophrenia and control subjects. Since that time, summer birth has been confirmed as a risk factor for deficit schizophrenia in a combined analysis of 10 datasets from 6 countries (10).

In a study with 88 deficit and 235 nondeficit patients, an association was found between cytomegalovirus seropositivity and deficit schizophrenia (11). The association remained significant after covarying for psychotic symptoms and for demographic features known to be associated with cytomegalovirus seropositivity, and after correcting for multiple comparisons. No association was found with five other human herpesviruses. Goff et al (12) found that serum folate concentration was significantly lower in patients with deficit than nondeficit schizophrenia, a result whose interest increases in view of their finding that the C677T polymorphism of methylenetetrahydrofolate reductase was associated with negative symptoms (13). Replication is needed.

A meta-analysis has confirmed that male gender is a risk factor for deficit (but not for nondeficit) schizophrenia (14).

## COURSE OF ILLNESS

### Premorbid functioning

Evidence of worse psychosocial functioning in patients with deficit than in those with nondeficit schizophrenia, both before the appearance of positive symptoms and later in the course of the illness, was reviewed in Kirkpatrick et al (3). The higher degree of impairment could not be attributed to more severe positive symptoms, depressive mood or other dysphoric affect, or substance abuse.

Since that review, Galderisi et al (15) have replicated the finding of poorer premorbid adjustment during childhood and adolescence, but not in adulthood, in patients with deficit schizophrenia than in those with nondeficit schizophrenia. They also showed that the association between the deficit state and poor premorbid adjustment was not due to the presence of more severe negative symptoms in the deficit group.

### Long-term prognosis

Recent studies confirmed that the diagnosis of deficit schizophrenia is associated with a worse long-term prognosis, as compared with nondeficit schizophrenia. Tek et al (16), in a prospective study including 46 patients with deficit and 174 with nondeficit schizophrenia, found that after an average of five years, the deficit patients had a poorer quality of life, poorer social and occupational functioning, and more severe negative symptoms, but were less distressed and did not show more severe positive symptoms. In a study by Chemerinski et al (17), 111 chronic patients with deficit schizophrenia and 96 with nondeficit schizophrenia were followed up for 6 years. The nondeficit group was further subdivided into delusional and disorganized types. Functional impairment was greatest in delusional, lowest in disorganized and intermediate in the deficit group.

## RESPONSE TO TREATMENT

Convincing evidence is available that both old and new-generation antipsychotics may act on secondary negative symptoms by removing, in part or completely, some of their causes, such as positive symptoms, depression or extrapyramidal symptoms. However, the efficacy of these drugs on primary and persistent negative symptoms has not been proven (18).

A meta-analysis by Leucht et al (19) showed that amisulpride was significantly superior to placebo, but not to conventional antipsychotics, in patients suffering predominantly from persistent negative symptoms. A study of Buchanan et al (20) found no efficacy for clozapine on negative symptoms among deficit patients. No other evidence supports the efficacy of clozapine on primary and enduring negative symptoms (see 17 for a systematic review). Kopelowicz et al (21) investigated the efficacy of olanzapine in 39 patients with deficit or nondeficit schizophrenia: an improvement of positive, negative and extrapyramidal symptoms was observed among nondeficit patients, while in the deficit group only extrapyramidal symptoms improved, strongly suggesting that olanzapine is efficacious for secondary but not for primary negative symptoms of schizophrenia. Lindenmayer et al (22) tested the efficacy of olanzapine on primary negative symptoms in 35 patients with deficit schizophrenia. They reported a significantly higher decrease of the negative symptoms score of the Positive and Negative Syndrome Scale (PANSS) in the olanzapine than in the haloperidol group, in the absence of significant changes of positive symptoms, general psychopathology and depression, and considered these findings as an evidence of olanzapine efficacy in the treatment of primary negative symptoms. However, in the absence of data on a nondeficit group, these findings are difficult to interpret and do not rule out the possibility that olanzapine reduces secondary but not primary negative symptoms.

Based on the hypoglutamatergic hypothesis, several studies investigated the possibility that primary negative symptoms would improve following treatment with compounds that increase NMDA receptor transmission. Full agonists of the glycine site, such as glycine and D-serine, as well as a partial agonist of the glycine site, D-cycloserine, when used as adjuncts to antipsychotic drugs, have shown a favorable effect in the treatment of negative symptoms, including deficit or primary negative symptoms (23-26). However, in a large multicenter, double-blind study, 157 patients with schizophrenia or schizoaffective disorder who had substantial negative symptoms but at most mild positive, depressive, or extrapyramidal symptoms, were randomly assigned to adjunctive treatment with glycine, D-cycloserine or placebo for 16 weeks (27). Neither glycine nor D-cycloserine was superior to placebo for negative symptoms; no evidence was found that treatment effects differed in deficit versus nondeficit subjects. According to the authors, the discrepancy between their findings and those from previous studies might be due to the high percentage of patients treated with new-generation antipsychotics in their trial; in fact, evidence has been provided that the efficacy of compounds increasing the NMDA transmission on negative symptoms is more robust in subjects treated with conventional antipsychotics than in those treated with new-generation antipsychotics (28).

A need for effective pharmacological treatment is one of the most important research issues in the area of deficit schizophrenia.

## NEUROCOGNITIVE AND NEUROLOGICAL FINDINGS

Early neurocognitive studies reported a greater impairment on tests sensitive to fronto-parietal dysfunction in deficit compared with nondeficit schizophrenia patients (29-31). With one exception (32), more recent investigations failed to confirm these results (15,33-38).

A recent meta-analysis (37) including 13 neuropsychological studies concluded that patients with the deficit syndrome were globally more neuropsychologically impaired than nondeficit patients. Most effect sizes were small, but those for tests of olfaction (1.11), social cognition (0.56), global cognition (0.52), and language (0.51) were moderate or large. According to Cohen et al (37), the neuropsychological profile of deficit patients does not support the hypothesis that deficit schizophrenia is the more severe end of a continuum: if it were so, the greatest effect sizes should be found for memory, attention and working memory, i.e. the domains most significantly involved in schizophrenia (39).

Studies including a structured neurological examination confirmed the previously reported greater neurological impairment in patients with deficit than in those with nondeficit schizophrenia (15,34,40), supporting the hypothesis that the former is related to non-progressive, non-localized brain damage. However, two out of these three studies did not confirm the previously reported association between the deficit syndrome and an impairment of sensory integration (40), and found instead an association with an impaired sequencing of complex motor acts (15,34). The most recent study reporting an association between deficit schizophrenia and sensory integration deficits included a small sample of patients with the syndrome (n=12) and did not assess the simultaneous effect of negative symptoms and deficit/nondeficit categorization on neurological impairment (41).

### Brain imaging findings

Four studies found no enlargement of the lateral ventricles in patients with the deficit syndrome (42-45). The negative finding is surprising: the enlargement of the lateral ventricles is one of the most replicated brain imaging findings in schizophrenia, and has been – although not consistently – reported to be associated with negative symptoms and poor outcome. Except for the study by Sigmundsson et al (43), all the others included a group of patients with nondeficit schizophrenia, in which lateral ventricles were larger than in healthy controls.

An involvement of fronto-parietal brain circuits in deficit schizophrenia was suggested by early functional brain imaging studies (46-49), in agreement with early cognitive findings. More recent investigations confirmed metabolism/cerebral blood flow abnormalities in the frontal and/or parietal regions in patients with deficit compared to nondeficit schizophrenia (50-52). Neuronal loss in prefrontal cortex is suggested by a proton magnetic resonance spectroscopy study reporting lower *N*-acetylaspartate/creatine ratio in this region in a small sample of deficit patients compared to nondeficit patients and healthy controls (53).

### Electrophysiological findings

Recent event-related potential (ERP) studies do not support the severity continuum hypothesis. Turetsky et al (54) investigated a putative endophenotype of schizophrenia, the left lateralized amplitude reduction of the P3 component of the event-related potentials (ERPs). This abnormality was found in nondeficit schizophrenia, while a right parietal reduction of the component was observed in the deficit group.

Bucci et al (55) investigated evoked and induced 40-Hz gamma power, fronto-parietal and fronto-temporal event-related coherence in patients with deficit or nondeficit schizophrenia and in matched healthy controls. A reduction of both induced gamma power and event-related coherence was observed only in nondeficit patients with respect to controls. As these measures reflect cortical functional connectivity, it might be speculated that the fronto-temporal and fronto-parietal dysconnection hypothesis only applies to nondeficit schizophrenia. In a partially overlapping sample, Mucci et al (56) found evidence of a double dissociation of ERP abnormalities: compared to healthy subjects, only patients with

deficit schizophrenia showed an amplitude reduction of the N1 component over the scalp central leads, and a reduced activity of its cortical generators in the cingulate and parahippocampal gyrus, whereas only patients with nondeficit schizophrenia showed a left-sided reduction of the P3 component and of its generators' activity, that was also reduced in bilateral frontal, cingulate and parietal areas.

### Other findings

A factor analysis of the Schedule for the Deficit Syndrome (SDS), used to assign patients to deficit or nondeficit subgroups, suggested that the six negative symptoms of the SDS loaded onto two factors (57). The first, which the authors of the study called the avolition factor, consisted of curbing of interest, diminished sense of purpose, and diminished social drive; the second one, named emotional expression, included restricted affect, diminished emotional range, and poverty of speech. A review of the literature suggested a fairly similar pattern in studies of schizophrenia as a whole (58). These findings raise the interesting possibility that there are somewhat separate circuits or mechanisms for these two broad groups of negative symptoms, a possibility that could be explored with imaging and other studies.

## DISCUSSION

Since the time of the 2001 review, additional studies have provided evidence for the separate disease hypothesis of deficit schizophrenia. Most notably, the findings that deficit subjects have increased summer births and more normal regional brain volume, compared to nondeficit subjects, have received further support.

Other intriguing findings have also emerged. The most important is the double dissociation of the deficit and nondeficit groups with event-related potentials (56), as a double dissociation supports the separate disease hypothesis. The association with cytomegalovirus seropositivity is also potentially important, as this marker could be used in studies of gene/environment interaction. Both findings, however, await replication.

There are also disappointments in the research to date. As noted above, earlier evidence had suggested that glycine agonists might be effective treatments for the negative symptoms of deficit patients, but a large multicenter trial did not confirm these preliminary studies. Thus there remains no proven treatment for primary negative symptoms (59). Drugs with innovative mechanisms of action will probably be required.

There has also been a lack of progress in the area of genetics. The most appropriate strategy at this juncture may be a genome-wide association study, in which deficit subjects are considered as if they were a separate disease. The existing family studies, as well as the replicated difference with regard to an environmental risk factor – summer birth – suggest that there may be genetic differences between deficit and nondeficit schizophrenia.

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# Early intervention in psychosis: concepts, evidence and future directions

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*The rise of the early intervention paradigm in psychotic disorders represents a maturing of the therapeutic approach in psychiatry, as it embraces practical preventive strategies which are firmly established in mainstream health care. Early intervention means better access and systematic early delivery of existing and incremental improvements in knowledge rather than necessarily requiring dramatic and elusive breakthroughs. A clinical staging model has proven useful and may have wider utility in psychiatry. The earliest clinical stages of psychotic disorder are non-specific and multidimensional and overlap phenotypically with the initial stages of other disorders. This implies that treatment should proceed in a stepwise fashion depending upon safety, response and progression. Withholding treatment until severe and less reversible symptomatic and functional impairment have become entrenched represents a failure of care. While early intervention in psychosis has developed strongly in recent years, many countries have made no progress at all, and others have achieved only sparse coverage. The reform process has been substantially evidence-based, arguably more so than other system reforms in mental health. However, while evidence is necessary, it is insufficient. It is also a by-product as well as a catalyst of reform. In early psychosis, we have also seen the evidence-based paradigm misused to frustrate overdue reform. Mental disorders are the chronic diseases of the young, with their onset and maximum impact in late adolescence and early adult life. A broader focus for early intervention would solve many of the second order issues raised by the early psychosis reform process, such as diagnostic uncertainty despite a clear-cut need for care, stigma and engagement, and should be more effective in mobilizing community support. Early intervention represents a vital and challenging project for early adopters in global psychiatry to consider.*

**Key words:** Early intervention, psychosis, staging, health care reform, youth mental health

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Psychotic disorders and particularly schizophrenia are serious and sometimes fatal illnesses which typically emerge during the sensitive developmental period of adolescence and emerging adulthood (1). For over a century, a corrosive blend of pessimism, stigma and neglect have confined therapeutic efforts to delayed and inconsistent palliative care. Much of this can be attributed to the conceptual error underpinning the concept of schizophrenia, namely that a true disorder could be validly defined by its (poor) outcome. This error was, in turn, a legacy of the 19th century degeneration theory, which has been allowed to influence the field well beyond its use-by date (2). Although Kraepelin himself and some of his contemporaries ultimately recognized the fallacy, his dichotomy (between dementia praecox and manic depressive insanity) has withstood several challenges and has been strongly reinforced with the advent of operational diagnostic systems. This has not only hampered neurobiological research, but has caused widespread iatrogenic harm and inhibited early diagnosis because of an exaggerated fear of the expected outcome.

Until recently, apart from transient and illusory optimism generated by the mental hygiene movement in the 1920s, early intervention for psychotic disorders has been the furthest thing from the minds of clinicians and researchers. Ironically, however, since the early 1990s, this hitherto barren landscape has seen the growth of an increasingly rich harvest of evidence, and widespread national and international efforts for reform in services and treatment approaches, setting the scene for more serious efforts in early intervention in other mental disorders (3-5).

## DEVELOPMENT OF EARLY INTERVENTION SERVICES

Building on seminal research on first episode psychosis from the 1980s (6-8), frontline early psychosis clinical services were established, first in Melbourne (9) and soon after in many key locations in the UK, Europe, North America and Asia (10). There are now hundreds of early intervention programs worldwide, of varying intensity and duration, which focus on the special needs of young people and their families. International clinical practice guidelines and a consensus statement have been published (11) and clinical practice guidelines for the treatment of schizophrenia now typically have a major section on early psychosis (12,13). The International Early Psychosis Association (www.iepa.org.au), an international organization which seeks to improve knowledge, clinical care and service reform in early psychosis, has been in existence for over ten years, led by a highly collegial leadership group of clinicians and researchers. This association has over 3000 members from over 60 different countries, and by 2008 will have held six international conferences, stimulating and capturing a large volume of research and experience.

In recent months, responding to the widespread international momentum, the US National Institute of Mental Health has announced a large new funding initiative to study and promote the development of better services for patients with first episode psychosis (www.nimh.nih.gov).

### Shift in thinking: pessimism to optimism

The advent of preventive thinking has required a shift in the way schizophrenia and other psychotic disorders are viewed. Rather than seeing them as having inevitably poor prognoses with deterioration in social and functional outcome as the norm, more recent thinking backed up by evidence from large international studies (14-25) views the course of these disorders as much more fluid and malleable.

Examination of risk factors which can influence outcome has revealed that many of these may be reversible. For example, disruption of peer and family networks and vocational drop-out commonly occur around and even before the onset of a first psychotic episode. Attention to these areas as part of treatment has the potential to limit or repair the damage.

Comorbid depression, substance use, personality dysfunction and post-traumatic stress disorder (PTSD) are all factors which may influence outcome in a person with first episode psychosis. Again, early and vigorous management of these problems can result in better outcomes (26).

### What is early intervention?

Early intervention is a potentially confusing term. Because there is no aetiopathological basis for diagnosing psychotic disorders, they can only be diagnosed by symptoms or combinations of symptoms. In addition, we have no known malleable causal risk factors which predict onset of psychotic disorder with any specificity. Thus, it seems that primary prevention is currently out of our reach. Early intervention, therefore, means early *secondary* prevention.

In keeping with the clinical staging model (27) articulated below, early intervention in psychosis can be defined as comprising three foci or stages: ultra-high risk, first episode, and the recovery or critical period. The principal reason for making such distinctions relates to the underlying risk of chronicity, and specifically the timing and duration of prescription of antipsychotic medication, since psychosocial interventions are needed at all stages, though these interventions too vary by stage.

### What is the target for early intervention: schizophrenia or psychosis?

Clinicians and researchers have debated whether to focus on the preventive target of schizophrenia or of psychotic disorders more broadly. There are several reasons for stepping out of the current diagnostic silos and preferring a relatively broad target.

As described above, schizophrenia is conceived and defined in part as an outcome as much as a diagnosis. While it is very stable once applied (28-31), it is intrinsically difficult to apply until the patient has been ill for a prolonged period of time. Within a sample of ultra-high risk cases (already defined in order to preferentially predict transition to non-affective psychosis), only 75% of those who go on to develop a first episode psychosis will progress to a schizophrenia diagnosis (32). So, the false positive rate is higher for schizophrenia than for first episode psychosis. Even within a first episode psychosis sample, only 30-40% will meet criteria for schizophrenia, and this percentage will increase over time with additional diagnostic flux. Thus, some cases of first episode psychosis which do not meet criteria for schizophrenia can be seen as being at risk for this in the future (33). Schizophrenia, therefore, is to some extent a more distal target than psychosis, which is a better and broader initial waystation for critical treatment decisions. An even earlier and broader point for intervention is the ultra-high risk clinical stage, where there is a need for care prior to the positive psychotic symptoms having become severe and sustained.

In addition, due to fear and stigma derived from the notion of intrinsic poor prognosis, clinicians are reluctant to use the label "schizophrenia" early on anyway, justifiably concerned about iatrogenic effects on hope and the potential for recovery (34). This has led some countries, such as Japan, to change their diagnostic terminology and eschew the word "schizophrenia" (35). Our preferred alternative is to retain it for the time being, as one subtype of psychotic disorder outcome, admittedly a major one, among a small range of distal targets.

Psychosis itself is a variable syndrome, defined by the presence of positive psychotic symptoms, especially delusions and hallucinations, and typically features one or many comorbidities, including negative symptoms, mood syndromes, personality disorders, substance use disorders, medical diseases and PTSD. The relative prominence of the positive symptoms and comorbidities varies, and this leads to a more heterogeneous group of patients. As a consequence of this, a broader range of clinical skills will be required in early psychosis programs than in narrower schizophrenia programs.

Some have argued that the schizophrenia focus allows the other psychotic disorders, especially psychotic mood disorders and psychoses associated with certain personality disorders and PTSD, to be treated in more appropriate settings. However, provided there is a flexible attitude and a broad range of clinical expertise available, both groups of patients benefit more from this broad, early, and inclusive focus on the spectrum of psychosis. It provides a good balance between specialization and addressing common needs, and also facilitates both clinical and aetiological research, which increasingly needs to transcend traditional diagnostic barriers.

## ENHANCING THE VALUE OF DIAGNOSIS: THE CLINICAL STAGING MODEL

Many of the problems of categorical diagnosis flow from a telescoping of syndromes and stages of illness which conceals and distorts the natural ebb and flow of illness, remission and progression. In addition to augmenting categorical approaches with symptom dimensions, consideration needs to be given to the dimensions of time, severity, persistence and recurrence.

The notion of staging can be borrowed

and adapted from mainstream medicine to assist us here. A clinical staging model provides a heuristic framework allowing the development and evaluation of broad and specific interventions as well as the study of the variables and processes underlying the evolution of psychiatric disorder (27,36).

### What is clinical staging?

Clinical staging is simply a more refined form of diagnosis (37,38). Its value is recognized in the treatment of malignancies, where quality of life and survival rely on the earliest possible delivery of effective interventions. However, it also has applicability in a diverse range of diseases. Clinical staging differs from conventional diagnostic practice in that it defines the extent of progression of disease at a particular point in time, and where a person lies currently along the continuum of the course of illness (36).

The differentiation of early and milder clinical phenomena from those that accompany illness extension, progression and chronicity lies at the heart of the concept. It enables the clinician to select treatments relevant to earlier stages, and assumes that such interventions will be both more effective and less harmful than treatments delivered later in the course.

While staging links treatment selection and prediction, its role in the former is more crucial than in the latter, particularly since early successful treatment may change the prognosis and thus prevent progression to subsequent stages. In addition to guiding treatment selection, a staging framework, which moves beyond the current diagnostic silos to encompass a broader range of clinical phenotypes, and which at the same time introduces subtypes along a longitudinal dimension, has the potential to organize endophenotypic data in a more coherent and mutually validating fashion (36).

### How do we define the stages of a disorder?

In other medical conditions, clinical stages are defined by the degree of extent, progression and biological impact of illness in the patient, which in turn must correlate with prognosis. This approach usually depends upon a capacity to define pathologically as well as clinically the limits or extent of the disease process.

In clinical psychiatry, this could involve not only a cross-sectional clinical definition, but a wider biopsychosocial definition of extent or progression. Therefore, in addition to the severity, persistence and recurrence of symptoms, biological changes (e.g., hippocampal volume loss), and the social impact of the disorder (e.g., the collateral damage affecting social relationships and employment), could also be drawn into the definition. Ultimately, something approaching a clinicopathological model could emerge.

### What are the potential benefits of staging?

On the clinical side, defining discrete stages according to progression of disease creates a prevention-oriented framework for the evaluation of interventions. The key positive health outcomes are prevention of progression to more advanced stages, or regression to an earlier stage. This requires an accurate understanding of those broad social, biological and personal risk and protective factors which influence progression from one stage to the next.

Furthermore, we need to know the relative potency of these risk factors and which of them may be responsive to current interventions. While some factors may operate across several or all stage transitions, others may be stage-specific, for example substance abuse or stress may be especially harmful in triggering onset of the first episode of illness, yet be less toxic subsequently (or vice versa). Gene-environment interactions almost certainly underpin and mediate these transitions, where environmental variables – such as substance abuse, psychosocial stressors, cognitive style, medication adherence and social isolation – may interact with genetic and other biological risk factors (39-41).

From an aetiological perspective, over a century of research with traditional diagnostic categories of psychosis and severe mood disorders has failed to relate these flawed concepts to any discrete pathophysiology (42,43). A clinical staging model, which allows the relationship of biological markers to stage of illness to be mapped, may help to validate the boundaries of current or newly defined clinical entities, distinguish core biological processes from epiphenomena and sequelae, and enable existing knowledge to be better represented and understood.

## THE STAGES OF EARLY PSYCHOSIS

### Stage 1: Ultra-high risk

In psychotic disorders, an early prepsychotic stage is known to exist, one in which much of the collateral psychosocial damage is known to occur (44). This earliest stage could, in retrospect, be termed the "prodrome", i.e., the precursor of the psychotic stage. However, since we can only apply the term "prodrome" with certainty if the definitive psychotic stage does indeed develop, terms such as the "ultra-high risk" (34) or "clinical high risk" (45) stage have been developed to indicate that psychosis is not inevitable and that false positive cases also occur. This symptomatic yet prepsychotic stage is the earliest point at which preventive interventions for psychosis can concurrently be conceived (46).

The challenge in detecting such a stage prospectively is firstly to define the clinical frontier for earliest intervention and "need for care" which represents the boundary between normal human experience and pathology. Secondly, a set of clinical and other predictors need to be defined which identify a subgroup at imminent risk for psychotic disorder. This is a complex task and the key issues involved have been covered in many recent publications (47-55). Earlier writers (56) aspired to the diagnosis of schizophrenia in the prodromal phase. German psychopathologists in the mid 20th century emphasized subtle changes in experience and behaviour, though

their complexity meant that they had little impact on Anglophone psychiatry initially. A practical operational definition of a prepsychotic "at risk" or "ultra-high risk" mental state, which could be shown to confer a substantially high risk of fully fledged psychosis within a 12 month period, was then developed and tested in the early 1990s (57). This has captured the attention of the field and has been the focus of much subsequent research, focusing on prediction, treatment and neurobiological aspects.

These criteria do indeed predict an "ultra-high risk" group for early transition to psychosis (32), leading to a relative risk of 40% compared to the incident rate of psychotic disorders in the general population (58). However, there is still a significant false positive rate of 60-80%, though they typically are or turn out to be true positives for other disorders, notably depression and anxiety disorders. While the predictive power for psychosis can be substantially sharpened *post-hoc* by the use of key variables such as genetic risk, depression, functional impairment and substance use (58,59), this is of limited utility due to the "prevention paradox". This means that increasing the positive predictive value reduces the number and percentage of cases that can benefit. So, if the sample is narrowed, one is on firmer ground, but most cases who do go on to develop the disorder are missed due to the narrower focus (51). We know already that most cases of first episode psychosis are already missed by prodrome clinics.

There have been a series of clinical trials of relatively small sample size examining both antipsychotics and/or cognitive therapy as preventive treatment strategies for ultra-high risk patients (60-62). These trials suggest that cognitive therapy and antipsychotics may prevent or at least delay the onset of psychotic disorder and reduce symptomatology. A second generation of single site clinical trials has recently been completed, with interesting results for a range of psychosocial and biological therapies, including cognitive therapy (62), lithium (63), omega-3 fatty acids (64), and atypical antipsychotics (60).

However, treating young people in the putative prodromal phase does cause some understandable concern that patients might be exposed to unnecessary and potentially harmful treatments. This has created controversy in the US in particular around this type of research. This in turn has led to so-called "naturalistic designs" (58,65) being preferred above the traditional randomized designs. Paradoxically, the ethical considerations that drove this thinking have allowed the same treatments that could not be researched under rigorous conditions of informed consent within a randomized controlled trial to be used off label in a widespread and uncontrolled fashion in these naturalistic studies. Hence the term "naturalistic" becomes a misnomer, since the natural course may be profoundly influenced by uncontrolled treatment. These "naturalistic" studies reveal that extensive non-evidence-based use of antipsychotic medications seems to be common in clinical settings in the US, ironically side by side with long delayed and inadequate treatment of first episode and established psychotic disorders (66).

### *Next steps*

Clinical trial data is crucial to determining the risks and benefits of various forms of treatment in a new clinical focus and creating solid foundations for an evidence-based approach. This is the best antidote to fears on widespread and potentially harmful and unnecessary use of antipsychotic medications in particular. The "prodromal" or ultra-high risk field remains in clinical equipoise, since we do not yet know which treatments will be most helpful and acceptable to patients, and crucially in which sequence or combination.

Prospective or naturalistic data can best be collected in the most sound and interpretable fashion in the context of a large well-funded multicentre clinical trial, with an "effectiveness" rather than efficacy design and a minimal intervention arm, to which non-consenters to randomisation can be assigned.

We can readily accept that antipsychotics and indeed antidepressants (67) and neuroprotective agents such as omega-3 fatty acids and lithium are legitimate therapies to be further researched, but their use in research should be protocolized within rigorous study designs. In the meantime, the international clinical practice guidelines on early psychosis (11), which advocate a conservative approach to the use of antipsychotic medications and more liberal use of psychosocial interventions, should be followed. This rather conservative approach to treatment of ultra-high risk individuals is even more imperative, as recently it has been discovered that the rates of early transition to first episode psychosis have been falling in the more established prodromal centres (52), with a much higher rate of so-called "false positives" being accepted into these services. This may be due to sampling variation, earlier detection of ultra-high risk cases, or improved efficacy of interventions provided (52).

This reduction in transition rate and uncertainty over treatment in the ultra-high risk group has led to valid concerns about identification of and intervention with these individuals. Yet help-seeking patients defined by the ultra-high risk criteria for first episode psychosis are at risk not only for schizophrenia or psychosis but for other adverse mental health outcomes (68). We may need to define an even broader pluripotential initial clinical stage with a range of possible exit or target syndromes. Consequently, we have broadened our own clinical and research strategy (69), cross-sectionally with the development of a broader and more accessible system of clinical care for those in the peak age of risk for all types of mental disorders (70-72), and longitudinally with the creation of a clinical staging model for psychotic, mood and anxiety disorders (27).

This enables a serial enriching strategy to unfold to ensure that the declining transition rates in ultra-high risk samples (52) and the consequently high false positive rate can be handled in future clinical trials, and that other exit syndromes and indeed remission and resolution can be included. These strategies help us to move beyond some of the obstacles to early diagnosis and

intervention: namely the "false positive" issue, potential problems with stigma, the challenge of comorbidity, and lack of predictive specificity. As we move further down this road, the problems with our historically determined classification systems loom larger and the need to loosen the shackles becomes more apparent.

### Stage 2: Early detection and treatment of first episode psychosis

The second stage involves a therapeutic focus on the period after the onset of fully-fledged psychosis (often known as "first episode psychosis"). This is divided into the period before psychosis is detected and the period after detection. Unfortunately, the undetected or untreated phase can be prolonged, even in developed countries (73). Of course, even when psychosis is detected, the initiation of effective treatment may still be delayed. The goal is to minimize this duration of untreated psychosis (DUP). Post-detection, the intervention goals are engagement and initiation of pharmacological and psychosocial treatments. Intensive interventions aimed at maximal symptomatic and functional recovery and the prevention of relapse are ideally delivered during the early weeks and months of treatment.

The controversy surrounding the importance of DUP and treatment delay in first episode psychosis seems to have been largely resolved following the publication of some key systematic reviews (74,75) and recent influential longitudinal research. These studies have now established that longer DUP is both a marker *and* independent risk factor for poor outcome. The Early Treatment and Identification of Psychosis (TIPS) study in Scandinavia has shown, through the best possible design, that reducing DUP leads to early benefits in reducing suicidal risk and severity of illness at initial treatment and sustained benefits in terms of negative symptoms and social functioning (18-21). The relationship between DUP and outcome is robust, being sustained over many years of follow-up (76,77). However, these studies do show that, though being a malleable risk factor, DUP accounts for a relatively modest amount of outcome variance, underlining the importance of treatment access and quality during the early years of illness.

There is an extensive literature attesting to the benefits of comprehensive care of the first psychotic episode. This is summarised in the International Clinical Practice Guidelines for Early Psychosis (11), published in 2005. Since 2005, the growth in research in this area has continued. This has led to the emergence of the following findings.

The large multicentre European First Episode Schizophrenia Trial (EUFEST) has shown that in the treatment of first episode schizophreniform and schizophrenic disorders, atypical or second-generation antipsychotics have some clear-cut advantages (78). While most patients responded surprisingly well to both typical and atypical medications, with no significant efficacy differences, discontinuation rates and tolerability were clearly superior for atypical agents. This was true even when contrasted with very low-dose haloperidol. While the authors' conclusions and recommendations were conservative, highlighting the equivalent efficacy of the two classes of drug, the EUFEST findings contrast markedly with those of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (79) in chronic schizophrenia, where no dramatic advantages were found for atypicals using similar outcome measures. The EUFEST data support the recommendations of the International Clinical Practice Guidelines in Early Psychosis (11), which favor the use of atypicals as first line therapy, because of better tolerability (a crucial issue in drug-naïve first episode patients) and reduced risk for tardive dyskinesia. However, some atypicals have a particularly high risk of weight gain and metabolic problems, and these risks need to be carefully managed and prevented wherever possible. A recent paper (80), however, suggests that weight gain is a problem in the first year of therapy for first episode patients on both typicals and atypicals, with the key difference being the rate at which it develops.

Psychosocial treatments in early psychosis have been extensively studied, and there are positive findings pointing to the value of cognitive therapies in accelerating and maximizing symptomatic and functional recovery (81,82). Increasingly there has been attention to the fact that medications, while assisting in symptomatic recovery, do not, by themselves, contribute to a return to functioning. This has led to an increased focus on the need to enhance social recovery (68) especially educational and vocational aspects (83-85), through the combination of effective psychosocial interventions with well-managed medication. There is also an increasing focus on targeted cognitive remediation (86) to limit the degree of cognitive decline that is often found as illness progresses.

#### *Next steps*

Initial scepticism regarding DUP has slowly melted in the face of evidence but also the logic of early diagnosis. If we believe we have effective interventions in psychosis, it is perverse to argue that delayed treatment is acceptable. Sceptics find themselves being asked how long a delay is acceptable: 2 months? 6 months? 2 years? In reducing the DUP the two key components of intervention are community awareness and mobile detection services. Both are important, as the data from TIPS (87) and other studies (88) have shown. When both are in place, it is possible to achieve very low levels of DUP (a median of a few weeks only). These strategies also result in a less risky and traumatic mode of entry into care and enable patients to be engaged without a surge of positive symptoms or disturbed behaviour being required to force entry into poorly accessible or highly defended service systems. They should be available in all developed communities and a standard feature of all mental health systems.

In terms of the specific elements of first episode psychosis intervention, a number of trials have shown that atypical antipsychotics in low dose are superior for first episode patients where tolerability and safety are at a premium, though

some may be ruled out on exactly these grounds in many patients. The recent EUFEST study is especially compelling (78). The place of new injectables and clozapine needs to be clarified, as well as that of adjunctive neuroprotective agents such as omega-3 fatty acids, lithium and N-acetyl cysteine. Cognitive behavioural therapy and vocational rehabilitation (89) are the key psychosocial interventions in early psychosis and need to be much more intensively and widely deployed. Assertive community treatment for the subset of poorly engaged patients is vital (11). Family interventions are also an essential element of care, even though the formal evidence is not yet fully available (90).

### Stage 3: The critical period of the first 5 years after diagnosis

This third stage involves the critical early years beyond the first episode, which can be viewed as the critical period (91). Treatment goals in this phase are the management of effective medication and the use of effective psychosocial interventions to minimize the development of disability and maximize functioning. Proof of concept is now established for these strategies (14,15). However, there remains a large gap in most communities between what works and what is available, even in high income countries and certainly in the low and middle income countries (92).

Beyond the first episode, we know that the first 2-5 years post-diagnosis are crucial in setting the parameters for longer term recovery and outcome. This is the period of maximum risk for disengagement, relapse and suicide, as well as coinciding with the major developmental challenges of forming a stable identity, peer network, vocational training and intimate relationships. It makes sense that a stream of care specially focused on young people and on this stage of illness is required to maximize the chances of engagement, continuity of care, appropriate lifestyle changes, adherence to treatment, family support and vocational recovery and progress. Indeed, the available evidence from naturalistic and randomized studies strongly supports the value of specialized early psychosis programs in improving outcome in the short term (89,93). If these programs are only provided for 1-2 years, there is also evidence that some of the gains are eroded, suggesting that, for a substantial subset at least, specialized early psychosis care needs to be provided for a longer period, probably up to 5 years in many cases (77,94,95).

#### *Next steps*

The best available evidence indicates that streamed care provides superior outcomes in the short to medium term compared to generic care (16,17). While this may be insufficient to meet the most stringent Cochrane criteria, such evidence, combined with face validity and obvious poorly met need, has been sufficient to convince mental health policy makers and service providers in hundreds of locations worldwide to adopt, adapt and implement this model. The randomized controlled trials so far have only tested partial versions of this streaming, with a specialized assertive community treatment model being the main feature evaluated. Even so the results are positive for the first 2 years of care. It seems likely that, for a significant subset at least, if these gains are to be maintained, the streamed early psychosis model must be continued for longer, perhaps up to 5 years (89). At this point, persisting illness and disability may be present in a much smaller percentage of people, whose needs may subsequently be well met by more traditional mental health services for older adults. This may be a much better point to transfer care.

## THE PROCESS OF REFORM

The pace of reform is typically slow in health care. While early intervention in psychosis has made great progress in recent years, dissemination remains in many ways frustratingly slow. Many developed and most developing countries have made no progress at all, and even those countries which have made significant investments have only achieved partial coverage. We have previously commented on this inertia and some of the reasons for it (92,96).

Evidence-based health policy (97) can be seen as a blend of evidence-based health care and public policy analysis, in which evidence is only one of a range of influential variables. Pure evidence-based health policy derives from a technical perspective and regards the task as identifying and overcoming barriers to smooth flow of best available evidence into practice. This has been characterised as "naïve rationalism" (98), since cultural and political values and the dynamics of change and reform are other key influences on policy making. Evidence is a product as well as a driver of reform and the evidence-based paradigm, by setting impossible prerequisite standards, and by shifting the goalposts once evidence is forthcoming, can be used as a weapon to frustrate and delay overdue reform in a manner that would be unacceptable in other branches of medicine (99).

In better understanding this phenomenon, it is worthwhile to reflect on how innovation and reform in health care works. Diffusion of innovations is a major challenge in all industries, from agriculture to manufacturing. The study of diffusion of innovation has a long history in the social sciences. Many nations have established centres and strategies to understand and promote this in health care (100,101).

There are many contextual factors involved, but there are also predictable characteristics of individuals and health care systems which influence the process (102). Firstly, we must consider perceptions of the innovation. There must be perceived benefit; the innovation should be compatible with the values and needs of those considering it. It should be simple or capable of simplification and, in the process of spread, it is vital that innovations be adapted and reinvented in relation to local needs. Secondly, there are several groups of adopters involved in the process of innovation. The innovators are the smallest group and create the novel ideas and skills. They are novelty seekers who form wider national and international networks or cliques

and they invest energy in these connections. They may be thought of as mavericks heavily invested in a specialized issue. The early adopters are a larger group of opinion leaders who draw on the innovators and cross-pollinate with one another. They are open to a range of new ideas and have the resources and risk tolerance to try new things. Most importantly, they are closely watched by the next group, the early majority, who are more local in their focus and more risk averse. The early majority look to the early adopters for guidance about what is safe to try. The fourth group, the late majority, are even more conservative and look to the early majority, adopting an innovation only when it appears to be the new status quo. Finally, we have the laggards, apparent members of a modern day flat earth society, whose point of reference is the past. To be fair, this description underestimates their value, since they usefully point to the need to retain some valuable elements of current and prior practice. However, they are also exposed defending the indefensible and demanding impossible and unrealistic levels of evidence before accepting change. Furthermore, the evidence standards demanded for innovations are rarely if ever applied to the status quo, which in mental health at least is typically less evidence-based than the new approach. This active rearguard action is aided and abetted by the tendency of systems to rapidly build inertia and reinstitutionalize after periods of progress.

Despite the welcome progress in early intervention, the laggards have been prominent in the early intervention field. While evidence-based medicine is by far the best antidote for taking wrong and potentially dangerous and wasteful turns in health care, opponents of change have been observed to misuse the paradigm to frustrate change which is overdue and in the best interests of the community. There is regrettably insufficient debate about where the onus of proof lies in such matters, and what considerations other than evidence should influence decisions, especially where changes have high face validity, such as emergency care and indeed early intervention. Finally, it is unlikely that oncologists would debate the relative value of early diagnosis and palliative care, which is where psychiatry has got stuck repeatedly.

Berwick points out that the dissemination of innovation has a tipping point (103), usually around 15-20% adoption. Certainly, once the early majority have swung in behind an innovation, the late majority are likely to feel comfortable to move as well. This is a process that can be facilitated by several strategies. These include identifying sound innovations, leading by example, supporting innovators and early adopters with resources and time, making the activities of early adopters highly visible, and valuing reinvention as a form of learning rather than requiring exact replication of innovations.

## CONCLUSIONS

Many of the obstacles to early intervention are the same ones which impede progress in mental health more widely, as illustrated in the Lancet Series on Global Mental Health (104). They include stigma, pessimism, the silence that surrounds the mentally ill, and a consequent failure to invest. Developed and rapidly developing countries need to recognize the public health importance of untreated and poorly treated mental disorders. A key aspect which is beginning to be recognized is that mental disorders are the chronic diseases of the young (105). Most adult type mental disorders – notably psychotic, mood, anxiety, substance use and personality disorders – have their onset and maximum impact in late adolescence and early adult life. A broader focus for early intervention would solve many of the second order issues raised by the early psychosis reform process, such as diagnostic uncertainty despite a clear-cut need for care, stigma and engagement, and should be more effective in mobilizing community support for investment and reform in mental health. This is occurring in Australia (106,107) and Ireland (108), and is attracting increasing attention in a number of other countries, along the lines of the innovation process described above. It currently represents a vital and challenging project for early adopters in global psychiatry to consider.

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# The promises and challenges of early intervention in psychotic disorders

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A burgeoning interest in understanding and treating the early phase of psychotic disorders, especially schizophrenia, has brought forth a sense of optimism of altering the course of these disorders. McGorry et al highlight many aspects of the progress made, as well as some of the challenges to furthering the application of a broader preventive model of care based on a hierarchical model of understanding mental disorders.

It may not be entirely ironic that development of early intervention theory and practice in psychiatric disorders should have started with the disorder viewed most pessimistically with poor outcome (schizophrenia). Indeed, a great deal of progress has been made since the initial seminal studies of first episode psychosis (1) and the influential review by Wyatt (2). Such progress has extended beyond understanding the effects of delay in treatment to a more substantial understanding of neurobiology and outcome during early phase of psychotic disorders. It has been particularly remarkable that, while research in phenomenology, neurobiology and cognitive psychology of first episode psychosis and the putative periods preceding the onset of psychosis has flourished, there has been a parallel and equally prolific development of services specializing in treatment of early phases of the illness. Such developments have taken research out of artificial settings to real life new specialized services, thus making available large epidemiologically based cohorts of subjects for investigation. Such research is likely to be more meaningful in the long run, as the findings will be applicable to larger groups of patients. As McGorry et al suggest, it is time now to think more broadly and extend the scope of such developments in service and research to a larger group of disorders without the constraint of a strictly categorical diagnostic system.

Despite the well justified enthusiasm, there are, however, a number of issues that remain either unclear or unaddressed. The term "early intervention" has often been taken to imply "earlier" intervention predicated on an association between duration of untreated psychosis (DUP) and clinical outcome. However, this is an oversimplification: there is in fact much more to "early intervention" than simply intervening early (3). The evidence to support enriched and comprehensive interventions is indeed strong and replicated in controlled studies (4-6) and confirmed in a recent meta-analysis (7). While it requires no more than face validity to support quick, unencumbered and user-friendly access to specialized treatment of new cases of psychotic disorders, the evidence for more elaborate and relatively expensive interventions to improve early case detection remains either confined to specific jurisdictions (8) or applicable only to a subgroup of patients (9). In order to benefit larger number of patients, it may be easier to convince mental health policy makers to apply a more effective treatment model with improved access than to expect them to support elaborate and expensive interventions to reduce DUP through active case detection. There is still a need to identify what methods of early case identification and improved access would work in which settings, given large variations in composition of populations (e.g. ethnicity, urban vs. rural setting) and nature and quality of the prevailing primary and specialist health care. On the other hand, large scale campaigns at the community level to improve general mental health literacy and engage communities in a dialogue about mental illness have heuristic value even if their direct impact on reducing delay in treatment of specific disorders may be difficult to demonstrate.

McGorry et al correctly identify the greater conceptual accuracy of "ultra-high risk" as opposed to "prodromal" patients to whom interventions could be provided to prevent or delay onset of psychosis. While there has been progress in demonstrating efficacy of individual interventions in small controlled trials, we are not yet at a stage to recommend any particular approach. Apart from the need for more substantial evidence, there are several reasons for such caution. The transition from a non-psychotic high risk state to psychosis occurs in only a fraction of such patients, even without the use of antipsychotic medications, especially if they are provided with adequate care and support for the problems they present with. This raises the risk of treating many more false positives for a putative impending psychosis. Further, not enough attention has been paid to the relatively fluid and ambiguous boundary between sub-threshold and threshold level of symptoms of psychosis, creating a risk of reporting results based on a categorical fallacy. Until such time as further methodologically sound research using large samples produces clear evidence based interventions, we run the risk of encouraging clinicians to become cavalier in using antipsychotic medications for treating symptoms they observe over a single assessment, as is already happening in many jurisdictions.

Other major challenges that must be faced, if "early intervention" is to benefit a larger population of patients, include the patients' refusal to accept or engage in treatment (estimate 15-50%), those who drop out early in the course of or do not adhere to treatment, and those who present with substance abuse as an additional problem. Lack of adherence to treatment and presence of substance abuse have been identified as major obstacles to achieving and maintaining symptomatic remission following treatment of first episode psychosis (10-12). Indeed, such malleable predictors of outcome overshadow the significance of delay in treatment in achieving better outcomes. Further, it appears that the gains made with specialized treatment of early phase of psychosis over the first two years are difficult to sustain (5), and further systematic study of the length of specialized treatment is required if we

are to make a difference in the long-term course of psychotic disorders. Last, but not least, there is a dire need to understand the process of recovery and what promotes or hinders it during the early "critical period". Both qualitative and quantitative research, which takes into account patients' and families' perspectives and examines the effect of various treatments on recovery (13), should be a priority for the early intervention field.

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# The case for early, medium and late intervention in psychosis


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As McGorry et al point out, the model for early intervention in psychosis draws on physical illness (typically cancer), where the idea is that early detection leads to treatment that is less radical, more successful and averts a poor or fatal outcome. Unfortunately in psychosis there is neither an early nor a specific biological marker, so that early intervention is really not early at all, but closer to secondary prevention where symptoms are already present, even if they are not yet severe. This means that all prodromal services can do is offer treatments to help seekers, up to 80% of whom will never make the transition. Prodromal services, by definition, do not offer help to those who deny they have problems and who may be at the more severe end of the spectrum with longer duration of untreated psychosis (DUP), more negative symptoms and poorer outcomes after an episode. Similarly, early intervention services can only offer help to those who will stay engaged.

Thus, the early intervention medical model is not correct for psychosis; those treated, or those who will accept treatment, by definition are unlikely to be those who will need it most. This is the first difficulty that services face, and until more specific markers are discovered, it will remain a stumbling block to the hope of preventing episodes or of offering comprehensive services to everyone at risk of an episode: a true early intervention model.

Of course, there are humanitarian reasons for offering services early; these are mainly to reduce the DUP, associated with a poorer response to antipsychotic medication (1), and the sometimes brutal and shocking realities of sectioning and admission that individuals can face if problems are left until a crisis. Offering a service that people collaborate with and take up before crises develop is entirely laudable. However, we have no evidence yet, apart from the DUP evidence, that such early treatment changes longer term course. We are still not able to look at 10 to 20 year follow-ups of early intervention, including deaths from all causes.

Further into his article, McGorry et al promote their idea of a "staged" model. Again this is a transfer of ideas from physical medicine. While a useful research programme, we have no way of yet knowing what markers, biological or social, predict better or worse outcomes, or would respond to less treatment (perhaps not needing medication for instance). While of interest, we are not in a position to implement anything like this kind of detailed and specified service delivery for psychosis.

McGorry et al touch on, but do not elaborate, the point that most successful early intervention psychosis treatment includes considerable social and vocational input. Young people with psychosis typically wish to reduce their social exclusion – they wish to "get back to normal", and have easy access to meaningful activity (jobs), study and relationships. Early intervention services typically include a large "dose" of vocational help. This suggests that it is not only psychosis that needs treating, but society's and the individual's attitude to the difficulties it can cause. Easing people back into "normal" environments, despite problems such as their sensitivity to stress and possible poor concentration, is made more difficult because of the poor public under-

standing, fear and stigma, that surrounds these diagnoses and prevents re-integration. The current anti-stigma campaigns in some countries are trying to improve this aspect.

However, it is not just society's reaction. Illness perception research shows that, as with physical illness, people with psychosis, and their carers, can have understandably negative views about the consequences of, and their ability to control problems, which can affect decisions about treatment. Because of this, as John Weinman has pointed out (2), "illness perceptions account for a significant and important amount of variance in outcome in physical illness". People with psychosis share these attitudes (3,4). Certainly we know that rejecting medication, because of its side effects, as well as failing to engage with our services, remain concerns for this population.

Thirdly, McGorry et al only touch on the issue of family intervention for early psychosis. There is some evidence that it is helpful (5,6). However, we also know that there are more carers at early episodes, perhaps 60%, and that these carers experience similar difficulties and reactions as do later carers (7). We also know that the impact of care for relatives is related to long-term depression, and higher levels of stress and exhaustion while the caring role continues (8). Therefore, in terms of improving service user and carer outcomes, offering early intervention, including family intervention, from the beginning of episodes has to be sensible.

Finally, it is hard to argue against the idea that early detection, prodromal and early intervention services are a "good" thing. It must be good practice to offer the best service we can. As Max Birchwood has noted, early intervention aims particularly to reduce the chaos and high suicide rates of the first "critical" years of psychosis (9). However, we only have emerging evidence that it can reduce relapse and improve engagement (10) and none showing that longer term course will improve. As I have suggested before (11), offering high quality, comprehensive, needs led services at *all* stages of presentation, early, medium or later, including offering optimism and hope of recovery (12), would seem to be a more reasonable strategy.

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# The clinical staging and the endophenotype approach as an integrative future perspective for psychiatry


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In their paper, McGorry et al advocate the international introduction of a clinical staging model into clinical diagnosis in the different mental health care systems.

For the early course of psychotic disorders, three stages with different implications for diagnosis and therapy are distinguished: a) the ultra-high risk stage according to the criteria developed by the Melbourne working group, b) the first-episode psychosis and c) the most crucial first 2-5-year period following the first diagnosis of psychosis.

Elsewhere (1), the staging model has already been extended to depressive and bipolar disorders and subdivided into eight different stage definitions. According to this more differentiated model, one more stage (Ia) with mild or non-specific symptoms, including neurocognitive deficits and mild functional changes or decline, precedes the ultra-high risk states in psychotic and severe mood disorders (Ib). Even prior to these, an increased risk stage (0) without symptoms might exist. Furthermore, the critical period (stage III) after first-episode psychosis (stage II) is subdivided into stages of incomplete remission (IIIa), recurrence or relapse (IIIb) or multiple relapses (IIIc), and a stage IV is identified for persistent or unremitting psychotic and severe mood disorders.

Any early intervention strategy, however, presupposes available retrospective and/or prospective findings on the early course and a clinical staging model re-

lated to these. In the German Research Network of Schizophrenia (GRNS, 2), for example, the early detection and intervention projects (3) proceeded from studies which had already aimed for a thorough characterization of the initial prodromal stages prior to first-episode psychosis with optimized retrospective (4,5) and prospective (6) methodologies. These studies had revealed a duration of the initial prodrome of 5-6 years on average and, within this phase, had identified some syndrome sequences, from nonspecific symptoms, via cognitive-perceptual basic symptoms, attenuated and transient psychotic symptoms, to first-episode psychosis (7). These early cognitive-perceptual basic symptoms had shown a good predictive accuracy, with a transition rate of 63% within the average 9.6-years follow-up (6). Thus, in combination with available data on transition rates for ultra-high risk criteria, a subdivision of the prodromal phase into an early initial and a late initial prodromal state has been proposed, that is quite similar to the above differentiation between stages Ia and Ib. This model has been the basis for the early detection and intervention projects in the GRNS (8) and, slightly modified, the multinational prospective European Prediction of Psychosis Study (EPOS, 9).

The EPOS results confirmed an emerging problem that the Melbourne group has described for its own ultra-high risk approach, i.e., that the short-term transition rates are lower in recently collected samples compared to the initially studied ones. As a solution to the resulting problem of increased false-positive predictions of first-episode psychosis, the EPOS group has proposed a two-step procedure: first, the combination of the more late prodrome-aligned ultra-high risk criteria with the more early prodromal-related basic symptom criteria will allow a more sensitive and more specific allocation to the initial prodromal risk stage. Second, new prognostic indices could be calculated, which, for each individual, determine the probability and the time expected to pass until transition into first-episode psychosis. Thereby, the clinical staging could be combined with an individual risk estimation.

The clinical staging model differs from the endophenotype approach (10,11). The clinical staging model assumes that at-risk subjects develop their first mild symptoms already in adolescent years. Depending on a variety of neurobiological, social and personal risk as well as protective factors, these can increase and transgress thresholds of more severe stages. Therefore, it is essential to prevent this progress as early as possible. This, in turn, requires detailed knowledge of the patient's stage of the disease and the risk and protective factors relevant to this stage. The endophenotype approach focuses on heritability, familial association, co-segregation and even state-independence. Candidate markers are regarded as constant traits, which are present at all clinical stages and, most importantly, even at the non-clinical at-risk state.

Within the GRNS, the two approaches have been combined. Substantial interest has been paid to possible changes of the neurobiological correlates during a person's transition across different stages from 0 to IV. The differentiation between early initial and late initial prodromal states, with its diagnostic and therapeutic implications, has been included in the new German Clinical Practice Guidelines. However, despite all progress, both the clinical staging and the endophenotype approach still require consolidation by further research, before they can be sensibly implemented in international diagnostic systems.

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# Staging intervention and meeting needs in early psychosis


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Kraepelin's idea to use outcome as a diagnostic criterion for dementia praecox, so that the outcome of this condition was by definition gloomy, was criticized from the very beginning. Bleuler (1) defended the view that a schizophrenia diagnosis should be set at the beginning of the illness, so that a patient with schizophrenia had the possibility to recover without retrospective re-diagnosing. The Bleulerian approach, fertilized by Freudian psychodynamic ingredients, led to the broadening of the schizophrenia concept, resulting, however, in unreliable schizophrenia diagnoses. In reaction to this untenable

situation, the neo-Kraepelinian diagnostic classification (DSM-III) was produced, and outcome once again became a diagnostic criterion. This diagnostic reform meant a setback for early intervention, because a clinician had to wait for a long time before the correct diagnosis could be confirmed and evidence-based intervention could be introduced.

To overcome the disadvantage caused by the current clinical diagnostic practice, McGorry et al suggest to concentrate not on schizophrenia, but on all (functional) psychotic disorders, considering their development as stages from risk state, via first episode, to recovery or critical period. From the point of view of early intervention, this psychosis staging is justified. Only a small proportion of ultra-high risk patients who develop psychosis will progress to a schizophrenia diagnosis. Early and comprehensive intervention could reach patients at their pre-psychotic stage and possibly prevent or delay their sliding into psychosis. These patients may suffer from rather severe (subclinical or subsyndromal) symptoms and functional decline: they do not fulfil the criteria for clinical diagnoses, but can progress to various types of psychoses, thus requiring a broader range of clinical skills than treatment for patients with confirmed schizophrenia. Actually, the care of ultra-high risk patients follows the principles of the dimensional approach, and focuses on treating various symptoms and functional deficits, without waiting for a structural diagnosis; preventive thinking characterizes the whole disorder detection and intervention process.

The ultra-high risk or late initial prodromal state is now well defined, and there are reliable instruments for detecting ultra-high risk subjects, although the distinction between an ultra-high risk condition (brief intermittent psychotic symptoms) and brief psychoses is not clear-cut. The early initial prodromal state, defined by basic symptoms, may precede the late initial prodromal one, and offer an earlier stage for psychosocial intervention (2,3). Although there is no consensus as yet on how to treat patients with early prodromal states, a few intervention studies suggest that both psychosocial and pharmacological intervention are promising.

It is rather surprising how vigorously the authors defend atypical over conventional antipsychotic drugs. It is true that, in the EUFEST study (4), the discontinuation rate among patients receiving low dose haloperidol was higher than among patients with atypical drugs. However, this study was open and, as the authors state, "expectations of psychiatrists could have led to haloperidol being discontinued more often". Both conventional and atypical antipsychotic drugs are heterogeneous groups, and we have no good comparative studies between different antipsychotics in the treatment of patients at risk of psychosis or with first-episode schizophrenia. A couple of studies using perphenazine (CATIE) (5) or several conventionals (CUtLASS) (6) as comparative drugs suggest that the differences in effectiveness between conventional and atypical drugs may be small. The poor reputation of conventional neuroleptics is mainly due to the high daily doses patients were prescribed. The clinical staging approach, when speaking about psychoses instead of schizophrenia, aims to reduce the stigma related to the concept of schizophrenia. This same strategy may also suit the names of antipsychotic drugs. As the authors state, it is paradoxical that antipsychotic drugs are widely used in the treatment of patients in the prodromal phase, while they are not allowed in clinical trials. By changing the names of drugs from antipsychotic back to neuroleptic drugs, a large amount of the fears related to the psychosis concept and use of drugs could be overcome.

Intervention studies have shown that, even in optimal conditions, only a part of psychoses, including schizophrenia, can be prevented. However, at the community level, the duration of untreated psychosis can be shortened (7). This is one of the most important achievements of the early detection and intervention approach. Still, the need for comprehensive care is considerable. On the basis of his studies and long experience, Alanen (8) launched the concept of need-adapted treatment, which includes five main elements: a) flexible and individually planned and carried out therapeutic activities; b) examination and treatment dominated by a psychotherapeutic attitude; c) different therapeutic approaches should supplement, not replace each other; d) treatment should attain and maintain a continuous interactional process, and e) follow-up of the individual patient and the efficacy of the treatment. Moreover, need-adapted treatment emphasizes that the needs of an individual patient may change. The treatment system should be sensitive to these changes and try to meet the actual needs comprehensively. This also means that the need for care can extend over the so-called critical period.

The question of special early detection and intervention clinics is important. Most patients with prodromal states attend primary care and/or community mental health centres, depending on the local treatment system. This means that all teams meeting patients with mental problems should be aware of the possibility of psychosis and should try to screen and examine patients also from this point of view. Specialized clinics may meet only a (small) proportion of patients at risk of psychosis, but they have on important role to play in educating community and other teams.

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# Understanding pathophysiology is crucial in linking clinical staging to targeted therapeutics

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McGorry et al in Melbourne, and a select number of other groups around the world, have been instrumental in a paradigm change in the approach to schizophrenia over the last fifteen years or so. They have infused an illness that was seen as inexorably deteriorating with new hope, new data and new therapeutic optimism. The academia and the clinicians have responded to their idea. A quick search of PubMed shows that from 1993, when the first articles entitled "early intervention in schizophrenia" appeared, there have been at least 480 publications in the field. There were 22 in the field in the years before 1992. Mental health services around the world have reconfigured and invested in establishing early intervention teams for psychosis, and there has been an explosion in research in this area. Of course, there have been other developments over the same period that have contributed to clinical and research optimism – developments in neurobiological research, and the introduction of new therapeutic agents for example – but few others have linked the clinical and research domains so directly. McGorry et al, in their article in this issue, show they are still leading the evolution of thinking in research and clinical practice in this field.

It is worth reflecting on how what was recently inconceivable – the prevention of schizophrenia – has become conceivable, though not achievable. Currently the best we can aim for is secondary prevention – intervention in individuals who are already symptomatic and functionally impaired to reduce the likelihood of their condition worsening. In this article McGorry et al draw on general medicine to introduce the concept of clinical staging to psychosis, with the proposal for three stages: ultra-high risk (putatively prodromal), first episode and recovery. However, a critical constraint on the applicability of a clinicopathological staging model to psychosis is our limited understanding of the underlying pathophysiology. Currently we rely on purely clinical factors to predict outcomes, for example which ultra-high risk patient will develop psychosis, or which first episode patient will respond to treatment. However, this approach still lacks satisfactory sensitivity and specificity and, in most cases, independent validation. More crucially, it does not suggest targeted, stage specific interventions.

Since our criteria for separating ultra-high risk from first episode are symptomatic, our treatments for the two must be distinct if we are to call one "secondary prevention" and the other "early treatment". Since McGorry et al borrow from the rest of medicine, let's take an example from the rest of medicine to illustrate this point. Understanding the pathophysiology that leads to a heart attack has enabled clinicians to identify biomarkers for risk that can be combined to target intervention most appropriately. To prevent coronary artery disease, doctors identify patients with elevated cholesterol levels and treat them with dietary intervention or statins; or, if the patient has hypertension in addition, they are offered a beta-blocker. However, they are not immediately offered a mini-angioplasty. The point being that the treatments used in secondary prevention are targeted at processes different from that used to treat the illness. We are not there as yet in psychosis. The treatments that are provided to patients in the first episode and have been evaluated in those with prodromal signs (antipsychotic drugs, cognitive-behavioural therapy and case management) are essentially the same interventions that are given to patients with established psychosis. Moreover, we do not know which form of intervention will work for whom, or what to give those who will respond poorly to treatment. Understanding the pathophysiology of risk factors, the prodromal signs of the illness, the first episode and determinants of recovery and response to treatment is a crucial first step towards the sort of clinical staging used in general medicine.

Nevertheless, there is some scope for optimism that the pathophysiology of these stages can be determined. The application of standardized criteria for characterizing people who are likely to be in the prodromal phase of psychotic illness (1,2) has provided a means of prospectively studying the development of psychosis, while the development of early intervention services has increased contact with patients in the early phases of psychosis. This has permitted the investigation of an area of clinical equipoise – whether to initiate treatment in people with prodromal signs – and informed the development of methods for secondary prevention. At the same time, it has enabled significant advances in the understanding the neurobiology of psychosis.

Structural and functional neuroimaging studies have shown that many of the abnormalities seen in chronic psychotic disorders are not only evident at the first episode of psychosis, but also in individuals with prodromal signs (reviewed in 3, 4). These include reduced frontal, cingulate and temporal grey matter volume (5-9), altered activation in these regions

during tasks that engage executive functions and working memory (10-11), and changes in the white matter tracts that interconnect them (12). Molecular imaging and magnetic resonance spectroscopy studies in people with prodromal signs have also revealed elevated presynaptic dopamine function, and alterations in glutamate levels and serotonin receptors (13-16). Moreover, longitudinal neuroimaging studies indicate that some of the structural anomalies evident in the prodromal phase progress as individuals make the transition to psychosis (5). Progressive reductions in grey matter volume appear to continue after the first episode and may be related to long term clinical outcome (17-19).

Whilst these studies are promising steps in identifying the neurobiology that might underpin a clinical staging model, a number of requirements need to be met before research findings can find clinical utility. Firstly, predictive findings need to be replicated in independent samples. This is beginning to happen for structural anomalies, but has yet to have been done for functional changes. Secondly, specificity not just to psychosis, but also to functional outcome and stage needs to be established. Biomarkers that meet these requirements can provide clear targets for the development of novel, stage specific therapies (20).

Progress in our field has come from many directions. Till now the major developments have been the result of astute clinical advances or new medications from the pharmaceutical industry. And while we should be truly grateful that this has happened, neither of them are explicitly linked to the underlying pathophysiology of the illness. As a result, the illness of schizophrenia has been a subject of constant reconceptualization and redefinition. Therefore, if the clinical staging model could be anchored to an evolving pathophysiology, it would offer the opportunity of a new conceptualization that might outlast its earlier counterparts.

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# Real-world implementation of early intervention in psychosis: resources, funding models and evidence-based practice


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It has been repeatedly pointed out that clinical practices are often based not on evidence but on accidents in the past. For the first time in the history of psychiatry, evidence is now building up to make a rational case for early intervention for psychosis. The successful implementation of this early intervention, however, is still inevitably determined by many contextual factors unrelated to our level of knowledge. Apart from perceptions and group dynamics, as highlighted in

McGorry et al's article, the availability of resources and local funding models are among the issues shaping early psychosis service provision in the real world.

In places with low mental health resources, systematic screening and preventive intervention for ultra-high risk individuals remain difficult. Certain areas have adopted a strategy to focus service on "stage 2", or early detection and treatment of first-episode psychosis. In the Hong Kong experience, limited public funding is carefully allocated to optimizing treatment in the first 2 years of a diagnosable psychotic illness (1). Although this approach means that some stages of psychosis might not be receiving enough attention, emerging evidence on cost-effectiveness of early intervention programmes will provide a more solid rationale for further developments.

The attitudes of service providers as "early adopters", "late majority" or "laggards" may largely be determined by local health service funding models or payment methods. Studies have revealed that these models exert different effects on service utilization (2) as well as service provision (3). It is likely that, in systems closer to the fee-for-service model, there will be lower motivation for providing health education and preventive intervention, as it may be perceived to result in reduced service usage and income. On the other hand, inertia against reform or development might be expected to be strongest in systems similar to fixed salaries: such system reduces incentives for care providers to outperform (4), and might create barriers for early help-seeking (as this leads to a perceived increase in workload). In this aspect, a budget or population-based funding model may be the most fertile ground for the development of early intervention programmes, where investment in preventive approaches can be favoured compared with less efficient tertiary care.

A clinical staging model of psychosis may provide a powerful tool that transcends monetary incentives by orienting patients and providers' awareness towards interventional outcome in a well-defined population. From the research perspective, staging psychosis could be an optimal way to identify specific factors affecting outcome, while minimizing noise due to sample heterogeneity. The 0-4 stage model proposed by McGorry et al (5) can serve as a useful framework, upon which future research can be based, to progressively construct an augmented model with more specific markers and best management strategies. A positive research-practice cycle towards "best practice" in psychosis can thus be started, whereby well organized services provide the setting for optimal research, and the new emergent data are then used to inform evidence-based clinical practice guidelines for specific stages in psychotic disorders.

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# Early intervention in psychosis: concepts, evidence and perspectives


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McGorry et al have persuasively and passionately advanced the case for early intervention in psychosis. The urgency to intervene early in life is underpinned by the fact that psychosis, like most other mental disorders, tends to have an onset in adolescence and early adulthood, which happen to be highly sensitive developmental periods in the life cycle.

Though heuristic, early intervention in psychosis is handicapped by problems of clinical staging and acceptability.

Clinical staging has a continuum, ranging from the earliest possible beginning of psychosis to first episode diagnosis of psychosis and the critical first 5 years after the diagnosis. The beginning pre-dates the "prodrome", which term assumes certainty that the psychotic state will develop. We are talking of the very thin boundary when normal *begins* to transit to abnormal.

The concept of ultra-high risk has been coined in the attempt to pre-date the "prodrome". Efforts to increase the predictive value of ultra-high risk criteria have the potential to produce false negatives and in the process deny people who would otherwise benefit from early intervention the opportunity for treatment. On the other hand, less predictive ultra-high risk criteria would lead to false positives and in the process end up putting people on treatment when they do not need it, more so given the side effects and the negative impact at an early age.

Despite the evidence, there are still skeptics who argue that there is not enough evidence for the concept of early psychosis and/or that early intervention works. Nevertheless, such skeptics have a role to play in keeping the inventors of the evidence on their toes while both appealing to a wider audience and eventually influencing policy and practice. This is indeed a healthy debate.

Nearly all research on early intervention in psychosis comes from resource-rich countries, and little from developing

countries and in particular from Africa. It is true there is a gross shortage of human and financial resources in this continent (1-3). This cannot, however, be an excuse for Africa to be left out of this endeavour. This continent has a young population, with more than 50% being less than 25 years of age, and a total population which is about 12% of the global one. Thus, Africa has a claim to this endeavour. The major players in this kind of research and their respective funders should collaborate with researchers operating in Africa in designing simple community-based identification of ultra-high risk individuals and initiating interventions. This does not require highly skilled psychiatrists. The social support is still intact in most societies in Africa and affordable drugs such as haloperidol, despite their limitations, are widely available.

As happens with any new ideas, regardless of the overwhelming supportive evidence, the progression from evidence to policy and practice will be on a continuum. On this continuum will be on the one hand the few researchers producing the evidence and, on the other, the skeptics or laggards demanding for more evidence. In between will be a continually increasing number of acceptors, initially on the basis of the evidence, then on the basis of an increasing number of opinion leaders who practice the intervention, and finally on the basis of standard practice without even questioning the evidence for or against.

The challenge to the inventors is whether or not they have the tenacity to generate both new and more evidence and navigate their inventions through this continuum while at the same time constructively engaging the skeptics. The way to achieve this is through research designs that will provide focused evidence of the earliest possible time intervention can be initiated, minimizing both false positives and false negatives. This should be a collective effort that takes on board globally representative participants with diverse sociocultural and economic backgrounds. This way, it will be much easier for the results to be co-owned and therefore easily accepted and implemented. Scientific evidence alone is not always enough.

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# HIV risk behaviors among outpatients with severe mental illness in Rio de Janeiro, Brazil

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*We conducted the first study to examine rates of sexual activity, sexual risk behaviors, sexual protective behaviors, injection drug use (IDU), needle sharing, and knowledge about HIV/AIDS among outpatients with severe mental illness (SMI) in Rio de Janeiro, Brazil. Using a measure with demonstrated reliability, we found that 42% of 98 patients engaged in vaginal or anal sex within the past three months. Comorbid substance use disorder was significantly associated with sexual activity. Only 22% of sexually active patients used condoms consistently, despite having better HIV knowledge than those who were sexually abstinent. Overall, 45% of patients reported not engaging in any HIV protective behaviors. There were no reports of drug injection. Adults with SMI in Brazil are in need of efficacious HIV prevention programs and policies that can sustain these programs within mental health treatment settings.*

**Key words:** HIV, risk behaviors, prevention interventions, severe mental illness, Brazil

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Relatively little is known about HIV risk taking among individuals with severe mental illness (SMI) outside the United States. Two recent reviews of more than 50 published studies of HIV risk behaviors among people with SMI (1,2) found only ten from non-US countries, and nearly all were conducted in developed countries. US studies reported higher rates of sexual risk behavior compared to international studies, particularly with respect to sex trade and injection drug use (IDU) (2). Across all of these studies, substantial rates of recent sexual activity and sexual risk behavior were reported: sexual activity in the past 3 to 12 months by 32% to 74% of patients; multiple sexual partners in the past 3 to 12 months by 13% to 69%; regular condom use in the past 3 to 12 months by 8% to 49%; sex trade in the past year by 2% to 42%; IDU ever by 12% to 45%; and needle sharing ever by 15% to 73% of injection drug users.

These risks were present despite relatively high levels of HIV/AIDS knowledge. Although measures used in prior studies of psychiatric populations varied, the average HIV knowledge score (i.e., percent correct responses) ranged from 63% to 80% (3-6). While not sufficient alone to change behavior, knowledge is a necessary component to effect risk behavior reduction (7).

In Brazil, sexual risk behavior studies about psychiatric patients are limited. In one study conducted in Minas Gerais, 68.2% of the sexually active sample reported not using condoms, 20.1% reported a risky partner, and 2.6% reported sex in exchange for alcohol, drugs or shelter (8). Another study in Rio de Janeiro found considerable sexual risk-taking in the previous year: 63% were sexually active; of those, 72% did not use condoms regularly and 49% never used condoms (9). However, the reliability of the measures used to obtain these data was not tested, and samples did not include only people with SMI. To date, no IDU or HIV knowledge rates have been reported among Brazilian adults with SMI.

This paper is the first report of HIV-related behaviors by people with SMI in Brazil obtained using a sexual risk behavior assessment that has demonstrated reliability with psychiatric patients (10-12). We report the degree of knowledge about HIV/AIDS, prevalence of IDU and needle sharing, rates of sexual activity, sexual risk-taking and protective behaviors, as well as reasons for sexual abstinence and for not using condoms in a sample of outpatients with SMI in Rio de Janeiro.

## METHODS

### Setting and participants

Participants were adults with SMI attending the outpatient psychiatric clinic and the day-hospital of the Psychiatric Institute of the Federal University of Rio de Janeiro. In this setting, patients whose primary treatment need is represented by substance use disorder are referred to dual diagnosis clinics elsewhere. As part of standard clinical care, informal sexual health drop-in group education sessions are offered every other week to all patients interested in participating.

All study procedures were approved by institutional review boards of both the New York State Psychiatric Institute and the Psychiatric Institute of the Federal University of Rio de Janeiro, as well as the National Ethics Commission on

Research of the National Council of Health, Brazilian Ministry of Health. Patients were either self-referred or referred by clinic providers. Eligible, consenting patients participated in a baseline interview before participating in a pilot risk-reduction intervention (13). This paper reports findings from baseline interviews.

Patients were eligible if they were 18 years of age or older; diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, major depression with psychotic features, or psychosis not otherwise specified; and capable of giving written informed consent. Patients were not eligible if they had acute psychosis or suicidality at the time of the screening interview; developmental disability as a primary diagnosis; or a substance-induced psychotic disorder. Inclusion criteria did not require participants to be sexually active in the last three months.

Both a licensed mental health professional who was a member of the patient's clinical treatment team and a research team psychiatrist evaluated patients' capacity to consent to participation in the study. Patients who declined to participate in the intervention pilot study or who met any of the exclusion criteria were informed about the ongoing sexual health drop-in groups that are part of standard clinical care.

Of the 221 patients (110 females/111 males) screened, 139 (63%) with interest and capacity to participate gave written informed consent. Of these, 36 (26% of those who consented) did not meet inclusion criteria. Reports of four participants were excluded due to responses that were rated by interviewers as unreliable. The remaining 98 patients comprised the study sample. Participation in the study was not compensated, but transportation vouchers and refreshments were offered to participants.

### Assessment procedures

All assessments were conducted in face-to-face interviews between October 2004 and August 2005. Instruments that had not been previously used in Brazil were translated and tailored to enhance cultural specificity for Brazilian SMI men and women after a year of formative ethnographic work (13). Patients completed all measures in approximately two and a half hours, on average.

Psychiatric diagnosis was obtained by research team psychiatrists using the Mini International Neuropsychiatric Interview – PLUS (MINI PLUS), a structured psychiatric assessment developed and validated for DSM-IV and ICD-10 diagnosis with both US and Brazilian patients (14,15).

Information on sexual risk behaviors in the past three months was obtained by research interviewers (clinical psychologists) using the Sexual Risk Behavior Assessment Schedule (SERBAS), adapted to encompass risk behaviors and contexts specific to the patient population in Brazil. The Brazilian SERBAS (SERBAS-B) is a semi-structured interview that elicits detailed information regarding sexual practices and related alcohol and other drug use in the past three months. Data collected include the number, gender, and type (casual, steady, new) of sexual partners; the types of sexual acts performed at each encounter; whether sexual acts were protected by condoms; whether alcohol or other drugs were used during sexual occasions; whether sex was bought, sold or exchanged for something (e.g., drugs, shelter); and a participant's knowledge of his/her partner's HIV testing history and status. The interview underwent rigorous reliability testing and showed reasonable to excellent test re-test reliability (11), comparable to findings in US samples (10,12). For exploratory purposes, data also were collected on HIV protective behaviors in the past three months, to determine whether participants had engaged in behaviors deliberately as a means of reducing the risk of contracting or transmitting HIV. Protective behaviors included reducing the number of sex occasions, reducing the number of sex partners, changing specific sexual practices, and using condoms more frequently.

Participants were asked how often in the past three months they injected drugs into their veins or under their skin, with answers scored on a 5-point scale ranging from never to daily. If any patient reported injecting behavior, information was to be collected on the use of injection implements (e.g., needles, syringes, wash water, cottons) after someone else had used them, and on any cleaning of implements prior to using them to inject themselves.

Knowledge about HIV transmission and prevention was assessed using the Brief HIV Knowledge Questionnaire (Brief HIV-KQ), an 18-item true/false scale (16), with higher scores indicating greater HIV-related knowledge. This instrument was translated from English into Portuguese, and back-translation from Portuguese to English was performed to check for errors and fidelity to the original English version. This process resulted in the elimination of one item due to confusing double-negative phrasing in Portuguese. Scores in the current study therefore range from 0 to 17.

After clarification of what an HIV test is, participants were asked if they had taken the HIV test in the past 3 months. A negative answer prompted inquiring about the last time the participant had been tested for HIV. "Not sure/don't know" responses prompted clarification. Known positive or negative test results were elicited, as were decisions not to return for testing results.

Participants were asked whether, within the last year, they had participated in any type of program specifically intended to help them decrease sexual risks or increase safer sex. Although the standard-care drop-in groups were focused on sexuality and not, specifically, on HIV prevention or sexual risk behavior, this question did not expressly include or exclude the ongoing sexual health drop-in groups offered in the treatment programs from which the sample was selected.

### Data analysis

Differences in being sexually active (versus not sexually

active) by key demographic and clinical characteristics were tested using Fisher's exact test for categorical data and t-tests for continuous data. Because engaging in sexual activity within the prior three months was not an eligibility criterion for study participation, some sexual risk and protective behaviors were reported by proportions of the sample that could not be reliably subjected to statistical tests of significance due to small cell sizes. We therefore present descriptive data on HIV risk and protective behaviors in the previous three months, as well as reasons given for not being sexually active and for not using condoms.

## RESULTS

The total sample (n=98) comprised 49.0% men and 51.0% women. Self-described racial/ethnic categories were 45.9% white, 37.8% multiracial, and 16.3% black. The mean age of participants was 41.8±11.1 years (range 21-70). Most of the sample (72.5%) was single; 13.3% reported being married/in a long-term relationship, and 14.3% were separated, divorced or widowed. Half of the participants (50.0%) had a diagnosis of schizophrenia, 27.6% of bipolar disorder, 10.2% of major depressive disorder with psychotic features, 4.1% of schizoaffective disorder, and 8.2% of psychosis not otherwise specified. A current comorbid substance use disorder was present in 11.2% of the sample. Of those with a substance use disorder, six reported abuse/dependence of marijuana (54.4%), two of alcohol (18.2%), two of benzodiazepines (18.2%), and one of cocaine (9%). About two-fifths of the sample (38.8%) had completed primary school, 40.8% had completed secondary school, 9.2% had completed college, while 11.2% had not completed or attended primary school.

The mean score for HIV knowledge for the entire sample was 10.4±3.3 out of 17 (range 1-16), corresponding to 61.2% correct responses.

Of the 98 study participants, 53 (54.1%) reported having been tested ever. Of those tested, one (1.9%) reported a positive HIV status and one (1.9%) reported not receiving the test result; the remaining 51 (96.2%) reported negative HIV test results. Twenty-two (41.5%) of the tested patients reported that their HIV test had been done in the past year.

Nineteen of 98 participants (19.4%) reported having participated in a program specifically provided to increase sexual safety or reduce unsafe sexual activity in the previous year. No participant reported IDU in the past 3 months.

A total of 41.8% of the sample reported engaging in vaginal or anal sex within the past three months. Table 1 presents differences in sexual activity versus inactivity by demographic variables. Significant differences included the following: those who were sexually active were younger (t=2.43, df=96, $p<0.01$), were more likely to be married or in a long-term relationship ($X^2=8.01$, df=2, $p<0.05$), had a higher prevalence of comorbid substance use disorder ($X^2=12.03$, df=1, $p<0.01$), had a higher mean HIV knowledge score (t=-2.92,

**Table 1** Demographic and clinical differences between sexually active and inactive SMI patients (n=98)

| | Inactive (n=57) | Active (n=41) | $\chi^2$ or t | p |
|---|---|---|---|---|
| Gender (% male) | 45.6 | 53.7 | 0.62 | 0.54 |
| Age (years, mean ± SD) | 44.0±11.1 | 38.7±10.4 | 2.43 | 0.02 |
| Race/ethnicity (%) | | | | |
| Black | 14.0 | 19.5 | 1.43 | 0.50 |
| White | 50.9 | 39.0 | | |
| Multi-racial | 35.1 | 41.5 | | |
| Marital status (%) | | | | |
| Single | 77.2 | 65.9 | 8.01 | 0.02 |
| Married/long-term relationship | 5.3 | 24.4 | | |
| Separated/divorced/widowed | 17.5 | 9.8 | | |
| Diagnosis (%) | | | | |
| Schizophrenia | 54.4 | 43.9 | 3.19 | 0.38 |
| Bipolar disorder | 21.1 | 36.6 | | |
| Major depressive disorder with psychotic features | 12.3 | 7.3 | | |
| Other (schizoaffective disorder and psychosis not otherwise specified) | 12.3 | 12.2 | | |
| Comorbid substance use disorder (%) | 1.8 | 24.4 | 12.03 | 0.001 |
| Education completed (%) | | | | |
| Grade school | 36.8 | 41.5 | 0.29 | 0.88 |
| High school and beyond | 50.9 | 48.8 | | |
| Did not attend/complete grade school | 12.3 | 9.8 | | |
| HIV-relevant history | | | | |
| HIV knowledge score (mean ± SD) | 9.6± 3.5 | 11.5±2.7 | -2.92 | 0.001 |
| HIV/AIDS prevention programs experience (past year, %) | 19.3 | 19.5 | 0.01 | 1.00 |
| HIV test (lifetime, %) | 40.4 | 73.2 | 10.34 | 0.001 |

SMI – severe mental illness

df=96, p<0.01), and were more likely to have received HIV testing ($X^2$=10.34, df=1, p<0.01). Same-gender sexual partners were reported by 10.4% of men and 2.0% of women. One sexually active participant reported being HIV positive. There were no differences in sexual activity by gender or diagnosis.

Fifty-two of 57 participants who were sexually inactive in the past three months provided one or more reasons why they did not engage in sexual activity. Almost half of the men (45.8%) and women (46.4%) reported not having a current partner as the most common reason for sexual inactivity. Lack of interest in sexual activity was cited by 16.7% of men and 28.6% of women. Among men, other common reasons given were mental illness/medication side effects (20.8%), and concern about being (re)infected with HIV by partner (16.7%). Among women, other common reasons given were concern about being (re)infected by partners (10.7%), and fear or anxiety related to sexual activity (10.7%).

Table 2 shows prevalence of HIV risk and HIV protective behaviors among those who were sexually active (n=41) within the past three months. Almost half (43.9%) of those who engaged in vaginal or anal sex reported no condom use in the prior three months and 34.2% reported inconsistent condom use; only nine participants (22.0%) reported using condoms on every sex occasion. Over half (53.7%) reported having partners whose HIV status was unknown, and 26.8% reported having more than one partner (partner range 2-12). Almost two-fifths (39.0%) reported using alcohol or drugs prior to sexual activity, and 19.5% (all men) reported sex exchange, with the majority of this activity involving purchasing sex. Of those who were sexually active, the range of risk behaviors was 0-6, with 56.1% engaging in three or more. Only 4.9% reported no risk behaviors.

Sexually active participants who did not use condoms (n=32) were asked to provide reasons for not doing so. Half (50.0%) of the 16 male participants cited trust in their partner(s). Other common reasons among men were perception of self as not at risk (18.8%), participant's own preference not to use condoms (18.8%), difficulty sustaining an erection when wearing a condom (12.5%), and other sexual dysfunction (12.5%). Among the 16 female participants, 60.5% reported not using a condom due to their partners' preference. Other common reasons among women were: condoms unavailable at the time of intercourse (31.3%), trust in their partner(s) (25.0%), not being in the habit of using condoms (18.8%), and participant's own preference not to use condoms (18.8%).

When asked to describe all methods they had used expressly to avoid HIV/AIDS in the past three months, 22.0% of sexually active patients said they used condoms for every sexual occasion, 25.0% reported using more condoms, 20.0% reported having fewer partners, and 12.5% reported having fewer sex occasions as practices to avoid contracting HIV. Overall, the range of protective behaviors reported was 0-3, with 25.0% engaging in two or more protective behaviors; 42.5% reported not engaging in HIV-protective behaviors.

**Table 2** Prevalence of HIV sexual risk and protective behaviors among SMI patients within the past three months (n=41)

| | |
|---|---|
| Any risk behavior (%) | 95.1 |
| <100% condom use (%) | 34.2 |
| No condom use (%) | 43.9 |
| High risk partners - unknown HIV diagnosis (%) | 57.5 |
| High risk partners - HIV+ partner (%) | 7.3 |
| Multiple partners (%) | 26.8 |
| Any sex exchange/trade (%) | 19.5 |
| Any drug during sex (%) | 39.0 |
| Any IDU history (%) | 0 |
| Any protective behavior (%) | 53.7 |
| Always use condoms (%) | 22.0 |
| Reduced sex occasions (%) | 12.5 |
| Reduced number of sexual partners (%) | 20.0 |
| Changed specific sexual practices (%) | 2.5 |
| Used more condoms (%) | 25.0 |
| Other (%) | 7.5 |
| No protective behaviors (%) | 42.5 |

SMI – severe mental illness; IDU – injection drug use

## DISCUSSION

We have presented findings from the first study to examine HIV risk behaviors among Brazilian SMI patients using a risk-assessment instrument with proven reliability among SMI populations. We found that almost 42% of SMI patients were sexually active in the past three months, a rate comparable to the weighted mean for sexual activity in the past three months across all prior studies of SMI patients (2). Almost all of those who were sexually active engaged in HIV-related sexual risk behaviors, and over half of them engaged in three or more such behaviors.

Though, from an HIV prevention perspective, sexual inactivity for the prior three months among nearly 60% of patients may seem reassuring, those patients who are abstinent now may be active in the future. In this study, the most common reason given by participants for sexual inactivity was lack of a current partner, cited by two-fifths of men and women; only one-fifth reported no interest in sex. The absence of a regular partner may lead to future sexual activity with poorly known or risky partners when opportunities present themselves (17). As a form of public health inoculation, efficacious prevention interventions should be offered to all interested patients, regardless of their current sexual activity. It is also possible that, from a quality of life perspective, sexual inactivity among psychiatric patients living in the community is a problem that needs to be addressed. Understanding more about the context and reasons why individuals with SMI are sexually inactive is an important goal of future research.

Compared to sexually inactive subjects, those who reported sexual activity were younger, were more likely to be in a long-term relationship, to have a comorbid substance use disorder and to have had an HIV antibody test, and had a

higher mean HIV knowledge score. As with SMI samples elsewhere (2) and other populations (7), these findings suggest that patients most at risk for HIV are aware of the problem/disease. HIV testing in the prior year was reported by 42% of participants, comparable to the rate of voluntary testing reported in the US (18), but the average HIV knowledge score in our Brazil sample was lower than the range found in prior studies of psychiatric populations (3-6), despite the fact that one in five of our subjects had participated in some type of HIV prevention program and all of them had access to ongoing sexual health drop-in groups. Patients who had attended prior HIV prevention programs did not have better HIV knowledge than those who had not received these services. Besides addressing sexual risk reduction skills, interventions developed for Brazilian SMI people must increase basic knowledge of HIV risk and transmission and attend to misperceptions about risk held by participants.

Almost 28% of our sample reported being in a current or prior marriage or long-term relationship. Although we did not ascertain to what extent the expectation of monogamy was part of these relationships, half of the sexually active men and a quarter of the sexually active women cited trust in their partners as the reason for not using condoms. As Gordon et al (19) found among SMI in the US, it may be that stable partnerships are perceived as "safe" and, as such, negotiation about HIV or condoms may not be considered necessary. Future research should examine closely these stable relationships, and, if they are unsafe, HIV interventions will need to address the difficult task of introducing condoms in a long-term or significant relationship. This task may be complicated by economic dependence (19,20) and the belief that people with SMI are not in the position to choose or negotiate with their partners (21).

Despite the low rate of substance use disorder among this sample, almost 40% of those sexually active reported using substances during sexual intercourse. Substance use during sexual activity has been associated with lower condom use rates among SMI patients elsewhere (22). Moreover, substance use in other populations (e.g., men who have sex with men, injection drug users) has been shown to increase sexual risk-taking, in part, by attenuating or counteracting anxiety around sexual activity (23,24). Individuals with SMI may use substances to some extent as a way to minimize stigma-related social or sexual anxiety. In addition to reducing risk behaviors and increasing skills associated with condom use such as assertiveness and negotiation (6,25-29), interventions for SMI in Brazil must also target the use of alcohol or drugs during sex.

It is important to highlight some key differences compared with prior SMI studies that may help to guide prevention intervention development, adaptation, and implementation in Brazil and in other countries where psychiatric patients are particularly vulnerable. While comparison with other studies of psychiatric patients is difficult, due to different instrumentation and assessment time periods, sexually active patients in this Brazilian sample had a lower rate of condom use compared to samples enrolled in previous studies (2). We did not collect data on condom acceptability or availability for this population, but patients did cite relationship (e.g., trust in partner) and sexual performance (e.g., difficulty sustaining an erection) aspects of condom use that deserve attention in future studies. Still, the most common (60%) reason among sexually active women for not using a condom was their partners' preference, a reason that was cited by none of the men. This finding is consistent with patterns seen among women in a variety of populations in the AIDS epidemic, and is an impetus for more widespread development and uptake of female controlled methods, such as the female condom and microbicides. In fact, Brazil's epidemic has been characterized as "feminizing, heterosexualizing, and pauperizing" (30). Distribution at a reasonable cost of female condoms and development of safe and effective microbicides should be viewed as priorities in the control of HIV in Brazil, including among those with SMI.

In this Brazilian SMI sample, about one-third of the sexually active men reported purchasing sex, a proportion much higher than previously reported in non-homeless or non-indigent persons with SMI (2), and none of the sexually active women reported engaging in sex exchange, in contrast with prior studies that found that women with SMI may engage in "survival sex" (2,20), exchanging sex for money, food, shelter, or drugs. Adults in treatment for SMI in Brazil tend to live with their families, which may protect them from having to give sex for food or shelter. Further, substance use during sex was common, but substance abuse/dependence, which may fuel sex trading, was not. Research that examines the context in which those with SMI purchase sex or exchange sex is important to undertake, as is examining those behaviors' relationship to condom use, in order to identify the salient social and economic factors (e.g., poverty, relational power imbalances) driving risk behaviors in this population and to design appropriate interventions to address those factors.

Unlike in previous studies, we examined whether sexually active SMI patients were deliberately taking measures to reduce HIV transmission regardless of participation in any type of prevention program: 58% of sexually active patients had taken at least one protective measure, most commonly using more condoms and having fewer partners. Nevertheless, only 5% of these patients reported no HIV-related risk behaviors, and 56% reported three or more risk behaviors. Understanding what motivates HIV-protective behaviors and changes and how those motivations can be incorporated into efficacious prevention interventions will be an important next step for researchers to take.

The absence of IDU is a major difference when compared to the weighted lifetime rate across all prior SMI studies of nearly 22% and the weighted past-year rates of 4% (2). This may simply reflect the geographic distribution of IDU, which is clearly more prevalent in some countries than in others and in some regions of Brazil, though less so in Rio de Janeiro, than elsewhere (31). Further, our sample was drawn

from clinical settings where the primary disorder being treated was not substance use disorder. IDU is more prevalent and frequent among those with primary substance use disorder than among SMI patients whose substance use is not a determinant of the presenting psychiatric problem (32). Moreover, substances preferred by those with comorbid substance use disorder in this sample (marijuana, alcohol, benzodiazepine, and cocaine) do not require being injected to achieve potency. Prevention interventions with demonstrated efficacy among psychiatric patients have focused on sexual behavior, including that which occurs while drinking or using drugs, rather than on IDU (6,25-29). Such focus seems appropriate for intervention with samples like ours, although harm reduction strategies for IDU may be an important component of interventions for SMI patients with even intermittent injection behaviors and should not be presumed to be irrelevant even if IDU is not a current behavior.

In our study, except for psychiatric diagnoses, all data were based on self-report and are therefore subject to response bias (33). With the exception of protective behaviors, we used dependent measures with documented test-retest reliability (11), thereby minimizing such bias. We examined vaginal and anal sex occasions, possibly missing opportunities to understand whether participants may have engaged in oral sex as a "safer" alternative. Also, the use of a convenience sample raises the possibility of selection bias: for example, our sample was older (mean age 42 years) relative to those in prior SMI risk behavior studies (2), possibly leading us to underestimate sexual activity and risk behavior. The results of the current study may not generalize to adults with SMI who are in treatment but are not inclined to participate in research, those who do not receive psychiatric treatment, or those whose personal, clinical, socioeconomic, or cultural situations differ from those of our sample. Moreover, the low rate of substance use disorders in this sample limits the generalizability to SMI with comorbid substance disorders. Finally, cross-sectional data were obtained; longitudinal studies with larger samples are needed to elucidate the direction and temporal nature of the relationships between HIV risk behaviors and patients' characteristics.

In Brazil, where sexuality is considered a human right, helping patients develop relationship skills and overcome mental illness-related obstacles to developing intimate connections is seen as a desirable goal by many mental health care providers and their patients. However, the unstructured, informal drop-in sexual health group is not the standard of care throughout Brazil, and policy there, as elsewhere, has been slow to address sexuality in the SMI population with anything but proscription (21).

HIV prevention interventions for the SMI population must be carefully tailored to their specific needs. An HIV prevention intervention is now being tested in a randomized controlled trial taking place in municipal mental health centers throughout Rio de Janeiro. Thus, Brazil is poised to continue its legacy as a world leader in fighting AIDS (30,34) by reaching the vulnerable population of people with SMI. Brazil's programmatic and policy decisions can aid in the development of integrated programs in other low- and middle-income countries, and inform similar programs and policies in developed countries as well.

We found similarities (i.e., similar rates of sexual activity and risk) and differences (i.e., no IDU and sex exchange primarily consisting of purchasing sex) in our Rio de Janeiro sample compared to other regions of the world. By looking at the differences between countries, we may learn more about the impact of environmental factors on risky and protective behaviors among adults with SMI, and target interventions to address them effectively.

## APPENDIX

The team members of PRISSMA 2002-2006 (Projeto Interdisciplinar em Sexualidade, Saúde Mental e AIDS – Interdisciplinary Project in Sexuality, Mental Health and AIDS) are Denise Feijó, Tatiana Dutra, Carlos Linhares, Alfredo Gonzalez, André Nunes, Fernanda Gomes, Abmael de Sousa Alves, Alexander Ramalho, Débora Salles, Denise Corrêa, Erínia Belchior, Márcia Silviano, Maria Tavares, and Vandré Matias Vidal.


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# Sex difference in age of onset of schizophrenia: findings from a community-based study in India

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*This study examined the sex difference in age of onset of schizophrenia in a community sample. Community-level health workers identified patients with symptoms of schizophrenia living in the community in a defined geographical area in South India. Two hundred and nine of them were diagnosed as having schizophrenia according to ICD-10 criteria by a team of psychiatrists. The age of onset of schizophrenia was assessed using the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS). The mean age of onset of schizophrenia did not significantly differ between males (29.2±8.8 years) and females (30.8±11.4 years) (t = 1.12; p = 0.27). Among those with an age of onset ≤33 years, females had a significantly earlier onset; among those with an age of onset >33 years, females had a significantly later onset. The results from this community-based study confirm the previous findings in hospital-based patients in Asia. There is a need to revise the description of schizophrenia in the classificatory systems, keeping in view the regional variations in the age of onset of the disorder.*

**Key words:** Schizophrenia, age of onset, sex

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A sex difference in the age of onset of schizophrenia has been reported since the time dementia praecox was described by Kraepelin (1). A later age of onset in females has been reported in several recent studies (2,3). Studies have also observed that females with schizophrenia have an older age at first admission (4,5). Overall, these studies suggested a difference of 3-5 years between the sexes for age of onset of the disorder. The ICD-10 (6) and the DSM-IV-TR (7) also note that females have a later age of onset of schizophrenia. This difference is proposed to be due to both males having an earlier and pronounced peak incidence in their early 20s and females having a second, later peak incidence in their late 40s (2).

However, some studies from Asia and Africa do not seem to support this finding. The International Pilot Study of Schizophrenia (IPSS, 8), the Madras Longitudinal study (9), and three studies from the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore (10-12) found no difference in age of onset of the disorder between the sexes. More recently, a study from Pakistan (13) also did not find a sex difference in the age of onset of schizophrenia. Actually, in one of the above studies (11), there was a female preponderance among patients with the earliest onset. A relatively greater loss of male infants due to poor perinatal care, which eliminated a proportion of earliest onset male schizophrenics, was hypothesized as a possible explanation. Indeed, a comparison of patients from regions with high and low infant mortality rate showed that there was a reversed gender effect on age of onset of schizophrenia in the former but not in the latter region (12).

One limitation common to the above reports was that all of them included patients who sought help. In a country like India, with a huge population/psychiatrist ratio (14), a large proportion of patients with schizophrenia live without treatment in the community. Treatment-seeking patients may not be representative of all schizophrenia patients. This study was conducted to explore whether the finding of a lack of sex difference in age of onset of the disorder could be replicated in a community sample consisting of both treated and untreated schizophrenia patients.

## METHODS

### Subjects

The sample for this study included patients with schizophrenia recruited for the Community Intervention in Psychotic Disorders (CoInPsyD) project in Thirthahalli (an administrative block in South India with a population of 143,000). The project aims to identify all patients with schizophrenia living in this rural community and treat them. Fifty-four rural health workers were trained in identifying patients with severe mental disorders in the community by a team of senior consultants from the NIMHANS. This included didactic lectures on symptoms and course of schizophrenia, video clippings of patients with schizophrenia, and question-answer sessions. These were done on three different occasions separated by about a month each. At the end of the training, the health workers were shown video interviews of different psychiatric patients and were asked to identify those with schizophrenia: they were able to identify them accurately.

Two trained social workers interviewed the Thirthahalli

health workers about the presence of persons with symptoms suggesting psychosis in each family (a total of 29,432 families for the entire community). All patients thus identified were clinically interviewed by a research psychiatrist, and diagnoses were assigned using the ICD-10-Diagnostic Criteria for Research (ICD-10-DCR, 6). The diagnosis of schizophrenia was confirmed by another psychiatrist after an independent clinical interview.

A total of 209 persons were diagnosed as having schizophrenia. Of these, five could not give reliable information about age of onset of the disorder. The diagnosis of two patients changed (one to bipolar disorder and the other to organic psychosis) during follow-up. The final sample thus consisted of 202 subjects. Of these, 103 were males and 99 were females. One hundred and fourteen (56.4%) were receiving treatment at the time of evaluation; the rest were living without any treatment.

The health workers reported about the presence, in the community, of 20 other persons with features suggesting schizophrenia. These could not be interviewed because of several reasons, including refusal to give consent or being severely ill with no caretakers to give any information.

### Assessments

Information concerning the age of onset of the disorder was collected by the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS, 15), used by a research psychiatrist. Subjects, family members who were in continuous contact with them and the health workers were interviewed and the age of onset of the first psychotic episode was determined. Two social workers collected the sociodemographic details of the subjects, including lifetime use of alcohol and illicit substances. This included a question on the age of onset of schizophrenia. The age of onset assessed using the IRAOS by the psychiatrist had a high degree of interrater reliability with the age of onset as recorded by the social worker (intraclass correlation coefficient: 0.86).

The study obtained ethical clearance from the Institute's Ethics Committee and all subjects were recruited after obtaining written informant consent.

### Statistical analysis

Independent-sample t-test and Kaplan-Meier survival analysis were used to analyze the difference between males and females in age of onset of schizophrenia. The Statistical Package for Social Sciences version 10.0.1 was used for the analysis.

## RESULTS

Table 1 shows the sociodemographic and clinical features of males and females. The mean age of onset of schizophrenia was 29.2±8.8 years for males and 30.8±11.4 years for females (t=1.12; p=0.27). A cut-off age of onset at 33 years was taken to classify patients as having earlier or later age of onset of the disorder. Figure 1 shows the survival analysis using Kaplan-Meier survival curve for both groups: in the earlier age-of-onset group, females had a significantly lower age of onset of the disorder; in the later age-of-onset group, they had a significantly higher age of onset.

Figure 2 shows the number of males and females who had their onset at different ages. Females had two peaks: the first, higher peak in the 20-25 years range and another in the 35-40 years range. Males had a steady rise through the early ages to a peak at 30-35 years; this was followed by a steep decline through the older age-range.

The results were not different among those with illness duration less than 10 years: 32.1±8.8 years for males (n=41) and 33.1±12.5 years for females (n=51) (t=0.45; p=0.66).

## DISCUSSION

This study shows that in India there is no significant difference between the sexes in the age of onset of schizophre-

**Table 1** Sociodemographic and clinical features of males and females

| Variables | Males (n=103) | Females (n=99) | t/chi-square | p |
|---|---|---|---|---|
| Current age (years, mean±SD) | 41.4±9.7 | 41.6±11.9 | 0.1 | 0.92 |
| Age of onset of schizophrenia (years, mean±SD) | | | | |
| Total sample | 29.2±8.8 | 30.8±11.4 | 1.12 | 0.27 |
| Age of onset < 33 years | 24.8±5.8 | 22.9±4.9 | 2.01 | 0.046 |
| Age of onset ≥33 years | 39.5±5.2 | 43.0±6.9 | 2.35 | 0.022 |
| Duration of illness (years, mean ±SD) | 12.7±6.9 | 10.8±9.3 | 1.07 | 0.29 |
| Socio-economic status (%) | | | | |
| Lower | 42.4 | 50.6 | | |
| Middle | 33.3 | 34.1 | 1.42 | 0.496 |
| Upper | 24.2 | 15.3 | | |
| Education (years, mean±SD) | 6.8±4.7 | 6.4±4.8 | 0.43 | 0.664 |
| Alcohol abuse/dependence (%) | 31.2 | 2.1 | 30.154 | <0.001 |

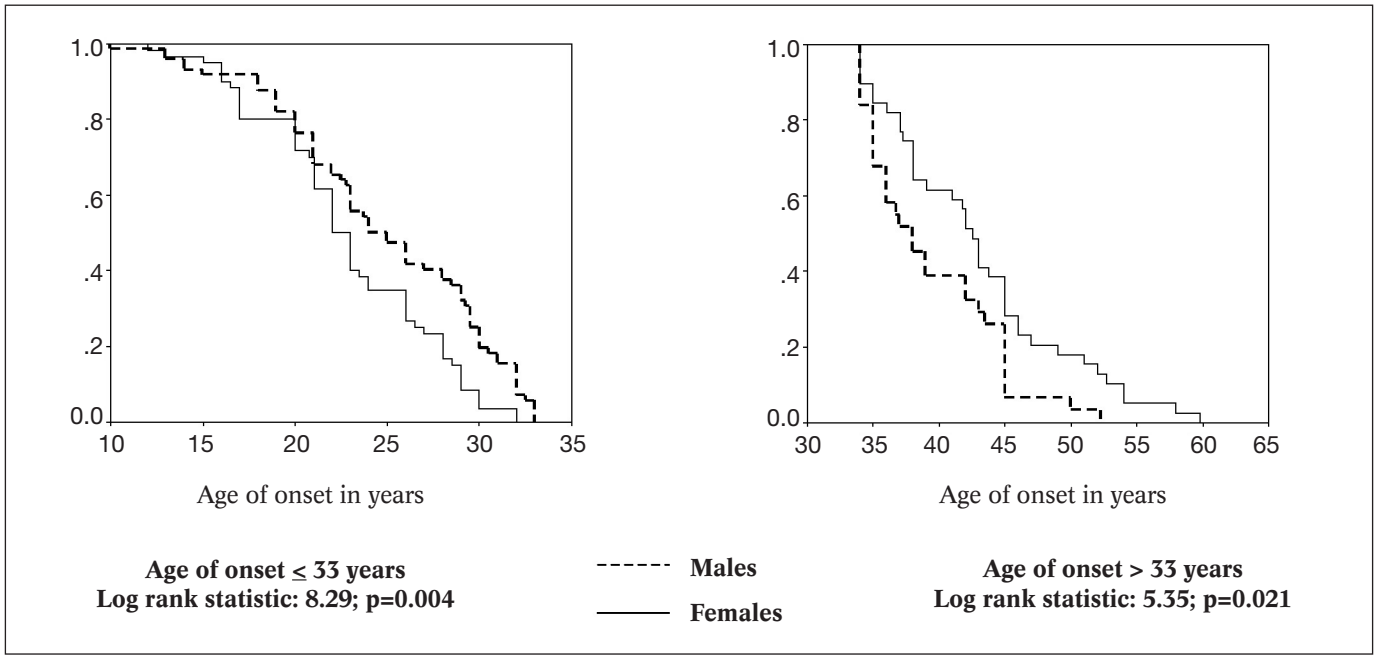


**Figure 1** Kaplan-Meier survival curves for age of onset of schizophrenia in males and females


**Figure 2** Distribution of age of onset of schizophrenia in males and females

nia. Among early-onset patients, females have a significantly earlier age of onset than males, and among late-onset patients, they have a later age of onset.

The important merit of this study is that it included all patients from a defined geographical area in a rural setting. The sample included both treated and untreated patients with schizophrenia living in the community. We found that about 39% of the patients were living untreated. Hospital-based studies would have missed these patients. Though this study was not aimed to assess the prevalence of schizophrenia in the community, the point prevalence, as can be made out, is 1.6 per thousand (95% CI: 1.3-1.8 per thousand). This is comparable to the prevalence reported from other areas in India (16) and other South Asian countries like Sri Lanka (17).

We identified patients who were either currently symptomatic (on or off treatment) or in remission while being on antipsychotic medications; we might have missed patients who had sustained remission of their schizophrenic episode despite being off treatment currently. We may have also missed a few patients as we conducted a "key informant" rather than a door-to-door survey. However, the number of such missing cases is likely to be low. The health workers visit the families once every month; they are thus quite knowledgeable about the families under their care and they would not have missed patients with symptoms of schizophrenia or receiving treatment for the same.

The diagnosis of schizophrenia was made by two psychiatrists after independent interviews and remained stable at six-month follow-up in the 202 subjects included in the analysis. There were only two subjects who had a duration of psychosis of less than 6 months – the sample was not "contaminated" by inclusion of acute psychosis patients.

A psychiatrist trained in administering the IRAOS assessed the age of onset of the disorder. There was a high degree of interrater reliability between his findings and the assessment by an independent interviewer. The age of onset recorded in this community sample is comparable with other hospital studies from India (10-12).

The duration of psychosis in this sample ranged from 4 months to 46 years. Eighty-one (50.3%) of the subjects had a duration of illness of ten years or more. To rule out a possible difficulty in recall in those with a long duration of psychosis, we compared the age of onset of males and females where the duration of psychosis was less than 10 years: this did not alter the findings.

Our results show that, similar to the literature from West-

ern countries (2), women have an earlier, higher peak in age of onset in the early twenties and a later, lower peak in their late thirties. However, unlike Western countries, men had a fairly later peak in age of onset in the early thirties, followed by a steep decline through the older age ranges. It may be reasoned that this is because of lesser number of men with very early age of onset in our sample.

Our sample had 80% power to detect a mean difference of 3.9 years, which is the reported figure in the similar studies from the West (2). The difference in mean age of onset for the whole sample was 1.6 years, and this difference was not statistically significant. One might argue that our study did not have adequate power to detect this difference. Though larger samples could detect this difference, the magnitude of the difference is likely to be substantially lower than what literature suggests.

In our previous studies on this issue, we have argued that poor perinatal care in India might result in preferential attrition of birth-injured male children, who, in the Western samples, would have contributed to age of onset being lower among males (12). This explanation may be true of the current sample too. An alternative explanation can be sought in the present study. None of the patients had used illegal substances anytime in their lives. It is known that abuse of illicit substances is associated with earlier age at onset (18-20). Greater proportion of male patients abuse illicit substances than female patients (21,22). This might contribute to earlier age at onset of schizophrenia in males in Western countries. Absence of such abuse also may contribute to the lack of sex differences in our sample. A lower rate of substance abuse has been suggested to explain the near-equal sex ratio in the incidence of schizophrenia in the developing countries (23). A sex ratio of 1:1 in our sample perhaps reflects a similar trend.

This work was done in a rural South Indian setting and the results may thus be generalized to similar populations. However, our earlier reports, which showed similar results, were from a mixed rural-urban population from a tertiary center, which draws patients from all over India. Taken together, these consistent findings suggest that the epidemiology of schizophrenia is different in India from Western countries, at least with respect to age of onset of the disorder: there seems to be a relative lack of earliest onset male schizophrenia patients in our population. The note in the diagnostic systems about sex differences in age of onset of schizophrenia cannot thus be generalized.


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# The mental health clinic: a new model

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*The role of psychiatrists into public mental health clinics has been hampered by a perceived restriction of the psychiatrist's role to prescribing and signing forms, limiting opportunities to engage in the kind of integrated care that attracted many physicians to this specialty. We propose a revision of the current model in a direction that maximizes the expertise of this specialist as well as other clinicians in the health care team. The basic unit would consist of a psychiatrist (with adequate background both in psychopharmacology and psychotherapy), an internist and four clinical psychotherapists, who may provide evidence-based treatment after the initial evaluation of the psychiatrist. Its functioning would emphasize repeated assessments, sequential combination of treatments, and close coordination of team members. Re-invigorating the role of the psychiatrist in the context of a team in which role assignments are clear could result in better outcomes and enhanced recruitment of psychiatrists into the public sector.*

**Key words:** Mental health clinic, role of psychiatrists, sequential treatment, integrated care

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In contrast to the decades-long tradition of a biopsychosocial model, many mental health clinics have adopted a model that promotes a split between biological and psychosocial treatments. Following a single initial assessment, psychiatrists see patients briefly for "medication checks", while non-medical clinicians provide psychotherapy. Team meetings occur to ratify treatment plans, but there is little time available for integration of pharmacotherapy with other treatment modalities.

In the US, the split model of care has principally been driven by a shortage of psychiatrists and by reimbursement protocols that are based on the unsubstantiated premise that it is cheaper to pay psychiatrists to write prescriptions and other clinicians to provide psychotherapy than it is to pay psychiatrists to provide comprehensive patient care. One outcome of this approach is that the domain of the psychiatrist is increasingly restricted only to prescribing medications, a service that itself is seen as so straightforward that a minimal amount of time is needed after a diagnosis has been made. To the extent that prescribing psychotropic medications is an uncomplicated process, nurse practitioners and other clinicians with prescribing authority have been recruited to replace rather than supplement psychiatrists on the grounds that they cost less and that they are just as effective – a belief equally unsubstantiated by any credible data.

In the UK, a dramatic example of the relegation of the psychiatrist to a marginal role was the proposal by Lord Layard (1) that led to expanding psychological therapy for anxiety and depression in the British national health system. In this initiative, a senior non-physician psychotherapist would make initial diagnoses and assign the patient to a junior therapist, who would be supervised, motivated and trained by senior therapists. Psychiatrists would be elsewhere in the national health system, with the task of administering drug treatment to the most severely ill patients, and would not be involved at all in the treatment of most mood and anxiety disorders.

There are a number of features of the treatment process that may also limit the role of the psychiatrist and inhibit comprehensive treatment. For example, in the current clinic model which is endorsed in many contexts worldwide, a diagnosis and treatment plan that are usually developed after a single initial visit are supposed to be followed in the subsequent months or years without any additional time for re-evaluation. This approach is based on a unidimensional, cross-sectional view of the disorder, assuming that the illness does not evolve and the diagnosis does not change over time. Yet, it is not uncommon for apparently clear-cut major depression to be re-diagnosed as bipolar disorder (2-4), because the prodromes of the manic episode were overlooked or masked at the initial assessment (5). Accurate diagnosis and effective treatment often depend on repeated assessments, but in some clinic settings there is insufficient time available to the prescriber for this process (5). Even if the therapist had sufficient expertise to refine the diagnosis, time and structure are not available for a collaborative discussion with the prescriber for comprehensive reconsideration.

Another common issue involves medical evaluation. Between 20% and 50% of psychiatric patients have active medical illnesses (6,7) and psychiatric medications such as some atypical antipsychotics pose additional medical risks (8). A full understanding of the patient's medical condition is important not only to clarify psychiatric symptoms, but also to determine the need for general medical care and to choose psychiatric treatments that do not interact adversely with the medical illness and its treatment (9). It is axiomatic that a medical diagnosis depends on a careful history and physical examination, with laboratory investigations as indicated (9). Yet, such evaluations are rarely performed in the clinic setting by psychiatrists or anyone else (10), despite their responsibility for the overall health of their patients (11). Indeed, psychiatric outpatient clinics generally operate in isolation from the rest of the medical system.

Recovery has increasingly become a stated goal of mental health treatment (12), but there is increasing awareness that

complete remission of symptoms and restoration of normal function is not frequent in such psychiatric disorders as major depression (13), panic disorder (14), obsessive-compulsive disorder (15), eating disorders (16) and schizophrenia (17). For example, only 28% of patients with fairly uncomplicated unipolar depression receiving flexible doses of citalopram were found to be symptomatically (let alone functionally) remitted (18). Lack of remission is associated with subsequent relapse, while treatment of residual symptoms may improve functioning and reduce the risk of relapse and recurrence (5).

Combinations of medications and of psychotherapy and pharmacotherapy can improve remission rates (19). In some cases, treatments that are administered in sequential order (psychotherapy after pharmacotherapy, psychotherapy followed by pharmacotherapy, one drug treatment following another or one psychotherapeutic treatment following another) may be more successful in eliminating residual symptomatology than introducing all treatments at the same time (20). Maximizing remission requires repeated assessments, modification of initial treatment plans and efficient integration of treatment team members, which requires more time than is usually allocated.

Psychotherapy is an obvious component of treatment in the mental health clinic, and over the past two decades there has been impressive progress in the effectiveness of short-term psychotherapeutic strategies such as cognitive behavioral therapies and interpersonal therapy in a number of psychiatric disorders (21). These psychotherapies have been found to be effective alternatives or supplements to pharmacotherapy, with enduring benefits after treatment is discontinued (20,21). However, while many clinics provide psychotherapies in various forms, true manualized evidence-based psychotherapies are often not available, and coordination with pharmacotherapy is rarely possible for most patients, because of brief "medication check" visits to psychiatrists that leave no time for consultation with therapists.

## A NEW MODEL

One way to develop a model of more comprehensive and integrated outpatient mental health care is to consider a mental health clinic affiliated with an academic department of psychiatry or other psychiatric organization in the community. Referral sources may be psychiatric inpatient units, psychiatrists in other settings, primary care physicians and other medical specialists or other agencies, or patients may refer themselves. We will discuss the staffing, functioning and modalities of integration of the basic operational unit of the clinic, which could be multiplied according to the number and needs of the patients served.

The basic unit includes a psychiatrist, an internist, and four psychotherapists, who could be clinical psychologists, nurse clinicians or social workers. The psychiatrist should have an adequate background both in psychopharmacology and psychotherapy. Experience in performing psychotherapy is essential, whether or not the psychiatrist will provide it in the clinic, since referral to psychotherapy requires a deep understanding of the indications, contraindications and expectations of the psychotherapeutic technique that is proposed.

The internist should be able to provide specialized medical evaluation, especially of endocrine and cardiovascular problems. Psychotherapists may have different levels of experience and training in evidence-based psychotherapeutic strategies (21). Individual, family or group formats may be performed, according to the needs of the patients and the skills of the therapists (22). Properly trained clinical psychologists and social workers may be most experienced at individual and group psychotherapy. Nurse clinicians, in the long-standing experience of the Maudsley Institute (23), may be the most appropriate individuals to supervise self-therapy approaches such as exposure, to monitor stable medication regimens, and to emphasize the role of the patient in the process of recovery (13), including diet and exercise (24). To illustrate the functioning of the clinic, consider the entry of a new patient into the system.

The initial assessment is performed by the psychiatrist. In addition to the customary psychiatric examination to determine categorical and dimensional diagnoses (9), the task of this assessment is to establish treatment priorities, since many patients qualify for more than one diagnosis (25-27).

The process of assessing the relationship between co-occurring syndromes to decide where treatment should commence is called macro-analysis (28,29). For instance, a patient may present with major depressive disorder, obsessive-compulsive disorder and hypochondriasis. In a macro-analysis, the clinician may give priority to the pharmacological treatment of depression, leaving to second stage assessment the determination of whether obsessive-compulsive disorder and hypochondriasis are epiphenomena that will resolve with resolution of depression, or whether they will persist, despite improvement of depression. In the latter case, it will be necessary to determine whether further treatment is necessary. If one syndrome is addressed initially, macro-analysis requires re-assessment after the first line of treatment has been completed. Treatment is therefore staged according to the seriousness, extension and course of the disorder (30-33). For instance, certain psychotherapeutic strategies can be deferred until antidepressant medications have improved mood to a point where cognitive reorganization with psychotherapy is more likely to be retained (34). Staging has the potential to improve the logic and timing of interventions in psychiatry, just as it does in many complex and serious medical disorders (31).

The planning of sequential treatment requires determination of the symptomatic target of the first line approach (e.g., vegetative symptoms and mental energy for pharmacotherapy), and tentative identification of other areas of concern to be addressed by concomitant or subsequent treatment

(e.g., dysfunctional thinking and relationships targeted by psychotherapy). Addressing one dimension of illness after an earlier feature has improved can increase the likelihood of more complete remission.

Medical assessment in the psychiatric setting is not as straightforward as in the medical setting (6). Medical evaluation requires familiarity with the interactions of psychiatric illnesses and medications with medical disorders and their treatment, as well as with the complex health attitudes of psychiatric patients (35,36). Collaboration of the psychiatrist with an internist who is familiar with psychiatric illness may be necessary for effective treatment planning when a comorbid medical illness is present.

While macro-analysis involves an assessment of the relationship between co-occurring syndromes, micro-analysis is a detailed analysis of symptoms for functional assessment (28). It involves consideration of the onset of complaints, their course, circumstances that aggravate or ameliorate symptoms, short-term and long-term impact of symptoms on quality of life, and work and social adjustment (28). Micro-analysis may also include specific tests and rating scales (9,37), which must be integrated into the rest of the assessment and not viewed in isolation (38). This dimension of micro-analysis is performed by a clinical psychologist and may either complete the diagnostic assessment or pave the way for further evaluation.

This information should facilitate the formulation of an initial treatment plan, which may involve no need for treatment; referral to other institutions; pharmacotherapy only; psychotherapy only; or use of both pharmacotherapy and psychotherapy, which may be simultaneous or sequential (20).

There is often a tendency to regard simultaneous administration of pharmacotherapy and psychotherapy as the optimal treatment. However, not all data support the initiation of both treatments at the same time, especially in anxiety and mood disorders (20,39). Sequencing pharmacotherapy and psychotherapy may be more effective in chronic and severe cases (39,40). Assignment to the first line of treatment may involve pharmacotherapy provided or monitored by the psychiatrist, psychotherapy provided by a psychotherapist with expertise in the proposed therapeutic modality, or both. However, even when pharmacotherapy alone is the preferred initial treatment, it is less likely to be effective if the patient does not have the opportunity to develop a therapeutic alliance with a prescriber who is sufficiently available to provide appropriate optimism, an opportunity to ventilate thoughts and feelings, and the development of an interest in self-examination (41,42).

If non-pharmacologic approaches are instituted before pharmacotherapy, they may involve sessions by nurse clinicians, emphasizing lifestyle modification, dietary measures, physical exercise, encouragement of exposure and use of computer aided strategies (43,44). Initial psychotherapy may involve cognitive behavioral therapy for panic disorder with agoraphobia, social phobia, obsessive-compulsive disorder or post-traumatic stress disorder; cognitive behavioral or interpersonal psychotherapy for major depression; or dialectic behavior or expressive therapy for a personality disorder (45). Conversely, certain psychotherapies, for example cognitive therapy for schizophrenia or family focused therapy or interpersonal and social rhythms therapy for bipolar disorder (46), are usually instituted at the same time as pharmacotherapy.

It is very important to reassess the patient after the first line of treatment has been completed, to reconfirm the diagnosis and refine the treatment plan. Certain approaches may limit a satisfactory assessment of the patient in this stage. The first is re-examination of only a few target symptoms, instead of the full spectrum of psychopathology as would be done with a new patient.

The second pitfall is to determine severity by the number of symptoms, not by their intensity, quality or impact on functioning (29). The result is treatment aimed at a diagnosis based on a certain number of symptoms (which may be of mild intensity and of doubtful impact on quality of life), instead of individual symptoms or dysfunctions that may be incapacitating. Conversely, subclinical symptomatology, as frequently occurs in partially remitted disorders (5,13,14), may require aggressive treatment, because it continues to impair functioning and because it increases the risk of relapse or recurrence of the full syndrome (13-15,17).

Another issue is that symptoms are usually elicited through a clinical interview. However, state-dependent recall may limit information available by this method and a diary or daily rating scale can be an important source of information that is not readily apparent in an interview.

Consistent with the principle that health is traditionally equated with the absence of illness rather than the presence of wellness (47), assessment in psychiatry is mostly based on appraisal of psychopathological dysfunction instead of a balance between positive and negative factors (41). To determine whether the patient is well, it is necessary to assess positive health and functioning in addition to symptoms. The most comprehensive reassessment after the completion of psychotherapy and somatic therapy should be performed by the psychiatrist. The assessment performed in this phase is crucial in determining the level of remission after the first course of treatment, whether residual symptoms are present and whether further treatment is necessary. Since the available data suggest that only a minority of patients are likely to display a satisfactory degree of recovery with monotherapy or a single phase of treatment (13,15,17,18), it is often necessary to decide whether psychotherapeutic or pharmacological approaches or both should substitute for or supplement the first line of treatment.

Since any residual symptoms increase the risk of relapse and recurrence (5,13,48), another reassessment is necessary after treatment is completed, for example when a depressed patient has completed psychotherapy following pharmacotherapy (20). If any residual symptoms persist, new treatment strategies, such as indefinite drug therapy and maintenance psychotherapy, should be considered.

At all stages of therapy, integrating treatments requires regular meetings of all team members (including the internist). The goals of these meetings include diagnosis and formulation of treatment plans; monitoring of treatment progress; modification of initial diagnostic formulations and treatment plans; discussion of the role of medical and psychosocial factors; introduction of brief, targeted interventions; supervision of psychotherapy by the psychiatrist or other designated senior psychotherapist; and consideration of maintenance treatment after completion of therapy. The cost of such meetings is compensated for by improved outcomes and less need for multiple episodes of acute treatment after relapse.

## CONCLUSIONS

The predominant model of the mental health clinic has the potential to marginalize the psychiatrist to a point that could impede recruitment of this specialist into clinic settings. By making use of the ability of the psychiatrist to synthesize psychiatric, medical and psychological data from diverse sources, interact with different specialists and disciplines, and develop a comprehensive treatment plan, the model proposed here defines a role that many psychiatrists would find desirable while not detracting from the skills of other clinicians working with the patient. Ideological influences that tend to minimize the psychiatrist's role are reduced while maintaining an effective team approach.

We believe that research into the effectiveness of the model would demonstrate that any increase in cost related to using some of the psychiatrist's time for treatment planning, which is normally not directly reimbursed, is offset by more efficient utilization of all services and improved outcomes as well as more successful recruitment of psychiatrists into the public sector.

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# An axis for risk management in classificatory systems as a contribution to efficient clinical practice

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*Comprehensive clinical assessment and patient management plans have been enhanced by the development of multiaxial classificatory systems. Assessment of risk is an essential clinical task for which the conclusions are not currently reflected in the multiaxial diagnostic schemata. Developments in the understanding of risk and its management make possible consideration of its place in multiaxial systems. The structure and principles of a potentially workable axis, summarizing current knowledge of risk in the domains of suicide, self-neglect and violence to others, are described. Clinicians are more likely to use this axis than the multiple, emerging, risk assessment guidelines. Incorporating risk management would be a practical addition to presently available axes and be very widely clinically applicable.*

**Key words:** Risk management, multiaxial classification, risk assessment, clinical recovery plan

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Consideration has often been given to placing greater emphasis on the utility of classificatory systems, particularly because of the lack of progress in developing an etiologically based system and the recognition that a "naturalistic" approach to classification might be unrealistic (1-3).

The classificatory system and clinical formulations are central to the clinical logic of connecting the assessment information to the patient recovery plan (4). Multiaxial classificatory systems can be thought of as attempts to standardize regularly informative components of formulation into a classificatory framework.

In recent years there has been increasing emphasis on the concept of risk assessment. For example, there have been several publications in the area of risk of suicide (5,6), risk of harm/violence to others (7) and more extended risks to the patient themselves, such as self-neglect (8). The understanding of these risk factors has been gradually increased by more precise epidemiologically guided research. Public and health service concerns about the consequences of inadequate risk management have led to the gradual emergence of a number of guidelines (9-11). Almost inevitably these guidelines, which connect risk assessment and risk management, concentrate on only one of the three major risk areas referred to above, despite the recognition that a single, comprehensive clinical management or recovery plan best serves patient/consumer needs.

We would argue that incorporating the clinical management consequences of risk assessment as one dimension of a multiaxial classificatory system would increase both clinical effectiveness and efficiency. This paper sets out a possible structure for such an axis, with its rationale.

## RISK ASSESSMENT VS. RISK MANAGEMENT

It has been noted that, when predicting risk of violence, psychiatrists are likely to be very often wrong (12-15). We also know that by developing the skills of risk formulation (12) and risk management (16) they are likely to achieve better results. The distinction between the tasks of risk assessment for clinical management and event prediction is subtle but significant. A classic study in this regard was conducted by Lidz et al (17), who reported that clinicians were reasonably accurate in assessing dangerousness, since the patients who did prove to be violent on follow-up over six months were detected with reasonable sensitivity. On the other hand, many patients who were rated as dangerous by clinicians did not prove to be more violent than the other patients (low specificity).

A clinical determination that a patient presents sufficient risk to justify intervention is one goal of assessment of risk. Risk assessment must identify clinical or situational factors which can be modified to reduce risk. It is noteworthy that inquiries into homicides by persons with mental illness have consistently found that only a minority of incidents are predictable, whilst the majority are preventable with good quality clinical assessment, communication and intervention (18,19). We can use our psychiatric training to introduce interventions according to the needs of an individual and master the art of risk management by constantly considering the dynamic nature of risk and paying attention to the needs and deficits of an individual.

The issue of shifting focus from risk prediction to risk management becomes more relevant when one considers the ethical implications of the two (14). Often the outcome of risk assessment is that a patient with a history of violence is identified as "potentially violent", which easily gets distorted as "violent". These adjectives accumulate in the file and are of little utility unless ways are identified to manage risk. Our responsibility as psychiatrists does not end with stating that a given patient is potentially dangerous. The ethical justification for risk assessment by a treating psychiatrist is risk reduction through risk management. Risk changes with time and circumstance and therefore the risk of violence needs to be assessed and reviewed regularly. While these factors are described in the context of assess-

ment of risk of violence to others, the same principles apply to the other two main types of risk that clinicians routinely assess in general adult psychiatric settings.

## AXIS DESIGN ISSUES

The major organizing principle for our proposed axis is that it should inform and assist the development of patient recovery plans. It will do that best by incorporating both positive and negative risk factors which need to be addressed or harnessed to facilitate patient recovery.

Clinicians most commonly undertake three types of risk assessment – violence, suicide and self-neglect – which are embedded in the legislations on compulsory treatment in many places (14,20). In order to be accepted and widely used, a risk axis will need to be simple yet comprehensive. It should be sufficiently comprehensive not only to capture all the types of risk assessed, but also to be able to address the unique aspects of each risk. It needs to be able to capture all three types of risk in one format, rather than the tripartite guidelines which are beginning to appear in a number of nations – for example, in the UK (9) and in New Zealand (10). Having a separate system for each type of risk is confusing and burdensome for clinicians, and therefore more likely to be observed in the breach than in the action. It also means there are often several different management plans in different parts of the clinical file.

A history of violence is known to evoke strong emotions and aversion in the people conducting such risk assessment (14). It is likely that in patients who have committed previous violent acts, clinicians may either miss or underestimate other types of risks such as of suicide or self-neglect. Incorporating the three types of risk in one axis will encourage their assessment in a manner similar to how detection of personality disorder and physical illnesses have improved with the introduction of multiaxial diagnostic systems (21-23).

A retrospective study (24), based on a case note review that looked at the practicality of extracting risk-related information, found that on average it took 5 hours to conduct a thorough review, rendering retrospective case note reviews an impractical, incomplete and misleading way of conducting the three types of risk assessment. The authors recommended prospective recording as a more practical method if used selectively, but cautioned that it required a standardized approach to clinical recording and case note maintenance. It may be worth noting that taking a (multidisciplinary) team approach to risk assessment may not only reduce biases in clinical decision making (25), but also speed the process due to cumulative knowledge about the risk issues.

We note that each type of risk has both dynamic or clinical factors and static or historical factors, which are assessed by clinical or actuarial methods respectively. It has been argued that for better outcomes the two methods should be combined (7,26). A risk axis could enable clinicians to attend to both tasks and serve as an "aide memoire", yet have sufficient in-built flexibility to allow individual or unique aspects of the patient's presentation to be taken into account in the clinical recovery plan.

We believe, as stated above, that risk assessment should be carried out primarily with a view to managing the risk, otherwise the task becomes unethical and disadvantageous to the patient. Therefore the risk axis should be able to inform the development of the individual care plan. For each of the three types of risk (self-neglect, suicide and violence to others), static, dynamic and management factors (targeting on the latter may well reduce the risk) will need to be described in a manner that informs the patient recovery plan. Some risk factors and their managements are common to all three.

Static factors for risk of self-neglect include male gender, older age, poverty, living alone and physical problems (e.g., history of hip fracture/stroke) (8); dynamic factors include clinically significant depressive symptoms, cognitive impairment, a deteriorating physical condition, non-compliance with treatment and/or support consistent with self-neglect, hoarding of rubbish and persistent neglect of rotting food, denial of danger from malfunctioning appliances, disconnection of essential services and leaving home with doors unlocked and open (27). To the best of our knowledge, no studies have looked at factors that may have a specific protective effect against the risk of self-neglect.

Static risk factors for suicide have been identified in a recent systematic review (10): they include sex (while more male die by suicide, many more females attempt suicide), age (aged 15-24 years and those over 60 years), history of previous attempts, ethanol and drug abuse, sexual abuse, comorbid anxiety disorders (particularly panic disorder), personality disorders (antisocial and borderline), conduct disorder and oppositional defiance disorder, and identifiable stressful events. Identified dynamic factors include depression, impaired rational thinking, presence of organized plan, loneliness or debilitating medical illness, and experiences of adversity. Management or protective factors are presence of support networks, relief about not completing suicide, people relying on them for ongoing care, a sense of unfinished business, framework for meaning (e.g., religious belief), beliefs about the need to care for children, good self-esteem, self-confidence and awareness of significant others about their suicidal thoughts.

Finally, static factors for risk of violence to others include previous violence, young age at first violence, psychopathy, early maladjustment, personality disorder, prior supervision failure; dynamic factors include relationship instability, employment problems, substance use problems, lack of insight, negative attitudes, active symptoms of major mental illness, impulsivity and unresponsiveness to treatment. Management or protective factors include level and type of personal support, dealing with stressors, working on medication adherence.

All the above could be combined in a qualitative or quantitative format which could be completed as a part of a multiaxial summary of the clinical assessment process.

## CONCLUSIONS

The assessment of risk of self-neglect, suicide and violence to others is a task that clinicians routinely undertake. However, current classificatory systems do not make any provision for it. A dedicated risk management axis would help clinicians by integrating the findings of the assessment into the clinical recovery plan and may improve the utility of the classificatory systems by aligning them better to routine clinical work. Such an axis will need to combine actuarial and clinical factors. Our understanding of actuarial factors associated with the three types of risks has improved greatly in the recent years, making the development of such an axis now possible.

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# Fighting the stigma caused by mental disorders: past perspectives, present activities, and future directions

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*People who live with mental illnesses are among the most stigmatized groups in society. In 1996, in recognition of the particularly harsh burden caused by the stigma associated with schizophrenia, the WPA initiated a global anti-stigma program, Open-the-Doors. In 2005, a WPA Section on Stigma and Mental Health was created, with a broader mandate to reduce stigma and discrimination caused by mental disabilities in general. In light of these important developments, and the growing public health interest in stigma reduction, this paper reflects on the past perspectives that have led us to our current position, reviews present activities and accomplishments, and identifies challenges that the Section members will face in their future efforts to reduce the stigma caused by mental disorders.*

**Key words:** Mental health related stigma, stigma reduction, discrimination, Open-the-Doors anti-stigma program

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Having now passed the 12th anniversary of the WPA Global Program to Fight Stigma and Discrimination Because of Schizophrenia, and the third year of operation of the WPA Scientific Section on Stigma and Mental Health, it is timely to reflect on the past perspectives that have led us to our current position, review present activities and accomplishments, and identify challenges that the Section members will face in their future efforts to reduce the stigma caused by mental disorders.

## PAST PERSPECTIVES

The pejorative use of the term *stigma,* reflecting a mark of shame or degradation, is thought to have appeared in the late 16th and early 17th centuries. Prior to that, *stigma* was more broadly used to indicate a tattoo or mark that might have been used for decorative or religious purposes, or for utilitarian reasons, such as a brand placed on criminals or slaves so that they could be identified if they ran away and to indicate their inferior social position. The evolution of the term notwithstanding, negative societal responses to the mentally ill have been ubiquitous throughout history – a situation that has persisted through changing concepts of mental illness – even through the rise of medical theories and biologically-based explanations for most mental disorders (1,2).

Contemporary notions of stigma are grounded in sociological and psychological theoretical traditions. For example, our modern understanding of stigma and its effects stems largely from the seminal work of Erving Goffman, conducted in the early 1960s. In *Stigma: notes on the management of spoiled identity,* Goffman describes the damaging effects of stigma, which reduces the bearer from a whole person to one that is irredeemably tainted (3). In Goffman's view, mental illness was one of the most deeply discrediting and socially damaging of all stigmas, such that people with mental illnesses start out with rights and relationships, but end up with little of either (4). Goffman was deeply critical of mental hospitals for their stigmatizing and anti-therapeutic effects (5) and, along with contemporaries such as Szasz (6) and Scheff (7), reinforced the perception that stigma was rooted in the nature of psychiatric diagnosis and treatment. From this original focus on stigma as a by-product of the social organization of psychiatry, contemporary social theorists have taken a much broader, ecological view; one that recognizes the complex interplay of social-structural, interpersonal and psychological factors in the creation and maintenance of stigma (8,9). From this perspective, stigma is pervasive, pernicious, and resistant to change and, to be successful, anti-stigma programs must be comprehensive, multipronged and directed to individual, interpersonal, and system-level determinants.

Psychological theories have helped us understand how cognitive and attributional processes at the social-psychological levels lead to the development and maintenance of the negative and erroneous stereotypes that form the internal scaffolding for stigmatized world views. Attribution theory provides a particularly useful framework for understanding stigma and for targeting anti-stigma interventions. Attribution theory traces a path from a signaling event (a label), to an attribution (or stereotype), to an emotion (negative), and finally to a behavioural response (discrimination). In the case of mental illness, extensive research has confirmed that people who hold moral models of mental illness – those who believe that the illness is controllable, or that people with mental illness are to be blamed for their symptoms – are more likely to respond in an angry and punitive manner. In theory, it is possible to replace incorrect attributions to reduce stigma and discrimination; however, it

has not yet been possible to definitively link improvements in knowledge or attitudes to behavioural change. The approaches that have been most successful in improving knowledge and attitudes (but not necessarily behaviours) have combined active learning with positive contact with people who have a mental illness. Fact-based and protest-based approaches have been less successful, though it has been difficult to generalize across studies with different outcomes, or determine whether changes in knowledge or attitudes have improved the lives of people with mental disorders (10,12).

## PRESENT ACTIVITIES

Over the last decade, public health interest in both the burden of mental illness and the hidden burden of mental health related stigma has grown. Organizations such as the World Health Organization (13-16), the WPA (17,18) and the World Association for Social Psychiatry (19), to name a few, have all recognized stigma as a major public health challenge. Growing support for stigma reduction is also evident in the number of government declarations, mental health system reviews, and action plans that have highlighted the disabling effects of stigma and the importance of reducing discrimination (20-23). Large-scale nationally coordinated population-based anti-stigma initiatives have also emerged during this time in Australia (24), New Zealand (25), the United Kingdom (26) and Japan (27).

In 1996, the WPA initiated a global program to fight stigma and discrimination because of schizophrenia. In the ten years since its inception, more than 20 countries have joined the WPA's *Open-the-Doors* global network, making this the largest and longest running anti-stigma program to date. Participating countries (in order of enrolment) include Canada, Spain, Austria, Germany, Italy, Greece, the United States, Poland, Japan, Slovakia, Turkey, Brazil, Egypt, Morocco, the United Kingdom, Chile, India, Romania, with several more in the planning phases. A brief overview of the program is presented in a previous issue of *World Psychiatry* (28). Detailed results for the first eighteen countries are reported in the recent book *Reducing the stigma of mental illness* (18).

The *Open-the-Doors* program is unique among anti-stigma efforts in that it reflects the work of an international consortium of members, all of whom endorse three core principles. The first is that program goals and objectives are to be developed from the priorities and needs of people who live with schizophrenia, garnered from quantitative and qualitative needs assessments and realized through their active participation in all aspects of program development, implementation, and evaluation. Second, local programs are to encourage broad participation from community members, making a concerted effort to move beyond the mental health sector. Early experience showed that it was particularly important to include members of target groups on local planning committees. Third, recognizing the pervasive nature of stigma, planning teams are committed to creating programs that are sustainable over the long term, often emphasizing smaller focused efforts which have greater long-term viability. Following the planning process that has been outlined, it typically takes 12-18 months for a group to have their program up and running.

A wide number of groups have been targeted by local programs to be recipients of anti-stigma interventions. Their diversity highlights the pervasiveness of stigma both within and across cultures, as well as the importance of adopting a program design process that allows for culturally relevant content. At the same time, because target groups are based on the priorities of local consumers and family members (at least those that could be most feasibly addressed), they give us a partial glimpse onto some of the most common sources of stigma experienced by people living with schizophrenia worldwide. Of the first eighteen sites profiled by Sartorius and Schulze (18), for example, fifteen targeted general practitioners and other health care personnel, making this the most frequent target group. Other target groups included primary and secondary school students (n=13), journalists and mass media (n=13), psychiatrists and mental health professionals (n=12), people who have schizophrenia (n=11), family and friends of people with schizophrenia (n=11), members of the general public (n=11); members of the religious community and clergy (n=6), government workers and non-governmental agencies (n=5), businesses and employers (n=5), medical students (n=3), and judicial and law enforcement personnel (n=2).

In contrast to the growing interest in stigma reduction, and a rich theoretical literature pertaining to stigma and discrimination, the evidence base needed to support stigma change is underdeveloped (29). Indeed, an important accomplishment of the WPA global program has been to increase the production of knowledge and practical experience concerning *better* practices in anti-stigma programming in both developed and developing countries. To date, the program participants have implemented over 200 interventions, ranging from speaker's bureaus and contact-based educational programs (n=12), to protest-based programs (n=6), to mass media campaigns using television or radio (n=10), and novel applications of drama and the arts, including consumer-run theatre productions and large benefit concerts featuring international celebrities (n=8). Thirteen of the first eighteen sites have already published their results in scientific journals (18) and four sites have now analyzed their data cross-culturally (30,31).

A third important contribution has been the development of a multi-disciplinary interest in the implementation and evaluation of anti-stigma programs. Previous research has tended to be theoretical and discipline-specific. Program members have collaborated to host three international scientific conferences focusing on the science of stigma reduction, giving important impetus to this emerging field. The first *Together Against Stigma International Conference* was held in Leipzig in 2001, hosted by the German *Open-*

*the-Doors* site. The second was held in Kingston, Canada in 2003, and the third was held in Istanbul, Turkey in 2006. Reviewing a decade of progress, it is possible to see how the field has developed from the presentation of results from initial needs assessment surveys, through goal-based evaluation results, to large-scale cross-cultural comparisons involving international consortia of researchers.

In order to build and expand on this momentum, program members have recently developed a WPA Scientific Section on Stigma and Mental Health. The Section was approved by the WPA General Assembly at the 13th World Congress of Psychiatry held in Cairo, Egypt in 2005. Since its inception, the Section has grown to include some sixty researchers from 25 countries.

## FUTURE DIRECTIONS

An important goal of the Section is to continue the momentum created by the *Open-the-Doors* program and enlarge the network to include new program sites. Toward this end, Section members will continue to provide training opportunities and materials through workshops and special courses organized at WPA and other international and national congresses. Members are also actively involved in the development of international research consortia devoted to the study of particular aspects of mental health stigma, such as consumer experiences with stigma and discrimination. The development of the specialized tools needed to support these efforts has been underway for some time.

With increasing recognition of the public health importance of stigma, and growing knowledge about how to fight stigma and discrimination both locally and internationally, the future of applied stigma research holds a number of exciting prospects for Section members. Much of the activity of Section members has been on fighting stigma and discrimination because of schizophrenia, as this was the original impetus behind the global program. The rationale for this choice was based on the knowledge that the stigma associated with schizophrenia is particularly harsh and intimately linked to fears and misconceptions concerning violence and unpredictability. The importance of focusing on a specific illness, rather than mental illnesses in general, was considered in light of the need for a clear program focus, the fact that the general public uses schizophrenia as a paradigm for mental illness (often describing psychotic and disorganized behaviours as characteristics of all mentally ill), and the idea that any gains made in this difficult area would certainly be useful to those working to eradicate stigma related to other mental illnesses (18). Given the broader interests of the members, also reflected in the broader mandate of the Section, an important focus for future work will be to develop international anti-stigma research consortia pertaining to other highly disabling mental illnesses, such as mood and anxiety disorders.

A clearer understanding of the cross-cultural nature of stigma and discrimination experienced by people living with mental disorders will also be an important avenue for future investigation. Instruments are now available to quantify the scope and impact of stigma experienced by people with a mental illness (32-34). However, much remains to be done to validate their use in different cultural settings and to ensure they are sensitive to change. To be judged effective, future anti-stigma interventions must do more than change public knowledge or attitudes toward the mentally ill. They must also fundamentally change the stigma experiences of people who live with mental disabilities. In developing an evidence-base for anti-stigma programs, then, consumer perspectives will be of increasing consequence, not only to identify targets for program activities, but also as an evaluation yardstick against which program improvements can be judged.

Finally, although people with mental illnesses are among the most stigmatized groups in society, mental illnesses are not the only stigmatized health conditions. Leprosy, HIV/AIDS, tuberculosis and cancer are among the many stigmatized health conditions for which advocates have battled social stigma, some more successfully than others. It is important that lessons be shared across groups. This will not only improve our understanding of the general social and psychological conditions that give rise to health-related stigmas, but also allow us to learn from and build on each other's successes and avoid each other's failures.

The members of the WPA Section on Stigma and Mental Health are committed to advancing scientific knowledge to improve social inclusion for people with mental illnesses and their families. Through the *Open-the-Doors* network and other collaborative means, they are developing international scientific projects, taking an active role in WPA-sponsored meetings and World Congresses, and contributing to the scientific literature dealing with mental health stigma and discrimination.

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# The WPA International Congress "Treatments in Psychiatry: A New Update" (Florence, April 1-4, 2009)

The WPA International Congress "Treatments in Psychiatry: A New Update" will take place in Florence, Italy, from 1 to 4 April, 2009. It will be the follow-up to the 2004 WPA International Congress "Treatments in Psychiatry: An Update", which was the second most attended psychiatric congress worldwide in that year, with almost 7,000 participants. This time, more than 8,000 participants are expected.

The Congress aims to provide a high-quality, comprehensive overview of all evidence-based treaments currently available for all mental disorders. Many of the most renowned experts in the various treatment areas will be among the speakers.

The Congress will consist of the following components: a) ESI[SM] Top-Cited Scientist Lectures (delivered by the scientists who attracted the highest total citations to their papers in indexed journals of psychiatry and psychology over the past 10 years, according to the Essential Science Indicators); b) Update Lectures (providing a comprehensive update on some of the most significant aspects of current treatments in psychiatry); c) Update Symposia (focusing on specific treatment issues, with an active interaction between speakers and participants); d) Advanced Courses (in which a well-renowned expert will interact with no more than 50 participants); e) Regular Symposia (high-quality Symposia selected from those submitted by April 30, 2008); f) Workshops (high-quality sessions dealing with very specific treatment issues, selected from those submitted by April 30, 2008); g) Section and Zonal Symposia or Workshops (organized by WPA Scientific Sections or Zones); h) New Research Sessions; i) Poster Sessions; j) Sponsored Events.

The preliminary programme of the Congress is the following.

### ESI[SM] Top-Cited Scientist Lectures

TL1. *R.C. Kessler* – The treatment gap in psychiatry

TL2. *K.S. Kendler* – Psychiatric genetics: a current perspective

TL3. *M. Rutter* – Environmentally mediated risks for psychopathology: research strategies and findings

TL4. *R.M. Murray* – The causes of schizophrenia: neurodevelopment and other risk factors

TL5. *J. Biederman* – Childhood antecedents of bipolar disorder: recognition and management

TL6. *A.J. Rush* – From the laboratory to patients: getting the evidence for evidence based care for depression

TL7. *H.S. Akiskal* – Clinical management of bipolar disorder based on pathophysiologic understanding

TL8. *S.L. McElroy* – Management of binge eating disorder associated with obesity

TL9. *P.E. Keck* – What is a mood stabilizer?

TL10. *M.E. Thase* – Long-term management of depression: the role of pharmacotherapy and psychotherapies

### Update Lectures

UL1. *R.J. Baldessarini* – Disorders, syndromes, target symptoms: how do we choose medications?

UL2. *P. Fonagy* – Psychotherapies: what works for whom?

UL3. *G. Thornicroft* – Steps, challenges and mistakes to avoid in the development of community mental health care

UL4. *P.D. McGorry* – Early intervention in psychiatry

UL5. *M.F. Green* – Improving cognitive performance and real-world functioning in people with schizophrenia

UL6. *E. Vieta* – Evidence-based comprehensive management of bipolar disorder

UL7. *K. Fulford* – Evidence and values in psychiatric practice

UL8. *S.G. Resnick* – Recovery and positive psychology: an update

UL9. *R. Drake* – Management of patients with substance abuse and severe mental disorder

UL10. *M. Stone* – Comprehensive management of borderline personality disorder in ordinary clinical practice

UL11. *W.W. Fleischhacker* – Comparative efficacy, effectiveness and cost-effectiveness of antipsychotics in the treatment of schizophrenia

UL12. *P.J. Weiden* – The art and science of switching antipsychotic medications

UL13. *G.A. Fava* – Combined and sequential treatment strategies in depression and anxiety disorders

UL14. *K.A. Halmi* – Multimodal management of anorexia and bulimia nervosa

### Update Symposia

US1. The future of psychotherapies for psychoses (*Chairperson*: *P. Bebbington*)

US2. Brain imaging in psychiatry: recent progress and clinical implications (*Chairperson*: *L. Farde*)

US3. Effectiveness and cost-effectiveness of pharmacological treatments in psychiatry: evidence from pragmatic trials (*Chairperson*: *J. Lieberman*)

US4. Intermediate phenotypes in psychiatry (*Chairperson*: *D. Weinberger*)

US5. Advances in the management of treatment-resistant psychotic disorders (*Chairperson*: *H.-J. Möller*)

US6. Advances in the management of treatment-resistant depression (*Chairperson*: *S. Kasper*)

US7. Advances in the management of treatment-resistant bipolar disorder (*Chairperson*: *G.B. Cassano*)

US8. Patterns of collaboration between primary care and mental health services (*Chairperson*: *V. Patel*)

US9. Genomics and proteomics in psychiatry: an update (*Chairperson*: *N. Craddock*)

US10. Managing comorbidity of mental and physical illness (*Chairperson*: *N. Sartorius*)

US11. The evolving science and practice of psychosocial rehabilitation (*Chairperson: R. Warner*)

US12. ICD-11 and DSM-V: work in progress (*Chairperson*: *M. Maj*)

US13. Violence, trauma and victimization (*Chairperson*: *A. McFarlane*)

US14. Cognitive impairment: should it be part of the diagnostic criteria for schizophrenia? (*Chairperson*: *R. Keefe*)

US15. Management of medically unexplained somatic symptoms (*Chairperson*: *O. Gureje*)

US16. Partnerships in mental health care (*Chairperson*: *B. Saraceno*)

US17. Outcome in bipolar disorders: new findings and methodological challenges *(Chairperson: M. Tohen)*

US18. Suicide prevention: integration of public health and clinical actions (*Chairperson*: *Z. Rihmer*)

US19. Novel biological targets of pharmacological treatment in mental disorders (*Chairperson*: *G. Racagni*)

US20. Prevention and early intervention strategies in community mental health settings (*Chairperson*: *S. Saxena*)

US21. Anxiety disorders: from dimensions to targeted treatments (*Chairperson*: *J. Zohar*)

US22. Cultural issues in mental health care (*Chairperson*: *P. Ruiz*)

US23. The challenge of bipolar depression *(Chairperson: J. Calabrese)*

US24. Current management of mental disorders in old age (*Chairperson*: *C. Katona*)

US25. Prevention of substance abuse worldwide (*Chairperson*: *M.E. Medina-Mora*)

US26. Treatment advances in child psychiatry (*Chairperson*: *J. Rapoport*)

US27. Gender-related issues in psychiatric treatments (*Chairperson*: *D. Stewart*)

US28. Mental health care in low-resource countries (*Chairperson*: *P. Deva*)

**Advanced Courses**

AC1. Interacting with families of people with severe mental disorders *(Director*: *C. Barrowclough)*

AC2. Management of the suicidal patient (*Director: D. Wasserman*)

AC3. The therapeutic alliance in psychiatric practice (*Director: A. Tasman*)

AC4. Management of mental disorders during pregnancy and post-partum (*Director*: *I. Brockington*)

AC5. How to organize a comprehensive community mental health service (*Directors: G. Thornicroft, M. Tansella*)

AC6. Prevention and management of burnout in mental health professionals (*Director*: *W. Rössler*)

AC7. Measures of outcome in schizophrenia (*Director: R. Kahn*)

AC8. Consultation-liaison psychiatry: learning from experience (*Director*: *F. Creed*)

AC9. Relevance of phenomenological psychiatry to clinical practice (*Director*: *G. Stanghellini*)

AC10. The psychiatrist in court (*Director*: *J. Arboleda-Florez*)

AC11. Management of the "difficult" child (*Director*: *S. Tyano*)

AC12. The public health approach: what psychiatrists need to know (*Directors*: *H. Herrman, S. Saxena*)

AC13. Assessing and training neurocognitive functions in patients with chronic psychoses (*Director*: *S. Galderisi*)

AC14. Interpersonal psychotherapy of depression (*Director*: *T. Gruettert*)

**Regular Symposia**

RS1. Interpersonal psychotherapy: overview and issues in dissemination (*Chairperson*: *M. Weissman*)

RS2. Current state and future prospects of early detection and management of psychosis (*Chairpersons*: *J. Klosterkötter, S. Ruhrmann*)

RS3. Treatment of depressive and anxiety disorders in children and adolescents (*Chairperson*: *B. Vitiello*)

RS4. New advances in diffusion magnetic resonance imaging and their application to schizophrenia (*Chairperson*: *M.E. Shenton*)

RS5. Supported employment for people with psychotic disorders (*Chairperson*: *T. Burns*)

RS6. Treatment of eating disorders: an update (*Chairperson*: *J.E. Mitchell*)

RS7. The emergence of subthreshold psychiatry (*Chairperson*: *A. Okasha*)

RS8. Mental health care in Europe: problems, perspectives and solutions (*Chairperson*: *M. Tansella*)

RS9. Chronotherapeutics for major affective disorders (*Chairperson*: *A. Wirz-Justice*)

RS10. Obsessive-compulsive disorders: translational approaches and new therapeutic strategies (*Chairperson*: *J. Zohar*)

RS11. Combination strategies for the stabilization of panic and generalized anxiety disorder (*Chairperson*: *A.W. Goddard*)

RS12. Evidence-based psychotherapies for personality disorders (*Chairperson*: *C. Maffei*)

RS13. Current clinical perspectives in psychosomatic medicine (*Chairperson*: *P. Ruiz*)

RS14. Classification of psychoses: are disease spectra and dimensions more useful for research and treatment purposes? (*Chairperson*: *E.J. Franzek*)

RS15. Clinical features and pharmacological treatment of bipolar mixed depression (*Chairperson*: *F. Benazzi*)

RS16. The effects of psychiatric conditions on driving: a primer for psychiatrists (*Chairperson*: *M. Rapoport*)

RS17. Key and unresolved issues in suicide research (*Chairpersons*: *R. Baldessarini, R. Tatarelli*)

RS18. Are we working with the right concepts in Alzheimer's disease? (*Chairperson*: *R. Bullock*)

RS19. Is cyclothymia the most common affective phenotype? (*Chairperson*: *G. Perugi*)

RS20. The cost of adolescence: a multidimensional approach (*Chairperson*: *M. Ernst*)

RS21. Issues in pharmacotherapy of drug addiction (*Chairpersons*: *F. Drago, W. van den Brink*)

RS22. Advances in the treatment of chronic and residual depression (*Chairpersons*: *M. Berger, E. Schramm*)

RS23. First and second generation antipsychotics: data from the EUFEST study (*Chairpersons*: *S. Galderisi, R. Kahn*)

RS24. Migration and mental health (*Chairperson*: *D. Moussaoui*)

RS25. Neurobiology of incipient psychosis: recent evidence from early rec-

ognition research (*Chairpersons*: *J. Klosterkötter, W. Maier*)

RS26. Reactions of children and adolescents to trauma: from coping strategies to PTSD (*Chairperson*: *E. Caffo*)

RS27. Recent advances in psychosocial rehabilitation (*Chairperson*: *M. Madianos*)

RS28. Recent advances in psychiatric genetics (*Chairpersons*: *N. Craddock, A. Serretti*)

RS29. Management of psychotic disorders in community mental health services: the gap between evidence and routine practice (*Chairperson*: *M. Ruggeri*)

RS30. How to teach non-psychiatrists to diagnose, treat and appropriately refer patients with psychopathology (*Chairpersons*: *D. Baron, R. Fahrer*)

RS31. Psychopharmacology in eating disorders: why, when and how (*Chairpersons*: *F. Brambilla, P. Monteleone*)

RS32. Pathophysiological mechanisms and treatment of depression associated with cerebrovascular disease (*Chairperson*: *R.G. Robinson*)

RS33. Management of treatment-resistant obsessive-compulsive disorders (*Chairperson*: *F. Bogetto*)

RS34. Early life interventions for later life mental disorders (*Chairpersons: K. Ritchie, M.-L. Ancelin*)

RS35. Delay in treatment of first episode of psychosis: pathways to care and impact of interventions (*Chairpersons*: *R. Fuhrer, A. Malla*)

**Workshops**

WO1. Recovery: what it is and how mental health professionals can support it (*Coordinator*: *M. Slade*)

WO2. Sexuality and mental health (*Coordinator*: *K. Wylie*)

WO3. Mentalization-based treatment for borderline personality disorder (*Coordinators*: *D.L. Bales, A.W. Bateman*)

WO4. Developing the new burden of disease estimates for mental disorders and illicit drug use (*Coordinators*: *H. Whiteford, L. Degenhardt*)

WO5. The therapeutic alliance with suicidal patients (*Coordinator*: *K. Michel*)

WO6. Mental health peer-support groups: outcome and mechanisms of action (*Coordinator*: *S. Eisen*)

WO7. Management of mentally disordered sexual offenders (*Coordinator*: *W.L. Marshall*)

WO8. Clozapine: indications and management of complications (*Coordinator*: *P.F.J. Schulte*)

WO9. Self-disturbance in early psychosis: a clinical and conceptual perspective (*Coordinators*: *B. Nelson, A. Raballo*)

WO10. Promoting the implementation of evidence-based treatments in mental health services (*Coordinator*: *U. Malm*)

WO11. Neurophysiology in psychiatry: standardization, training and certification (*Coordinators*: *S. Galderisi, N. Boutros*)

WO12. Anti-stigma strategies in a developing country (*Coordinator*: *M.R. Jorge*)

WO13. Management of co-occurring mental illness and substance use disorders (*Coordinator*: *J. Pasic*)

WO14. Functional family therapy in youth at high risk for delinquent behavior (*Coordinator*: *D. Baron*)

WO15. Management of geriatric depression in community settings (*Coordinator*: *D. Roane*)

WO16. Recent changes in psychiatric care settings: educational and practical implications for young psychiatrists (*Coordinators*: *A. Fiorillo, J. Beezhold*)

WO17. Practical issues in the long-term management of schizophrenia (*Coordinator*: *I. Bitter*)

WO18. Promoting primary care intervention in child and adolescent mental health (*Coordinator*: *J. Jureidini*)

WO19. Family-involved treatment for bipolar disorder: compelling approaches (*Coordinator*: *I. Galynker*)

**WPA Section and Zonal Symposia**

SS1. Service user involvement in mental health research *(Organized by the Section on Public Policy and Psychiatry)*

SS2. Perils and perplexities in treating eating disorders *(Organized by the Section on Eating Disorders)*

SS3. Access to mental health care: global perspectives *(Organized by the Section on Conflict Management and Resolution, the Section on Psychiatry and Public Policy, and the Section on Mental Health Economics)*

SS4. Processes of inclusion for people with intellectual disability and mental health problems *(Organized by the Section on Psychiatry of Intellectual Disability)*

SS5. Puerperal and menstrual psychoses: an update *(Organized by the Section on Perinatal Psychiatry and Infant Mental Health)*

SS6. Stigma: current challenges for care and treatment *(Organized by the Section on Public Policy and Psychiatry and the Section on Stigma and Mental Health)*

SS7. Ethical issues in the relationship of psychiatry to the pharmaceutical industry *(Organized by the Section on Public Policy and Psychiatry and the Section on Psychiatry, Law and Ethics)*

SS8. New therapies for schizophrenia: an outlook into the future *(Organized by the Section on Schizophrenia)*

SS9. Social psychiatry: the basic piece of the puzzle to understand the patient as a person *(Organized by the Section on Stigma and Mental Disorders, in collaboration with the World Association for Social Psychiatry)*

SS10. The association between impulsivity and addiction: causes, consequences and treatment implications *(Organized by the Section on Impulsivity and Impulse Control Disorders)*

SS11. Implementing mental health care through developing caring communities *(Organized by the Section on Public Policy and Psychiatry)*

SS12. Genetics of suicide: what's around the corner? *(Organized by the Section on Suicidology)*

SS13. The enigma of psychiatric brain drain and possible solutions *(Organized by the Section on Psychiatry in Developing Countries)*

SS14. Psychiatry at the end of life: clinical and therapeutic challenges *(Organized by the Section on Psycho-oncology)*

SS15. Aesthetics of treatment in psychiatry *(Organized by the Section on Clinical Psychopathology and the Section on Philosophy and Humanities in Psychiatry)*

SS16. Evolutionary psychopathology: clues for treatment *(Organized by the*

*Section on Psychotherapy)*

SS17. Addiction psychiatry: an update *(Organized by the Section on Addiction Psychiatry)*

SS18. Education and training in transcultural psychiatry: prospects and challenges *(Organized by the Section on Transcultural Psychiatry)*

SS19. The role of psychiatry in sport *(Organized by the Section on Exercise, Psychiatry and Sports)*

SS20. International perspectives of forensic psychiatry *(Organized by the Section on Forensic Psychiatry)*

SS21. Hope in psychiatry *(Organized by the Section on Philosophy and Humanities in Psychiatry and the Section on Public Policy and Psychiatry)*

SS22. Awake and sleep EEG changes in dementia: implications for treatment *(Organized by the Section on Psychiatry and Sleep Wakefulness Disorders)*

SS23. Recovery beyond rhetoric *(Organized by the Section on Public Policy and Psychiatry)*

SS24. Psychiatry and the general hospital *(Organized by the Section on Psychiatry, Medicine and Primary Care)*

SS25. Management of mental and behavioural disorders in people with intellectual disabilities *(Organized by the Section on Psychiatry of Intellectual Disability)*

SS26. Social inclusion of people with mental disorders: towards solutions *(Organized by the Section on Public Policy and Psychiatry and the Section on Stigma and Mental Health)*

SS27. Common inflammatory pathways in depression, somatoform disorder and chronic fatigue syndrome *(Organized by the Section on Biological Psychiatry)*

SS28. The provision of psychosocial treatment: facts and indications *(Organized by the Section on Psychotherapy)*

SS29. Advances in the management of treatment resistant mental disorders *(Organized by the Section on Psychiatry, Medicine and Primary Care)*

SS30. Depression and medical comorbidity *(Organized by the Section on Conflict Management and Resolution and the Section on Psychiatry, Medicine and Primary Care)*

SS31. Prevention of suicidal behaviour: the role of health promotion programmes *(Organized by the Section on Suicidology)*

SS32. Advances in the assessment of people with intellectual disability *(Organized by the Section on Psychiatry of Intellectual Disability)*

SS33. Contributions of new technologies in the mental health field *(Organized by the Section on Informatics and Telecommunications in Psychiatry)*

SS34. Challenges in community-oriented psychiatric care *(Organized by the Section on Emergency Psychiatry)*

SW1. Integrating rural mental health with primary care in diverse cultures *(Organized by the Section on Rural Mental Health)*

SW2. Culture, humor and psychiatry: a synthesis *(Organized by the Section on Transcultural Psychiatry)*

SW3. Treatments for pregnant women with chronic mental disorders *(Organized by the Section on Perinatal Psychiatry and Infant Mental Health)*

SW4. The role of art in treatment, rehabilitation and social inclusion *(Organized by the Section on Art and Psychiatry)*

SW5. Pregnancy related psychiatric problems: sorting them out and addressing real issues *(Organized by the Section on Perinatal Psychiatry and Infant Mental Health)*

SW6. Humanities in medical training and in the healing process *(Organized by the Section on Literature and Mental Health)*

ZS1. Improving treatment and care for people with comorbid mental and somatic disorders *(Organized by the Southern Europe Zone)*

ZS2. Recent advances in mental health care in sub-Saharan Africa *(Organized by the Southern and Eastern Africa Zone)*

ZS3. Psychiatric care in Eastern Europe: an update *(Organized by the Eastern Europe Zone)*

ZS4. Disaster management: the South Asian scenario *(Organized by the Southern Asia Zone)*

ZS5. Bipolar disorders in child and adolescent population: a Latin American perspective *(Organized by the Northern South America Zone)*

ZS6. Government initiatives for better mental health of Canadians *(Organized by the Canada Zone)*

ZS7. Towards a global network of depression centers *(Organized by the United States of America Zone)*

ZS8. The future of child psychiatry in North Africa *(Organized by the Northern African Zone)*

ZS9. Psychiatry in Southern South America *(Organized by the Southern South America Zone)*

ZS10. Current mental health issues in the Northern European region *(Organized by the Northern Europe Zone)*

CS1. Ethical challenges in psychiatry *(Organized by the Standing Committee on Ethics)*

For further information, please contact the Scientific Secretariat (secretariat@wpa2009florence.org) or visit the website of the Congress (www.wpa2009florence.org).

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