World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

Volume 2, Number 3 *October 2003*

MASSON

ISSN 1723-8617

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World Psychiatry

World Psychiatry is the official journal of the World Psychiatric Association. It is published in three issues per year and is sent free of charge to psychiatrists whose names and addresses are provided by WPA member societies and sections. State-of-the-art, research and mental health policy papers are welcome for publication in the journal. The relevant proposals should be sent to the office of the Editor.

Published by Masson Italy, a MediMedia Company, Via Muzio Attendolo detto Sforza 7/9, 20141 Milan.

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EDITORIAL

The Presidential WPA Program on Child Mental Health

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Half of the world population are children. Worldwide children are impacted by war, exploited for labor and sex, orphaned by AIDS and forced to migrate for economic and political reasons. It is estimated that in 26 African countries the number of children orphaned for any reason will more than double by 2010, and 68% of these will be as a result of AIDS. 40 million children in 23 developing countries will lose one or both parents by 2010 (1).

20% of children and adolescents under the age of 18 have a diagnosable mental disorder. Moreover, suicide is the third leading cause of death among adolescents. The latest mean worldwide annual rates of suicide per 100,000 were 0.5 for females and 0.9 for males among 5-14 years-olds, and 12.0 for females and 14.2 for males among 15-24 year-olds. The main target of effective prevention of youth suicide is to identify and reduce risk factors, foremost depression (2).

The prevalence of attention deficit/hyperactivity disorder (ADHD) has been estimated at 3-7% in school-aged children. Over a nine-year period, the median medical costs for children with ADHD were found to be $4306 compared with $1944 for children without ADHD (3).

Conduct disorder related behaviors tend to persist into adolescence and adult life through drug abuse, juvenile delinquency, adult crime, antisocial behavior, marital problems, poor employee relations, unemployment, interpersonal problems and poor physical health (4).

Major depressive disorder often has an onset in adolescence and is associated with substantial psychosocial impairment and risk of suicide (5). Children with pre-pubertal major depressive disorder, as adults, have significantly higher rates of bipolar disorder, major depressive disorder, substance use disorders and suicidality than a normal comparison group (6).

Eating disorders are becoming more prevalent and observable across cultures (7). These difficult to treat disorders also demonstrate a continuity between adolescent and adult life (8). 21.6% of college age females with eating disorders also met clinical criteria 10 years later (9).

Only a small proportion of children affected by mental disorders receive adequate care. Barriers to treatment are several, but reflect a few dominant themes, such as lack of resources (financial, human, facilities), fear of stigma and lack of awareness. Also, a significant concern is the applicability of the diagnostic categories used in the West in areas where there are limited resources.

Even in highly developed industrialized countries, mental disorders in childhood are often not recognized nor taken seriously. Health professionals and others involved in child care have often only rudimentary knowledge about appropriate methods of prevention and treatment of these conditions. The situation is made worse by the lack of awareness by health decision makers and the general public of the magnitude and severity of the problems caused by childhood mental disorders.

There is a virtually worldwide absence of an identifiable national child and adolescent mental health policy. A child and adolescent mental health policy should not focus solely on the treatment of psychopathology, but should encompass a broad range of supportive and educative interventions to permit children to follow a normal trajectory of development. Such policy can facilitate the ability to gather more precise epidemiological data essential for the development of treatment and prevention programs tailored to individual country requirements.

It is against this background that the WPA established its Presidential Program on Child Mental Health, in collaboration with the World Health Organization and the International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP), with an unrestricted grant of Eli Lilly Foundation.

The objectives of the program include:

1. Increasing the awareness of health decision makers, health professionals and the general public about the magnitude and severity of problems related to mental disorders in childhood and possibilities of their resolution.
2. Introducing and promoting the implementation of primary prevention of child mental disorders.
3. Providing support to the development of mental health services for children with mental disorders and to the development, adaptation and use of effective methods of treatment.

The WPA program will function through three international Task Forces: Task Force on Awareness, Task Force on Primary Prevention, Task Force on Service Development and Management.

The program will, in the course of the three years of its duration, produce outputs that will be demonstrably useful to child mental health care. These outputs will include:

1. The publication of critical reviews of the literature on child mental health and of information about child mental health in different countries.
2. A functional network of individuals and institutions committed to the achievement of the program objectives.
3. Manuals and guidelines concerning the prevention, early recognition and detection, and treatment of mental disorders in childhood for health professionals and others concerned with child care and upbringing (e.g. teachers, parents, religious leaders, social welfare workers).
4. Internationally accepted guidelines for activities promoting child mental health.
5. A data base containing information about the current epidemiological situation and about policies and programs relevant to the promotion of child mental health in different parts of the world.

Child and adolescent psychiatry must be integrated into the training curricula of medical students in every university. Services should be based on empirical grounds using epidemiological data and modern methods of treatment evaluation and quality assurance. Improving mental health will lead to improved physical health, enhanced productivity and increased stability.

Our target is promotion of the mental health of half of the world population. And it is the younger half that in a few years will be in charge of our world. It is a cost effective enterprise, no matter how much effort and resources are spent on it.

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Personality disorder diagnosis

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Every person has a characteristic manner of thinking, feeling, and relating to others. Some of these personality traits can be so dysfunctional as to warrant a diagnosis of personality disorder. The World Health Organization's International Classification of Diseases (ICD-10) includes ten personality disorder diagnoses. Three issues of particular importance for the diagnosis of personality disorders are their differentiation from other mental disorders, from general personality functioning, and from each other. Each of these issues is discussed in turn, and it is suggested that personality disorders are more accurately and effectively diagnosed as maladaptive variants of common personality traits.

Key words: Personality, personality disorder, antisocial, borderline, diagnosis

Every person has a characteristic manner of thinking, feeling, behaving, and relating to others (1). Some persons are typically introverted and withdrawn, others are extraverted and outgoing. Some are invariably conscientious and organized, whereas others are consistently carefree. Many of these traits, however, can be problematic and even maladaptive. If one or more of them result in a clinically significant level of impairment to social or occupational functioning or personal distress, it would be appropriate to suggest that a disorder of personality is present. The World Health Organization's International Classification of Diseases (ICD-10) (2) includes ten personality disorder diagnoses, as does the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (3). However, there are important differences between these two prominent nomenclatures (Table 1). For example, ICD-10 does not include narcissistic personality disorder, DSM-IV does not include enduring personality change after catastrophic experience or enduring personality change after psychiatric illness, and ICD-10 classifies the DSM-IV schizotypal personality disorder as a form of schizophrenia rather than a personality disorder (4).

No section of ICD-10 or DSM-IV lacks a diagnostic issue or controversy. Three issues of particular importance for the diagnosis of personality disorders are their differentiation from other mental disorders, from general personality functioning, and from each other. Each will be discussed in turn.

AXIS I AND II

In DSM-IV (3), personality disorders (along with mental retardation) are diagnosed on a separate axis (Axis II). ICD-10 (2) does not include a multiaxial system. There are compelling reasons for the separate axis placement. Personality disorders can provide a disposition for the onset of many of the Axis I disorders, as well as have a significant effect on their course and treatment (5,6). The reason that the authors of the multiaxial system of DSM-III wanted to draw attention to personality disorders was precisely because of the "accumulating evidence that the quality and quantity of preexisting personality disturbance may… influence the predisposition, manifestation, course, and response to treatment of various Axis I conditions" (7).

In addition, "personality features are typically ego-syntonic and involve characteristics that the person has come to accept as an integral part of the self" (8). Personality traits are integral to each person's sense of self, as they include what people value, how they view themselves, and how they act most every day throughout much of their lives. Most Axis I disorders, like most medical disorders, are experienced by persons as conditions or syndromes that come upon them. Personality disorders, in contrast, will often concern the way persons consider themselves to be.

Finally, personality disorders can be related conceptually to the general personality functioning evident in all persons, the assessment of which would be of potential relevance to virtually every psychiatric patient. Some of these personality traits will be problematic to treatment, and others will be facilitative. Much of the research on the contribution of personality to the etiology of Axis I disorders has in fact concerned personality traits, such as neuroticism, introversion, and sociotropy, that are evident within general personality functioning (5,6).

The placement of personality disorders on a separate axis has been effective in increasing their recognition in clinical settings, but perhaps the pendulum has swung so far that clinicians and researchers are now confusing Axis I disorders with personality disorders (9). The boundaries of the anxiety, mood, and other Axis I disorders have also been expanding with each edition of the diagnostic manual. Axis I now includes diagnoses that shade imperceptibly into normal personality functioning and have an age of onset and course that are virtually indistinguishable from

a personality disorder (e.g., generalized social anxiety and early onset dysthymia). Some clinicians and researchers have therefore suggested that the multiaxial system be abandoned and others have even proposed that the personality disorders be deleted altogether from the diagnostic manual and replaced by early onset and chronic variants of existing Axis I disorders (10). A precedent for this proposal is the ICD-10 classification of DSM-IV schizotypal personality disorder as a variant of schizophrenia (2).

Many of the existing personality disorders could not be replaced meaningfully by an early onset variant of an Axis I disorder, notably the narcissistic, dependent, and histrionic. One potential solution might be to simply delete them. The loss of the narcissistic personality disorder might not be missed internationally, as it is already excluded from ICD-10 (2). Clinicians with a neurophysiological orientation may also fail to miss the dependent and histrionic diagnoses, as they lack any meaningful understanding from this theoretical perspective (11). Another potential solution would be to include a new section of the diagnostic manual for disorders of interpersonal relatedness (12). DSM-IV and ICD-10 currently have sections devoted to disorders of mood, anxiety, impulse dyscontrol, eating, somatization, sleep, substance use, cognition, sex, learning, and communication but, surprisingly, no section devoted to disorders of interpersonal relatedness. Interpersonal relatedness is a fundamental component of healthy and unhealthy psychological functioning that is as important to well being as the existing sections of the diagnostic manual. A new section devoted to disorders of interpersonal relatedness would provide marital and family clinicians with a section of the manual that is more compatible with the focus of their clinical interventions (10) and would account for much of the personality disorder symptomatology that is not well accounted for by existing Axis I diagnoses (12,13).

There are, however, significant problems with both options. Both would remove from the diagnostic manual any meaningful reference to or recognition of the existence of personality functioning, for which there is substantial and compelling empirical support (1). In addition, reformulating personality disorders as early onset and chronic variants of existing (or new) Axis I disorders may simply create more diagnostic problems than it solves. For example, persons have constellations of maladaptive personality traits that are not well described by just one or even multiple personality disorder diagnoses (9,13). These constellations of maladaptive personality traits will be even less well described by multiple diagnoses of 'comorbid' mood, anxiety, impulse dyscontrol, delusional, disruptive behavior, and interpersonal disorders (12).

DIFFERENTIATION FROM GENERAL PERSONALITY FUNCTIONING

Researchers have been unable to identify a qualitative distinction between normal personality functioning and personality disorder (9,10,13). DSM-IV and ICD-10 provide specific and explicit rules for distinguishing the presence versus absence of each of the personality disorders, but the basis for these thresholds are largely unexplained and are weakly justified (14). The DSM-III schizotypal and borderline personality disorders are the only two for which a published rationale has ever been provided (4).

The heritability and structure of personality disorder symptomatology is as evident within general community samples of persons lacking the personality disorders as it is in persons who have been diagnosed with these disorders (15). All of the fundamental symptomatology of the personality disorders can be understood as maladaptive variants of personality traits evident within the normal population (16). For example, much of the symptomatology of borderline personality disorder can be understood

Table 1 Personality disorders in ICD-10 and DSM-IV

ICD-10	DSM-IV[a]
Paranoid	Paranoid
Schizoid	Schizoid
Schizotypal[b]	Schizotypal
Dyssocial	Antisocial
Emotionally unstable, borderline type	Borderline
Emotionally unstable, impulsive type	
Histrionic	Histrionic
	Narcissistic
Anxious	Avoidant
Dependent	Dependent
Anankastic	Obsessive-compulsive
Enduring personality change after catastrophic experience	
Enduring personality change after psychiatric illness	
Organic personality disorder[c]	Personality change due to general medical condition[d]
Other specific personality disorders and Mixed and other personality disorders	Personality disorder not otherwise specified

[a] Included within an appendix to DSM-IV are proposed criteria sets for passive-aggressive (negativistic) personality disorder and depressive personality disorder.
[b] ICD-10 schizotypal disorder is consistent with DSM-IV schizotypal personality disorder but included within the section of Schizophrenia, schizotypal, and delusional disorders.
[c] Included within section of Organic mental disorders.
[d] Included within section of Mental disorders due to a general medical condition not elsewhere classified.

as extreme variants of the angry hostility, vulnerability, anxiousness, depressiveness, and impulsivity included within the broad domain of neuroticism (17). Similarly, much of the symptomatology of antisocial or dyssocial personality disorder appears to be extreme variants of low conscientiousness (rashness, negligence, hedonism, immorality, undependability, irresponsibility) and high antagonism (manipulative, deceptive, exploitative, aggressive, callous, ruthless) that are evident within the general population (18,19).

PERSONALITY DISORDER DIAGNOSTIC CO-OCCURRENCE

Patients often meet diagnostic criteria for more than one personality disorder (20,21). Some patients may even meet criteria for five or more personality disorders (22,23). Comorbidity is a pervasive phenomenon across both axes of DSM-IV that has substantial importance to clinical research and treatment (21,24), yet comorbidity may be grossly under-recognized in general clinical practice (25). Clinicians tend to diagnose personality disorders hierarchically. Once a patient is identified as having a particular personality disorder (e.g., borderline), they often fail to assess whether additional personality traits are present (26). Multiple diagnoses are not provided by practicing clinicians, perhaps because they are problematic to the "categorical perspective that personality disorders are qualitatively distinct clinical syndromes" (3).

The intention of ICD-10 and DSM-IV is to help the clinician determine which particular mental disorder is present, the selection of which would purportedly indicate the presence of a specific pathology that will explain the occurrence of the symptoms and suggest a specific treatment that will ameliorate the patient's suffering (8). It is evident, however, that DSM-IV routinely fails in the goal of guiding the clinician to the presence of one specific disorder (27). Despite the best efforts of the leading clinicians and researchers who have been the primary authors of each revision of the diagnostic manual, diagnostic comorbidity rather than the presence of one particular mental disorder is the norm (24).

Personality and personality disorders appear to be the result of a complex interaction of biogenetic dispositions and environmental experiences that result in a wide array of adaptive and maladaptive personality traits. Providing a

Table 2 Description of the five factor model of general personality functioning (adapted from Widiger et al [33])

Neuroticism versus emotional stability		
	Anxiousness:	wary, apprehensive, tense, fearful *versus* relaxed, unconcerned, cool
	Angry hostility:	hypersensitive, bitter, angry, rageful *versus* even-tempered, good-natured
	Depressiveness:	worried, pessimistic, despondent *versus* not easily discouraged, optimistic
	Self-consciousness:	timid, embarrassed, ashamed *versus* self-assured, glib, shameless
	Impulsivity:	tempted, urgent, dyscontrolled *versus* controlled, restrained
	Vulnerability:	fragile, helpless, panicked *versus* stalwart, unflappable, brave, fearless
Extraversion versus introversion		
	Warmth:	warm, cordial, attached, affectionate, loving *versus* cold, aloof, indifferent
	Gregariousness:	sociable, outgoing, can't tolerate aloneness *versus* withdrawn, isolated
	Assertiveness:	forceful, dominant, bossy *versus* unassuming, quiet, resigned
	Activity:	active, energetic, frantic *versus* inactive, passive, lethargic
	Excitement-seeking:	daring, reckless, foolhardy *versus* cautious, monotonous, dull
	Positive emotions:	high-spirited, giddy, euphoric *versus* serious, austere, placid, anhedonic
Openness versus closedness to experience		
	Fantasy:	imaginative, unrealistic, dreamer *versus* practical, concrete, sterile
	Aesthetic:	aesthetic, aberrant, preoccupied *versus* unappreciative, no interests
	Feelings:	aware, responsive, preoccupied *versus* constricted, alexythymic
	Actions:	open, exotic, unconventional *versus* routine, repetitive, monotonous
	Ideas:	creative, odd, peculiar, aberrant *versus* pragmatic, realistic, closed-minded
	Values:	broad-minded, permissive *versus* traditional, inflexible, dogmatic
Agreeableness versus antagonism		
	Trust:	trusting, naive, gullible *versus* skeptical, cynical, suspicious, paranoid
	Straightforwardness:	honest, open, confiding *versus* shrewd, cunning, manipulative, deceptive
	Altruism:	generous, self-sacrificing *versus* stingy, selfish, greedy, exploitative
	Compliance:	cooperative, docile, meek *versus* oppositional, combative, aggressive
	Modesty:	humble, self-effacing, self-denigrating *versus* confident, boastful, arrogant
	Tender-mindedness:	kind, empathic, gentle, soft-hearted *versus* tough, callous, ruthless
Conscientiousness versus undependability		
	Competence:	able, efficient, perfectionistic *versus* relaxed, carefree, lax, negligent
	Order:	organized, ordered, methodical *versus* intuitive, haphazard, sloppy
	Dutifulness:	dependable, principled, rigid *versus* casual, undependable, unethical
	Achievement:	ambitious, diligent, workaholic *versus* relaxed, aimless, desultory
	Self-discipline:	devoted, dogged, single-minded *versus* indulgent, hedonistic, negligent
	Deliberation:	reflective, circumspect, ruminative *versus* intuitive, hasty, careless, rash

diagnosis that refers to a particular constellation of traits can be useful in highlighting features that would be evident within a prototypic case (e.g., 19), but a categorical diagnosis will suggest the presence of features that are not in fact present and will fail to identify important features that are present (13). A single DSM-IV personality disorder diagnosis will fail to adequately describe the complexity and individuality of any particular person's personality profile.

CONCLUSIONS

"Personality disorders are now at a crossroads with respect to theory, research, and conceptualization" (28). The diagnosis of personality disorders should perhaps follow the lead taken by its brethren on Axis II, mental retardation (29). Mental retardation, like personality disorders, is diagnosed at an arbitrary but meaningful point of demarcation along a multivariate and continuous distribution that shades imperceptibly into normal psychological functioning.

A number of alternative dimensional models of personality disorder have been developed, many of which were outlined in the Journal of Personality Disorders' first two issues of the 21st century (29-32). Table 2 provides a brief description of the five factor model of general personality functioning, including illustrations of both the adaptive and maladaptive aspects of each of the two poles for each of its 30 facets (33).

An important question for the eventual clinical application of a dimensional model is how it would be used by a clinician to render a personality disorder diagnosis. It remains unclear if simply an elevation on a particular personality scale would warrant a diagnosis (e.g., self-directedness or neuroticism), whether a disorder could be suggested instead by particular constellations of maladaptive personality traits (e.g., high antagonism and low conscientiousness), and whether a separate, independent assessment of social and occupational functioning or personal distress should be required. Several approaches have been taken to try to delineate personality disorder from normal personality traits using a dimensional system. For example, Cloninger (30) suggests that the presence of a personality disorder would be diagnosed by levels of cooperativeness, self-transcendence, and, most importantly, self-directedness (the ability to control, regulate, and adapt behavior); the specific variants of personality disorder would be determined by the temperaments of novelty seeking, harm avoidance, reward dependence, and persistence. Livesley and Jang (31) propose an assessment of self-pathology as a fundamental distinction between personality and other mental disorders. Widiger et al (33) provide a four step procedure. The first step is a description of an individual's personality structure in terms of the five-factor model; the second is the identification of problems and impairments associated with these personality traits (a comprehensive list of problems and impairments associated with each of the 30 facets of the five factor model is provided); the third is a determination of whether these impairments reach a specified level of clinical significance (modeled after Axis V of DSM-IV); and the fourth is a matching of the personality profile to prototypic cases to determine whether a single, parsimonious diagnostic label could or should be applied.

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The underlying neurobiology of bipolar disorder

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Clinical studies over the past decades have attempted to uncover the biological factors mediating the pathophysiology of bipolar disorder (BD) utilizing a variety of biochemical and neuroendocrine strategies. Indeed, assessments of cerebrospinal fluid chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have demonstrated a number of abnormalities in the amine neurotransmitter systems in this disorder. However, recent studies have also implicated critical signal transduction pathways as being integral to the pathophysiology and treatment of BD, in addition to a growing body of data suggesting that impairments of neuroplasticity and cellular resilience may also underlie the pathophysiology of the disorder. It is thus noteworthy that mood stabilizers and antidepressants indirectly regulate a number of factors involved in cell survival pathways - including MAP kinases, CREB, BDNF and bcl-2 protein - and may thus bring about some of their delayed long-term beneficial effects via underappreciated neurotrophic effects.

Key words: Mania, norepinephrine, dopamine, acetylcholine, serotonin, glutamate, neuroplasticity, CREB, BDNF, ERK MAP kinase, bcl-2

Although genetic factors play a major, unquestionable role in the etiology of bipolar disorder (BD), the biochemical abnormalities underlying the predisposition to and the pathophysiology of BD remain to be fully elucidated. Early biologic theories regarding the pathophysiology of BD have focused upon various neurotransmitters, in particular the biogenic amines. In recent years, however, advances in our understanding of the cellular mechanisms underlying neuronal communication have focused research into the role of post-receptor sites. Indeed, the 'molecular medicine revolution' has resulted in a more complete understanding of the etiology and pathophysiology of a variety of medical disorders (1,2). However, in contrast to the progress that has been made in elucidating the etiology and/or pathophysiology of a variety of medical conditions, we have yet to identify the specific abnormal genes or proteins in BD. The behavioral and physiological manifestations of BD are complex and must account not only for the profound changes in mood, but also for the constellation of neurovegetative and psychomotor features. The pathophysiology is undoubtedly mediated by a network of interconnected limbic, striatal and fronto-cortical neurotransmitter neuronal circuits, and the interacting cholinergic, catecholaminergic and serotonergic neurotransmitter systems thus represent very attractive candidates. Thus, it is not surprising that clinical studies over the past 40 years have for the most part rested upon the conceptual foundation that monoamine signaling and hypothalamic-pituitary-adrenal (HPA) axis disruption are integral to the pathophysiology of both depression and mania (3,4).

A true understanding of the pathophysiology of BD must address its neurobiology at different physiological levels, i.e. molecular, cellular, systems, and behavioral. Abnormalities in gene expression undoubtedly underlie the neurobiology of the disorder at the molecular level and this will become evident as we identify the susceptibility and protective genes for BD in the coming years. Once this has been accomplished, however, the even more difficult work must begin to examine the impact of the faulty expression of these gene-products (proteins) on integrated cell function. It is at these levels that some compelling protein candidates have been identified as the targets for the actions of mood stabilizing agents; however, the precise manner in which these candidate molecular and cellular targets may or may not relate to the faulty expression of susceptibility gene-products is yet to be determined. The task becomes even more daunting when one considers the possibility that a major component of the pathophysiology of BD may stem from discordant biological rhythms ranging from ultradian to infradian that ultimately drive the periodic recurrent nature of the disorder (5-7). The subsequent challenge for the basic and clinical neuroscientist will be the integration of these molecular/cellular changes to the systems and ultimately to the behavioral level wherein the clinical expression of BD becomes fully elaborated. However, considerable progress has been made in our understanding of this fascinating but devastating mental disorder. This article will focus upon recent data linking signaling abnormalities and impairments of neuroplasticity with the underlying neurobiology of BD. Space limitations necessitate the citing of review articles in many instances. A full reference list upon which this article is based is available upon request.

CLASSICAL MONOAMINERGIC NEUROTRANSMITTER AND NEUROENDOCRINE SYSTEMS

The stimulus for the study of the biogenic amines in patients with BD was provided by the discovery of effec-

tive pharmacologic treatments for depression and mania (3). In addition to these compelling pharmacological data, the biogenic amine neurotransmitter systems are distributed extensively in the limbic system, which is implicated in the regulation of sleep, appetite, arousal, sexual function, endocrine function, and emotional states such as fear and rage. The clinical picture of BD involves disruption of behavior, circadian rhythms, neurophysiology of sleep, neuroendocrine and biochemical regulation within the brain (3,8). These complex illness manifestations are undoubtedly mediated by a network of interconnected neurotransmitter pathways; the monoamine neurotransmitter systems are ideally placed to mediate such complex behavioral effects, and thus represent attractive candidate systems underlying the pathophysiology of BD (9).

Noradrenergic system

Despite methodological difficulties in assessing central nervous system (CNS) noradrenergic (NE) functions in humans, extensive investigation supports the presence of NE systems abnormalities in BD (3,10,11). Postmortem studies have shown an increased NE turnover in the cortical and thalamic areas of BD subjects (12,13), whereas in vivo studies have found plasma levels of NE and its major metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), to be lower in bipolar than unipolar depressed patients, and higher in bipolar patients when manic than when depressed (3,11). The same occurs with urinary MHPG levels, which are lower in bipolar depressed patients, while longitudinal studies show that MHPG excretion is higher in the manic compared to depressed state (3,4,10,11). Finally, in a consistent mode, cerebrospinal fluid (CSF) NE and MHPG are also reported to be higher in mania than in depression.

Other paradigms studying NE receptor function tend to suggest the possibility of an altered sensitivity of α_2- and β_2-adrenergic receptors in mood disorders (10,11). Genetics studies have also been carried out, showing that polymorphic variation of enzymes involved in amine metabolism (i.e. tyrosine hydroxylase, catechol-O-methyltransferase) could confer different susceptibility to develop bipolar symptomatology (14-16). However, although promising, these findings need to be replicated and subgroups of bipolar patients to whom these alterations may apply need to be identified.

Serotonergic system

There is a consistent body of data from CSF studies, neuroendocrine challenge studies, serotonin receptor and reuptake site binding studies, pharmacologic studies, and most recently, brain imaging studies supporting a role for alterations of serotonergic neurotransmission in major depressive episodes (3,17,18). Overall, investigators have reported reduced levels of 5-hydroxyindoleacetic acid (5-HIAA) in a subgroup of patients, especially those with impulsivity, aggression and suicide attempts. In BD subjects, studies of CSF 5-HIAA in manic patients have generally produced variable and inconsistent results (3,19). Thus, baseline CSF 5-HIAA levels in manic patients, compared to non-depressed controls, have been reported as decreased in four studies, unchanged in nine studies, and increased in three studies; by contrast, most studies find no difference in the levels of CSF 5-HIAA between manic and depressed patients. Of the four studies that examined CSF 5-HIAA accumulation following administration of probenecid in manics, depressives and controls, two reported that both manic and depressed patients have diminished CSF 5-HIAA formation compared to controls, and one reported that manic patients have significantly lower CSF 5-HIAA accumulation than depressives and controls (3).

Studies have also reported decreased radioligand binding to the serotonin transporter (which takes up serotonin from the synaptic cleft) both in platelets and in the midbrain of depressed patients (17,18). Most recently, an intriguing preliminary positron emission tomography (PET) study reported decreases in 5-hydroxytryptamine (5-HT)$_{1A}$ receptor binding potential in raphe and hippocampus-amygdala of brain in depressed patients, in particular in bipolar depressives and in unipolar patients with bipolar relatives (20). One factor which may contribute to the reduction in 5-HT$_{1A}$ receptor binding in depression is increased cortisol secretion (known to occur in many depressed patients, vide infra), since postsynaptic 5-HT$_{1A}$ receptor mRNA expression is under tonic inhibition by corticosteroid receptor stimulation in some brain regions. The magnitude of the reduction in 5-HT$_{1A}$ receptor density and mRNA levels induced by stress-induced glucocorticoid secretion in rodents is similar to that of the differences between depressed and healthy humans. For example, in rats, chronic unpredictable stress reduced 5-HT$_{1A}$ receptor density an average of 22% across hippocampal subfields, similar to the 25% reduction in hippocampal 5-HT$_{1A}$ receptor binding potential found in depression. Similarly, in tree shrews, chronic social subordination stress (for 28 days) decreased the density of 5-HT$_{1A}$ receptors in the posterior cingulate, parietal cortex, prefrontal cortex (PFC), and hippocampus (by 11% to 34%), similar to the magnitude of reduced 5-HT$_{1A}$ receptor binding potential found by Sargent et al (21) and Drevets et al (22) in these regions.

Neurotransmitter depletion models, specifically in this case tryptophan depletion to lower serotonin levels, permit a more direct strategy to clarify the involvement of serotonergic systems in mood disorders. Tryptophan depletion (achieved by the ingestion of preparations containing high levels of other aminoacids, but devoid of tryptophan) results in reversal of the response to certain antidepressant medications and recurrence of depression; however, depletion in healthy subjects without evidence of mental illness and in nonmedicated patients with depression does not consistently cause or intensify depression (23). These stud-

ies again substantiate the underlying complexity of neurobiologic systems not only in depression but by analogy in BD. With respect to BD, recent studies have investigated the effect of tryptophan depletion in lithium-treated euthymic patients and have generally found no recurrence of symptoms (24). Thus, although lithium has often been postulated to exert many of its beneficial effects via an enhancement of serotonergic function, the tryptophan depletion studies suggest that other mechanisms may be more important.

Most recently, investigators have explored the possibility that sensitivity to the deleterious mood and cognitive effects of lowered serotonin may represent an endophenotype for BD, by studying unaffected relatives of BD patients. In a double-blind, crossover design, 20 unaffected relatives from multiple bipolar families and 19 control subjects underwent acute tryptophan depletion (ATD) (25). Unlike the control subjects, unaffected relatives experienced a lowering of mood during ATD but not with the placebo. Furthermore, unaffected relatives tended to show increased impulsivity in the ATD condition. Measurements obtained before ingestion of the aminoacids drink indicated that, relative to control subjects, unaffected relatives exhibited lower serotonin platelet concentrations, lower affinity, and fewer binding sites of the serotonin transporter for imipramine; these differences were unaffected by tryptophan depletion. In more recent studies, Sobczak et al (26) investigated the effects of ATD on cognitive performance in healthy first-degree relatives of bipolar patients (FH) (N= 30) and matched controls (N= 15) in a placebo-controlled, double-blind crossover design. Performances on planning, memory and attention tasks were assessed at baseline and 5 hours after ATD. They found that speed of information processing on the planning task following ATD was impaired in the FH group but not in the control group. Furthermore, FH subjects with a bipolar disorder type I (BD-I) relative showed impairments in planning and memory, independent of ATD. In all subjects, ATD impaired long-term memory performance and speed of information processing. ATD did not affect short-term memory or focused and divided attention. Together, these results suggest that vulnerability to reduced tryptophan availability may represent an endophenotype for BD and warrants further investigation.

Studies assessing the sensitivity of the serotonergic system by exploring changes in plasma levels of prolactin and cortisol after administration of d-fenfluramine in manic patients have shown contradictory results (27,28). More consistent results have been found after administration of sumatriptan (a 5-HT_{1D} agonist): the growth hormone (GH) response is blunted in manic compared with depressed patients (29), revealing a subsensitivity of 5-HT function.

Dopaminergic system

Several lines of evidence point to a role of dopamine (DA) system in mood disorders. A relevant preclinical model derives from the crucial role of mesoaccumbens DA in the neural circuitry of reward and/or incentive motivational behavior (30). Loss of motivation is one of the central features of depression and indeed anhedonia is one of the defining characteristics of melancholia. Thus, a deficiency of DA systems stands out as a prime candidate for involvement in the pathophysiology of depression (31,32). The strongest direct finding from clinical studies implicating DA in depression is reduced homovanillic acid (HVA, the major DA metabolite) in the CSF; indeed, this is one of the most consistent biochemical findings in depression (3,11). There is also evidence for a decreased rate of CSF HVA accumulation in subgroups of depressed patients, including those with marked psychomotor retardation versus agitation (33). Furthermore, depression occurs in up to 40% of patients with idiopathic Parkinson's disease and may precede motor symptoms. Interestingly, some case reports have documented abolition of symptoms of Parkinson's disease during a manic episode (34,35).

The pharmacological bridge also supports the notion that manipulation of the dopaminergic system is capable of modulating the illness. Thus, DA agonists appear to be effective antidepressants and are able to precipitate mania in some bipolar patients (3,11). Most recently, investigators have utilized a catecholamine depletion strategy (via use of the tyrosine hydroxylase inhibitor α-methylparatyrosine, AMPT) in lithium-treated, euthymic BD patients (36). Intriguingly, they did not observe any mood-lowering effects of AMPT, but observed a 'rebound hypomania' in a significant percentage of the patients. Although preliminary, these results are compatible with a dysregulated signaling system wherein the compensatory adaptation to catecholamine depletion results in an 'overshoot' due to impaired homeostatic mechanisms. Most recently, McTavish et al (37) reported that a tyrosine-free mixture lowered both subjective and objective measures of the psychostimulant effects of methamphetamine and manic scores. These preliminary studies suggest that tyrosine availability to the brain attenuates pathological increases in dopamine neurotransmission following methamphetamine administration and putatively in mania.

In more recent neuroimaging studies, the concentration of the vesicular monoamine transporter protein (VMAT2) was quantified with (+)[^{11}C]dihydrotetrabenazine (DTBZ) and PET (38). Sixteen asymptomatic BD-I patients who had a prior history of mania with psychosis (nine men and seven women) and individually matched healthy subjects were studied. VMAT2 binding in the thalamus and ventral brainstem of the bipolar patients was higher than in the comparison subjects. In a follow-up study, the same research group attempted to assess the diagnostic specificity of the findings, by comparing VMAT2 concentrations between euthymic BD-I (N=15) patients, schizophrenic patients (N=12), and age-matched healthy volunteers (N=15) (38). They found that VMAT2 binding in the thalamus was higher in BD-I patients than in control sub-

jects and schizophrenic patients. The authors interpreted the intriguing findings of increased VMAT2 expression in euthymic BD-I patients as representing trait-related abnormalities in the concentration of monoaminergic synaptic terminals. However, chronic lithium treatment has recently been demonstrated to increase VMAT2 protein in rat frontal cortex (the only region examined) (39), raising the possibility that the PET human studies may have been confounded by treatment effects.

Most recently, Yatham et al (40) assessed presynaptic dopamine function in 13 neuroleptic- and mood-stabilizer-naive nonpsychotic first-episode manic patients by measuring [^{18}F]6-fluoro-L-DOPA (^{18}F-DOPA) uptake in the striatum by PET. No significant differences in ^{18}F-DOPA uptake rate constants in the striatum were found between the manic patients and the comparison subjects; however, treatment with valproate (VPA) significantly reduced ^{18}F-DOPA uptake rate.

Cholinergic system

Much of the evidence supporting the involvement of the cholinergic system in mood disorders comes from neurochemical, behavioral and physiologic studies in response to pharmacologic manipulations. These studies, carried out in the early 1970s, showed that the relative inferiority of noradrenergic compared to cholinergic tone was associated with depression, while the reverse was associated with mania (41). Additional support is found from a study on the central cholinesterase inhibitor physostigmine (administered intravenously), in which transient modulation of symptoms in manic cases and induction of depression in euthymic bipolar patients stabilized with lithium were observed.

A decrease in the cholinergic tone during mania has also been described when increased requirements of the cholinergic agonist pilocarpine were needed to elicit pupillary constriction: consistently, this responsiveness increased after lithium or VPA treatment (42,43), adding evidence on the effects of lithium perhaps potentiating brain cholinergic systems (44,45). However, the therapeutic responses observed with antidepressant and antimanic pharmacological agents are not reliably matched with effects on the cholinergic system.

Stress and glucocorticoids modulate neural plasticity: implications for mood disorders

Numerous reports document HPA axis hyperactivity in drug-free depressed (46) and bipolar depressed patients. With respect to BD, increased HPA activity has been associated with mixed manic states, depression, and less consistently with classical manic episodes (3,18). Chronic stress or glucocorticoid administration has been demonstrated to produce atrophy and death of vulnerable hippocampal neurons in rodents and primates. In humans, magnetic resonance imaging (MRI) studies have also revealed reduced hippocampal volumes in patients with Cushing disease and post-traumatic stress disorder (other conditions associated with hypercortisolemia). Indeed, one of the most consistent effects of stress on cellular morphology is atrophy of the CA3 hippocampal neurons (47,48), which also occurs upon exposure to high levels of glucocorticoids, suggesting that activation of the HPA axis likely plays a major role in mediating the stress-induced atrophy (48). Thus, recurrent stress (and presumably recurrent mood episodes which are often associated with hypercortisolemia) may lower the threshold for cellular death/atrophy in response to a variety of physiological (e.g. aging) and pathological events, likely involving the inhibition of glucose transport (diminishing the capability for energy production and augmenting susceptibility to conditions which place a high demand or load on the neuron), and the abnormal enhancement of glutamatergic signaling leading to excitotoxicity (48).

SIGNALING NETWORKS: THE CELLULAR COGWHEELS UNDERLYING LONG-TERM NEUROPLASTICITY

More recently, research into the pathophysiology and treatment of mood disorders has moved from a focus on neurotransmitters and cell surface receptors to intracellular signaling cascades.

Multicomponent, cellular signaling pathways interact at various levels, thereby forming complex signaling networks which allow the cell to receive, process, and respond to information (49-51). These networks facilitate the integration of signals across multiple time scales, the generation of distinct outputs depending on input strength and duration, and regulate intricate feed-forward and feedback loops (49-51). Given their widespread and crucial role in the integration and fine-tuning of physiologic processes, it is not surprising that abnormalities in signaling pathways have now been identified in a variety of human diseases (2,52,53). Furthermore, signaling pathways represent major targets for a number of hormones, including glucocorticoids, thyroid hormones, and gonadal steroids (2,52). These biochemical effects may play a role in mediating certain clinical manifestations of altered hormonal levels in mood disorder subjects (e.g. the frequent onset of bipolar disorder in puberty, triggering of episodes in the postpartum period, association of depression and potentially rapid cycling with hypothyroidism, and triggering of affective episodes in response to exogenous glucocorticoids).

Complex signaling networks may be especially important in the CNS, where they 'weigh' and integrate diverse neuronal signals and then transmit these integrated signals to effectors, thereby forming the basis of a complex information processing network (49-51). The high degree of complexity generated by these signaling networks may be one mechanism by which neurons acquire the flexibility for generating the wide range of responses observed in the

nervous system. These pathways are thus undoubtedly involved in regulating such diverse vegetative functions as mood, appetite and wakefulness and are therefore likely to be involved in the pathophysiology of BD. We now turn to a discussion of the direct and indirect evidence supporting a role for abnormalities in signaling pathways in the pathophysiology and treatment of BD.

The Gs/cAMP generating signaling pathway

Several independent laboratories have now reported abnormalities in G protein subunits in BD (54,55). Post-mortem brain studies have reported increased levels of the stimulatory G protein ($G\alpha_s$) accompanied by increases in post-receptor stimulated adenylyl cyclase (AC) activity in BD (55,56). Several studies have also found elevated $G\alpha_s$ protein levels and mRNA levels in peripheral circulating cells in BD, although the dependency on clinical state remains unclear (45,55,57-60). It should be emphasized, however, that there is at present no evidence to suggest that the alterations in the levels of $G\alpha_s$ are due to a mutation in the $G\alpha_s$ gene itself (61). There are numerous transcriptional and post-transcriptional mechanisms which regulate the levels of G protein subunits, and the elevated levels of $G\alpha_s$ could potentially represent the indirect sequelae of alterations in any one of these other biochemical pathways (54,55,57,62).

There is growing consensus that the ability of a 'simple' monovalent cation like lithium to treat multiple aspects of an illness as complex as BD arises from its major effects on intracellular signaling pathways, rather than on any single neurotransmitter system per se (9,44,60). Although it appears that the lithium ion (at therapeutic concentrations) does not directly affect G protein function, there is considerable evidence that chronic lithium administration affects that function (9,44). Although some studies have reported modest changes in the levels of G protein subunits, the preponderance of the data suggests that chronic lithium does not modify G protein levels per se, but rather modifies G protein function (62,63). Although speculative, it might be postulated that these G protein effects - which would theoretically attenuate excessive signaling through multiple pathways - likely contribute to lithium's long-term prophylactic efficacy in protecting susceptible individuals from spontaneous-, stress-, and drug (e.g. antidepressant, stimulant)- induced cyclic affective episodes.

The protein kinase C signaling pathway

Protein kinase C (PKC) exists as a family of closely related subspecies, has a heterogenous distribution in brain (with particularly high levels in presynaptic nerve terminals), and, together with other kinases, appears to play a crucial role in the regulation of synaptic plasticity and various forms of learning and memory (64-67). PKC is one of the major intracellular mediators of signals generated upon external stimulation of cells via a variety of neurotransmitter receptors (including muscarinic M1, M3, M5 receptors, noradrenergic $\alpha 1$ receptors, metabotropic glutamatergic receptors, and serotonergic 5-HT_{2A} receptors), which induce the hydrolysis of various membrane phospholipids.

To date, there have only been a limited number of studies directly examining PKC in BD (68). Although undoubtedly an over-simplification, particulate (membrane) PKC is sometimes viewed as the more active form of PKC, and thus an examination of the subcellular partioning of this enzyme can be used as an index of the degree of activation. Friedman et al (69) investigated PKC activity and PKC translocation in response to serotonin in platelets obtained from BD subjects before and during lithium treatment. They reported that the ratios of platelet membrane-bound to cytosolic PKC activities were elevated in the manic subjects. In addition, serotonin-elicited platelet PKC translocation was found to be enhanced in those subjects. With respect to brain tissue, Wang and Friedman (70) measured PKC isozyme levels, activity and translocation in post-mortem brain tissue from BD patients; they reported increased PKC activity and translocation in BD brains compared to controls, effects which were accompanied by elevated levels of selected PKC isozymes in cortices of BD subjects.

Evidence accumulating from various laboratories has clearly demonstrated that lithium, at therapeutically relevant concentrations, exerts major effects on the PKC signaling cascade. Currently available data suggest that chronic lithium attenuates PKC activity, and downregulates the expression of PKC isozymes α and ε in frontal cortex and hippocampus (62,71). Chronic lithium has also been demonstrated to dramatically reduce the hippocampal levels of a major PKC substrate, MARCKS (myristoylated alanine rich C kinase substrate), which has been implicated in regulating long-term neuroplastic events (62,71). Although these effects of lithium on PKC isozymes and MARCKS are striking, a major problem inherent in neuropharmacologic research is the difficulty in attributing therapeutic relevance to any observed biochemical finding. It is thus noteworthy that the structurally dissimilar antimanic agent VPA produces very similar effects as lithium on PKC α and ε isozymes and MARCKS protein (63,71). Interestingly, lithium and VPA appear to bring about their effects on the PKC signaling pathway by distinct mechanisms. These biochemical observations are consistent with the clinical observations that some patients show preferential response to one or other of the agents, and that one often observes additive therapeutic effects in patients when the two agents are co-administered.

In view of the pivotal role of the PKC signaling pathway in the regulation of neuronal excitability, neurotransmitter release, and long-term synaptic events (68,72), it was postulated that the attenuation of PKC activity may play a role in the antimanic effects of lithium and VPA. In a pilot study it was found that tamoxifen (a non-steroidal antie-

strogen known to be a PKC inhibitor at higher concentrations (73)) may, indeed, possess antimanic efficacy (74). Clearly, these results have to be considered preliminary, due to the small sample size thus far. In view of the preliminary data suggesting the involvement of the PKC signaling system in the pathophysiology of BD, these results suggest that PKC inhibitors may be very useful agents in the treatment of mania. Larger double-blind placebo-controlled studies of tamoxifen and of novel selective PKC inhibitors in the treatment of mania are warranted.

Abnormalities of calcium signaling

Calcium ions play a critical role in regulating the synthesis and release of neurotransmitters, neuronal excitability, and long-term neuroplastic events, and it is thus not surprising that a number of studies have investigated intracellular Ca^{2+} in peripheral cells in BD (54,75). These studies have consistently revealed elevations in both resting and stimulated intracellular Ca^{2+} levels in platelets, lymphocytes and neutrophils of patients with BD. The regulation of free intracellular Ca^{2+} is a complex, multi-faceted process, and the abnormalities observed in BD could arise from abnormalities at a variety of levels (54). Ongoing studies should serve to delineate the specific regulatory sites at which the impairment occurs in BD.

IMPAIRMENTS OF NEUROPLASTICITY AND CELLULAR RESILIENCE

Structural imaging studies have demonstrated reduced gray matter volumes in areas of the orbital and medial PFC, ventral striatum and hippocampus, and enlargement of third ventricle in patients with mood disorders relative to healthy controls (76). Complementary post mortem neuropathological studies have shown abnormal reductions in cortex volume, glial cell counts, and/or neuronal densities/sizes in the subgenual PFC, orbital cortex and dorsal anterolateral PFC in unipolar and bipolar patients. However, many of these preliminary reports, although extremely interesting, require further replication.

The marked reduction in glial cells in these regions is particularly intriguing in view of the growing appreciation that glia plays critical roles in regulating synaptic glutamate concentrations and CNS energy homeostasis, and in releasing trophic factors that participate in the development and maintenance of synaptic networks formed by neuronal and glial processes (77). Abnormalities of glial function could thus prove integral to the impairments of structural plasticity and overall pathophysiology of mood disorders.

It is not presently known whether this evidence of neuronal deficits constitutes developmental abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to other pathogenic processes, the sequelae of recurrent affective episodes or other factors that are difficult to control in patient populations.

Underlying mechanism for cell loss

Activation of the HPA axis appears to play a critical role in mediating hippocampal atrophy, as was already discussed. In addition to directly causing neuronal atrophy, stress and glucocorticoids also appear to reduce cellular resilience, thereby making certain neurons more vulnerable to other insults, such as ischemia, hypoglycemia, and excitatory aminoacid toxicity.

The reduction in the resilience of hippocampal neurons may also reflect the propensity for various stressors to decrease the expression of brain derived neurotrophic factor (BDNF) in this region (78). BDNF and other neurotrophic factors are necessary for the survival and function of neurons, implying that a sustained reduction of these factors could affect neuronal viability. Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by (in large part) activating the mitogen activated protein (MAP) kinase signaling cascade, and upregulating major cell survival proteins such as bcl-2 (79). Bcl-2 is now recognized as a major neuroprotective protein, since bcl-2 overexpression protects neurons against diverse insults, including ischemia, the neurotoxic agent methyl-phenyl-tetrahydropyridine (MPTP), β-amyloid, free radicals, excessive glutamate, and growth factor deprivation (80). Accumulating data suggests that bcl-2 is not only neuroprotective, but also exerts neurotrophic effects and promotes neurite sprouting, neurite outgrowth and axonal regeneration (80). If enhanced bcl-2 expression appears to be capable of offsetting the potentially deleterious consequences of stress-induced neuronal endangerment (81), then, pharmacologically induced upregulation of bcl-2 may have considerable utility. Overall, it is clear that the neurotrophic factors/MAP kinase/bcl-2 signaling cascade plays a critical role in cell survival in the CNS, and that there is a fine balance maintained between the levels and activities of cell survival and cell death factors. Modest changes in this signaling cascade or in the levels of the bcl-2 family of proteins (potentially due to genetic, illness or insult-related factors) may therefore profoundly affect cellular viability.

Do antidepressants and mood stabilizers have neurotrophic properties?

'Neuroplasticity' subsumes diverse processes of vital importance by which the brain perceives, adapts and responds to a variety of internal and external stimuli. The manifestations of neuroplasticity in the adult CNS have been characterized as including alterations of dendritic function, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and even neurogenesis (82).

There are several reports supporting the hypothesis that antidepressant treatment produces neurotrophic-like effects (78). Chronic administration of an atypical antidepressant, tianeptine, was reported to block the stress-

induced atrophy of CA3 pyramidal neurons (83) and to block other stress-induced changes in brain structure and neurochemistry (84). Male tree shrews subjected to a chronic psychosocial stress paradigm were found to have decreased N-acetylaspartate (NAA), a putative marker of neuronal viability (85), measured in vivo by ^{1}H-magnetic resonance spectroscopy (MRS), decreased granule cell proliferation in the dentate gyrus of the hippocampus and a reduction in hippocampal volume as compared to non-stressed animals. All these stress-induced effects were prevented/reversed in the animals treated concomitantly with tianeptine (84). However, the generalizability of these effects to other classes of antidepressants is unclear.

Elegant recent studies have demonstrated that another pathway involved in cell survival and plasticity, the cyclic adenosine monophosphate (cAMP)-cAMP response element binding protein (CREB) cascade, is up-regulated by antidepressant treatment (86). Up-regulation of CREB, a gene promoter, and one of its major targets, BDNF, occurs in response to several different classes of antidepressant treatments, and occurs in a time frame consistent with the therapeutic action of antidepressants (87). Furthermore, chronic, but not acute, antidepressant treatments have been found to increase the number of new neurons in the dentate gyrus granule cell layer. These effects have been observed with different classes of antidepressants, but not with several other psychotropic medications investigated (87). A role for the cAMP-CREB cascade and BDNF in the actions of antidepressant treatment is also supported by studies demonstrating that up-regulation of these pathways has effects similar to antidepressant medications in behavioral models of depression such as the learned helplessness and forced swim test models (88-90).

Several endogenous growth factors, including nerve growth factor (NGF) and BDNF, exert many of their neurotrophic effects via the MAP kinase signaling cascade. The net result of stimulation of this cascade is an increase in the transcription and/or activity of a number of cell survival proteins, such as bcl-2 and BDNF. It is thus noteworthy that recent studies have demonstrated that chronic lithium and VPA robustly activate the MAP kinase cascade in cells of human neuronal origin and in rat frontal cortex and hippocampus (91,92). Consistent with this activation, both treatments produced a *doubling* of bcl-2 levels in frontal cortex, an effect primarily due to a marked increase in the number of bcl-2 immunoreactive cells in layers II and III of frontal cortex (93). Interestingly, the importance of neurons in layers II-IV of the frontal cortex in mood disorders has recently been emphasized, since primate studies indicate that these areas are important for providing connections with other cortical regions, and that they are targets for subcortical input (94). Furthermore, chronic lithium also increases bcl-2 levels in the mouse hippocampus (95) and in cerebellar granule cells in culture (96), as well as VPA increases bcl-2 levels in human cells of neuronal origin (91).

Consistent with the neurotrophic and neuroprotective effects of MAP kinase activation and bcl-2 upregulation, lithium, at therapeutically relevant concentrations, has been shown to exert neuroprotective effects in a variety of preclinical paradigms. Consistently, VPA has been demonstrated to exert neuroprotective actions in cellular models as well, including glutamate toxicity, β-amyloid toxicity, and following exposure to other toxins (97-100).

Glycogen synthase kinase: a common target for mood stabilizers

Lithium and VPA regulate the activity of a crucial kinase that functions as an intermediary in numerous intracellular signaling pathways, the enzyme glycogen synthase kinase-3 (GSK-3), suggesting the importance of this enzyme in BD research (101,102). While lithium inhibits GSK-3 - a constitutively active and a highly conserved enzyme in evolution - by direct competition with magnesium for a binding site, the precise mechanisms by which VPA exerts its action is still uncertain (102-104). Other signals deactivating GSK-3 arise from insulin stimulation, developmental signals, and numerous growth factors (e.g. NGF and BDNF). Thus, growth factors may bring about many of their neurotrophic/neuroprotective effects, at least in part, by GSK-3 inhibition. Rapidly increasing evidence suggests that GSK-3 also plays important roles in regulating neuroplasticity and cellular resilience. GSK-3 phosphorylates - and thereby inactivates - transcription factors and cytoskeletal proteins (such as the Alzheimer's protein tau). Furthermore, changes in GSK-3 mediate MAP-1B (a cytoskeletal protein) phosphorylation, associated with the loss and/or unbundling of stable axonal microtubules. Finally, GSK-3β inhibition results in the accumulation of synapsin I, a protein involved in synaptic vesicle docking and release, at growth cone-like areas.

This evidence suggests that lithium's and VPA's effect on GSK-3 may play important roles in regulating processes such as synaptic plasticity and cell survival in the mature CNS. It is thus interesting that all of these processes have been implicated in the pathophysiology and treatment of BD (102).

Glutamatergic interventions: do they represent a neurotrophic strategy?

Another neurotransmitter system that has been implicated in regulating neuronal plasticity and cellular resilience in a variety of neuropsychiatric disorders is the highly complex glutamatergic system. In fact, glucocorticoids can induce the release of glutamate in the hippocampal CA3 region, and very high levels of type II corticosteroid receptor activation markedly increase calcium currents and lead to increased expression of N-methyl-D-aspartate (NMDA) receptor (a subtype of glutamatergic ionotropic receptor) on hippocampal neurons, that could predispose to neurotoxicity and finally atrophy. Interest-

ingly, NMDA blockade can prevent stress-induced atrophy in that region and it is thus noteworthy that recent preclinical studies have shown that the glutamatergic system represents a target (often indirect) for the actions of antidepressants and mood stabilizers (105).

Further evidence of the glutamatergic system involvement in mood disorders comes from brain imaging studies. These have shown that glucose metabolic signal, which correlates tightly with regional cerebral blood flow (CBF) during physiological activation, is likely to predominantly reflect glutamatergic transmission (106). PET imaging studies of BD patients have demonstrated abnormalities of CBF and glucose metabolism and, since projections from the regions involved in these abnormalities are glutamatergic, depression- and mania-related hypo/hyperactivity may be suggestive of either decreased (depression) or increased (mania) activation of glutamatergic cortico-limbic pathways. Thus, the hypothesis that a mood-stabilizing drug might modulate glutamate release or the consequences of glutamate release could be consistent with these data from functional neuroimaging studies.

There are a number of glutamatergic 'plasticity enhancing' strategies which may be of considerable utility in the treatment of mood disorders. Presently, lamotrigine and ketamine, two anti-glutamatergic agents, have shown to have antidepressant properties in bipolar and unipolar depression. Other agents - including NMDA antagonists, glutamate release reducing agents, and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors potentiators - are under development or currently being clinically tested (107).

Human evidence for the neurotrophic effects of mood stabilizers

While the body of preclinical data demonstrating neurotrophic and neuroprotective effects of mood stabilizers is striking, considerable caution must clearly be exercised in extrapolating to the clinical situation with humans. In view of lithium's and VPA's robust effects on the levels of the cytoprotective protein bcl-2 in the frontal cortex, Drevets et al re-analyzed older data demonstrating ~40% reductions in subgenual PFC volumes in familial mood disorder subjects (108). Consistent with neurotrophic/neuroprotective effects of lithium and VPA, they found that the patients treated with chronic lithium or VPA exhibited subgenual PFC volumes that were significantly higher than the volumes in non-treated patients, and not significantly different from controls (109). It should be noted that, in contrast to mood stabilizers, chronic treatment of patients with selective serotonin reuptake inhibitors did not have any effect on gray matter volumes. In a more recent study, Drevets and colleagues have investigated glial cell densities in mood disorder patients. Although the sample sizes are quite small, they made the intriguing observation that unipolar patients exhibited reduced glial cell densities, whereas only the bipolar patients off chronic lithium or VPA exhibited similar reductions (110). Considerable caution is warranted in view of the small sample sizes and cross-sectional nature of the studies.

To investigate the potential neurotrophic effects of lithium in humans more definitively, a longitudinal clinical study was undertaken using proton MRS to quantitate NAA levels. It was found that chronic lithium increased NAA concentration in the human brain in vivo (111). These findings provide intriguing indirect support for the contention that chronic lithium increases neuronal viability/function in the human brain. Furthermore, a ~0.97 correlation between lithium-induced NAA increases and regional voxel gray matter content was observed, thereby providing evidence for co-localization with the regional specific bcl-2 increases observed in the rodent brain cortices. These results suggest that chronic lithium may not only exert robust neuroprotective effects (as it has been demonstrated in a variety of preclinical paradigms), but also exert neurotrophic effects in humans.

In follow-up studies to the NAA findings, it was hypothesized that, in addition to increasing functional neurochemical markers of neuronal viability, lithium-induced increases in bcl-2 would also lead to neuropil increases, and thus to increased brain gray matter volume in BD patients. In this clinical research investigation, brain tissue volumes were examined using high resolution three dimensional MRI and validated quantitative brain tissue segmentation methodology to identify and quantify the various components by volume, including total brain white and gray matter content. Measurements were made at baseline (medication free, after a minimum 14 day washout) and then repeated after 4 weeks of lithium at therapeutic doses. This study revealed that chronic lithium significantly increases total gray matter content in the human brain of patients with BD (112). No significant changes were observed in brain white matter volume, or in quantitative measures of regional cerebral water content, thereby providing strong evidence that the observed increases in gray matter content are likely due to neurotrophic effects as opposed to any possible cell swelling and/or osmotic effects associated with lithium treatment. A finer grained sub-regional analysis of this brain imaging data is ongoing. The increased gray matter finding has recently been replicated in a cross-sectional MRI study: Sassi et al (113) found that lithium treated bipolar patients had a statistically higher cortical gray matter volume when compared either to non-treated bipolar patients or control subjects.

CONCLUDING REMARKS

A considerable body of data confirms that the amine neurotransmitter systems are dysfunctional in BD, explaining why they have become a common target for pharmacological interventions. However, conceptual and

experimental evidence suggests that abnormalities in the regulation of signal transduction cascades and neuroplasticity could more primarily underlie the pathophysiology of BD. This concept is becoming increasingly important when considering that, for many refractory patients with this disorder, new drugs simply mimicking the 'traditional' medications which directly or indirectly alter neurotransmitter levels and those which bind to cell surface receptors may be of limited benefit (114). Therefore, the existence of abnormalities in signal transduction pathways suggests that, for patients refractory to conventional medications, improved therapeutics may only be obtained by the direct targeting of post-receptor sites (e.g. CREB/BDNF/MAP kinase/bcl-2). Strategies to enhance neurotrophic factor signaling are currently under research and they hold much promise for the development of novel therapeutics for the long-term treatment of severe BD.

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The future of psychological therapies for psychosis

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The need for psychological therapies for psychosis is increasingly recognised. In recent years, two psychological approaches, cognitive behavioural therapy (CBT) and family interventions (FI), have emerged from among a range of psychological approaches as effective therapies with the strongest evidence base. The theoretical basis of these approaches, within a broader biopsychosocial stress-vulnerability framework, is described. The evidence of effectiveness, drawn from the results of recent systematic reviews of CBT and FI, is summarised. CBT is found to reduce symptoms and FI to reduce relapse, with some evidence of improvement in other outcomes for both approaches. Future directions for these therapies are considered, with particular emphasis on their role in early intervention services and relapse prevention. Promising newer applications of these approaches are also discussed, for example in work with people with a dual diagnosis of psychosis and substance misuse disorder. Finally, training and dissemination issues are addressed. It is emphasised that the integration of psychological therapies within comprehensive service provision is important.

Key words: Psychosis, schizophrenia, psychological therapies, family interventions, cognitive behavioural therapy

The need for psychological therapies for psychosis is increasingly acknowledged. There are a number of reasons for this. First, while antipsychotic medication has been the mainstay of psychiatric treatment and shows considerable benefits, it does not guarantee good outcome, being only partially effective or minimally effective in approximately 40% of cases (1). Secondly, adherence to antipsychotic medication is frequently poor, with up to 70% of individuals failing to take medication as prescribed (2). Thirdly, even when long-term antipsychotic medication is taken, a substantial proportion of patients will relapse (approximately 20% in one year) (3), the probability of which will be influenced by the social context, such as the nature of the family environment or the experience of life events (4). Finally, although medication may improve certain symptoms, it typically does not impact on a wide range of individuals' other concerns about their illness or experiences and often fails to remediate a number of other disabling problems, particularly of a social or cognitive nature.

In recent years, two psychological treatment approaches have particularly emerged as potentially effective therapies to be considered in the treatment of people with schizophrenia: 'family interventions' (FI) and cognitive behavioural therapy (CBT) (5). Two other approaches have been the focus of research activity, particularly in the United States: social skills training and cognitive remediation. The evidence derived from randomised controlled trials for these four approaches has recently been systematically reviewed, using meta-analytic techniques (6,7). In the UK, an evidence-based treatment guideline for schizophrenia has also just been developed, which reviews the evidence for these four psychological treatments together with three other distinct psychological approaches: psychoeducation, psychoanalytic or psychodynamic therapies and supportive counselling (8). When examined together, the evidence clearly indicates that CBT and FI have the strongest evidence base for effectiveness (5-8). In this paper, CBT and FI will be described and discussed; interested readers are referred to the foregoing references for detailed evaluations of the other approaches.

The rationale for psychological treatment approaches for psychosis does not only derive from the limitations of medication. Current conceptualisations of psychosis, within a stress-vulnerability framework (9), offer a positive rationale for their action (10). Here, psychosis is viewed as multi-factorial, and results from an interaction of a predisposing vulnerability (of biopsychosocial origin) with environmental stressors. The vulnerability factors include emotional difficulties, such as low self-esteem and social anxiety, cognitive biases or deficits, and biological factors of genetic and neuro-developmental origin (11). The stressors, such as stressful life events, hostile environments, psychoactive drugs or prolonged social isolation, affect both the cognitive and emotional processes of the vulnerable individual, causing changes such as anxiety or depression, and information processing difficulties and resulting anomalous experiences (e.g. hallucinatory experiences). These changes are disturbing and are actively interpreted by the individual; the resulting interpretations of the meaning of these changes to the self and of the triggering events lead to the fully formed psychotic symptoms. Similar processes then maintain the psychosis and, in addition, the experience and consequences of psychosis itself and its treatment may provide further maintaining factors, such as a reluctance to take medication or depressed mood and hopelessness.

It will be apparent how psychological therapies, whether aimed at the individual's ways of interpreting events and/or experiences and resulting beliefs and emotions (CBT), or at improving the atmosphere and coping of the family members (FI), are suited to addressing stress and vulnerability factors and may therefore be beneficial in the treatment of the psychosis. In this paper, I will describe CBT and FI approaches, discuss the current evidence for them and consider key future directions for psychological therapies.

THERAPEUTIC APPROACHES

Cognitive behavioural therapy

CBT for psychosis, which has been developed largely in the UK over the past decade, draws on two main sources: stress-vulnerability models of psychosis, as discussed above, and cognitive theory and therapy for emotional disorders (e.g. 12). CBT takes as its central focus the experiences of psychosis, that is, the symptoms and the individual's attempts to understand them. The main goal will be to help the individual to arrive at an understanding of the psychosis which is less distressing, and assist the individual in preventing reoccurrence or in managing any unwanted experiences and in developing as full and satisfying a life as possible (13).

The thoughts, beliefs and images experienced by people are the core material with which therapists work (14). The approach draws extensively on the cognitive therapy of Beck and colleagues, both in content and style. In style, the approach is collaborative and enquiring, aiming to work with the individual towards a new shared understanding. The content of therapy involves identifying key beliefs and thoughts, and reviewing evidence for these beliefs, identifying thinking biases and relating thoughts to mood and behaviour. The person with psychosis will be encouraged to try out new ways of behaving or thinking in 'homework' exercises between sessions. However, the standard cognitive therapy approach is modified to take account of the particular needs of people with psychosis and to be tailored to the cognitive model of psychosis and the stress-vulnerability framework. Modifications include taking longer over the early stages of therapy, so as to engage people who may be very suspicious or experience cognitive difficulties, and flexibility about session timing and length, to ensure that therapy sessions are not experienced as excessively stressful.

CBT for psychosis is delivered as a structured and time-limited therapy, although with considerable flexibility. Most studies have provided an average of about twenty sessions offered weekly to fortnightly over nine months, ranging from ten to thirty sessions over three months to two years. CBT is delivered alongside other services and medication, and is ideally integrated with the whole package of care, although it can be offered to people who do not engage in services or take medication. More detailed descriptions of the therapy are available (13,14).

Family interventions

FI also draw explicitly on the stress-vulnerability model of psychosis. The approach derives from the pioneering work of Brown, Leff and Vaughn in identifying the role of aspects of the emotional atmosphere in the family (criticism, hostility and emotional involvement - collectively termed 'expressed emotion', EE) in contributing to relapse (15). The first FI studies were published in the early 1980s (16,17) and the approach has been disseminated across the world in the twenty years since. FI have been primarily aimed at reducing the risk of relapse in a vulnerable individual, by altering one possible source of stress - the emotional climate of the family environment. It should be noted that, in this context, 'family' includes people who have a significant emotional connection with the person with psychosis, such as parents, siblings and partners.

This FI approach is described in detail by Kuipers and colleagues, who specify five basic assumptions (18):

1. Schizophrenia is seen as an illness with a biological origin within a stress-vulnerability model. Stresses might bring on the illness or relapse.
2. Families are seen as invaluable allies in care, and the formation of a therapeutic alliance with the family is seen as essential. Families are not blamed but enlisted as therapeutic agents, in order to help the patients.
3. There is an emphasis on collaboration and openness. Information about the illness is discussed, and together therapists and family members, including the patient, agree goals, priorities and tasks.
4. Families are seen to have needs and strengths.
5. The FI approach is offered alongside other interventions, including medication.

Overall, the aim of FI is to improve the family atmosphere and to reduce relapse. It typically involves a number of components. These are: the provision of information about psychosis (sometimes called 'psychoeducation'), improving coping with the affected member's psychosis by identifying problems and agreeing solutions, and helping the family members to communicate in a positive fashion and to set appropriate boundaries within the family. There is some variety in the way FI are provided (6). Some FI aim explicitly also to reduce the distress felt by the carers, rather than keeping a main focus on just the patient's outcomes. In such cases families may be seen without the identified patient present or in groups of relatives. Some FI involve very explicit communication or skills training, and, more rarely, some employ systemic or psychodynamic principles or methods. There is also considerable variability in the duration and frequency with which FI are delivered. Typically, FI are offered for about one year, although this may range from a few months to three years, with sessions fortnightly to monthly. Two therapists will generally be present in family sessions.

EVIDENCE OF EFFECTIVENESS

Cognitive behavioural therapy

Randomised controlled trials of CBT were first reported in the early 1990s and the research evidence base is small but developing rapidly. Pilling et al (6) report a meta-analysis of eight randomised controlled trials. When this review was updated by the UK National Schizophrenia Guideline Group, recent publication of new trials enabled a total of thirteen trials to be reviewed, including data on a total of 1293 patients (8). All the patients in these trials

were prescribed antipsychotic medication and most of the trials were targeted at individuals with long-standing or medication-unresponsive symptoms. Most of the studies (10) were conducted in the UK, while two were from the USA and one was from Israel.

Symptoms

The Schizophrenia Guideline review found that CBT reduces symptoms, both during treatment and at 9-12 month follow-up. This finding applied both when CBT was compared with treatment as usual and when compared to other psychological interventions, such as supportive counselling.

Relapse and suicide

There was insufficient evidence to determine whether CBT reduced suicide, with very low numbers of suicide in total reported. There was also insufficient evidence to determine whether CBT reduces relapse; however, there was evidence that CBT of longer duration (more than 3 months) is effective at reducing relapse.

Other outcomes

CBT was found to improve 'medication adherence' and improve insight. There was some evidence for improvements in social functioning.

Methods of delivery

Some evidence was found that CBT of longer duration (6-12 months rather than less than three months) and/or of more sessions (at least ten planned sessions) was more effective in symptom reduction. The reviewers also noted that the evidence was stronger for the treatment of people with persisting symptoms than for short treatments in the acute phase of the first episode of schizophrenia.

Family interventions

Pilling et al (6) also report a meta-analysis of the outcome data from 18 randomised controlled trials of FI, which involved a total of 1467 patients with a diagnosis of schizophrenia. Studies were conducted in a wide range of countries, dating back two decades. The mean age of the patients included was 31.2 years, 31% of the patients were women, and the mean number of admissions, reported in 13 of the trials, was 2.7. There were a number of different outcomes targeted by the FI and reported in the studies. Pilling et al report on relapse, readmission, suicide, family outcomes and adherence to medication regimes. This review was also used as the basis for the UK National Schizophrenia Guideline, whose authors updated and conducted some additional analyses of the data (8).

Relapse and readmission

It was found that there is strong evidence that FI reduce relapse rates during the treatment and at follow-up, up to 15 months after the FI ended. They are also effective at reducing admission to hospital during treatment, although not when the FI had ended. There is also evidence that FI are effective in reducing relapse both for people who have persisting symptoms and for those who have recently relapsed.

Other outcomes

There were no differences in suicide rates between FI and control treatments. There was evidence that medication adherence is increased by FI and that the family members' 'burden of care' was decreased by FI, when these were delivered to single families rather than groups of families. There was insufficient evidence to indicate whether FI reduce psychotic symptoms; many studies did not report any symptom data.

Methods of delivery

The Schizophrenia Guideline (8) reports on analyses of different methods of delivery. Stronger evidence was found for relapse prevention with programmes of longer duration (6 months or longer) and a greater number of sessions (ten or more planned sessions). The evidence was also stronger for relapse prevention when the service user was included in the sessions.

Summary of evidence

These systematic reviews have demonstrated that both CBT and FI, under the conditions of research trials, are effective for certain key outcomes. Consistent with the stated key goals of these approaches, CBT reduces symptoms and FI reduce rates of relapse. Both approaches also show some evidence of benefits for certain other outcomes under certain conditions - CBT for insight, relapse, medication adherence and social functioning, and FI for medication adherence and relatives' 'burden of care'. The evidence concerning CBT is overwhelmingly UK based and predominantly relates to people with persisting symptoms, while the FI evidence base is more international and is drawn mainly from relapsing and persisting symptom groups. There is a great deal that is yet to be investigated. It is to the future of these psychological approaches that I now turn.

FUTURE DIRECTIONS

Early intervention

The evidence reviewed here raises further questions. First, there is the question of which patients are helped by these methods. Globally, there is currently considerable interest in the early identification and treatment of people

with psychosis. Stimulated by the pioneering work of McGorry and colleagues in Melbourne, Australia, a worldwide movement has developed for the establishment of services for early psychosis (19). This constitutes two elements - the early identification and (possible) treatment of people at high risk of developing psychosis, and the early identification and treatment of people who have a diagnosable psychosis. Interventions with 'high risk' groups, identified by being a first degree relative of a person with psychosis and/or the presence of prodromal symptoms or brief psychotic symptoms (20) are currently research based. A number of trials of CBT to prevent transition to psychosis, with or without low dose antipsychotic medication, are underway (21-23). The early reports suggest that a CBT intervention, alone or in combination with medication, may delay or prevent transition to psychosis in a proportion of people.

In the UK, the comprehensive first episode services which are being set up frequently incorporate psychological approaches, most commonly CBT and FI, alongside medication, and other psychosocial approaches, such as vocational and social programmes (24,25). It is not yet clear what the place of CBT and FI in such services should be. For example, should either or both psychological approaches be routinely offered to all or should they be targeted at certain groups, such as those with persistent symptoms or relapses? The evaluation of these specialised services for early psychosis is at an early stage, with no randomised controlled trial of an integrated comprehensive first episode service yet published, and teasing apart the different treatment components will prove difficult. There have, however, been a very small number of published trials (and even fewer randomised controlled trials) of CBT or FI in early psychosis in the context of more standard inpatient or community services. Those that have been published concerning first episode treatments have not yet yielded very strong positive findings. Two studies of a CBT approach, one focussed on the acute inpatient stay (26) and the other on community follow-up, where only some participants received specialised first episode services (27), show only modest and temporary benefits. However, we do have some data from a pilot study of CBT and FI for first episode patients in an adolescent inpatient unit, which suggests clear benefits in terms of symptom reductions from CBT and social functioning improvements with FI (28). Another study, which combined an individual psychosocial approach with FI, in both the inpatient and the community follow-up phases of care, did not find clear benefits of relapse reduction from the FI (29). One possible reason for the failure to find a specific benefit for the psychological intervention in these studies is that a high proportion of these first episode participants are improving considerably with medication and other interventions, and thus the additional benefits of specific psychological interventions are relatively small or subtle and difficult to detect; alternatively, they may not confer additional benefit at this stage for most and, as a scarce resource, should be targeted at sub-groups with specific needs. However, we are at the early stages of this research effort and more evidence will help to determine the place of psychological interventions with this first episode group.

Relapse prevention

A second group to consider is those who experience repeated relapse. This is in contrast to the people with relatively stable persisting symptoms who have been included in many CBT and FI studies; the evidence suggests these patients with persisting symptoms are helped by both approaches, but with different outcomes - reducing symptoms and relapse, respectively. People at high risk of relapse have been selected for FI studies, but no CBT studies have yet been published with this group. However, Gumley et al (30) report one such study and demonstrate significant reductions in relapses with a CBT intervention designed for this purpose. This, together with the systematic review evidence suggesting relapse reduction benefits with CBT (8), raises the question as to the relative merits of FI and CBT in reducing relapse.

Other groups and targets for intervention

There are a number of other sub-groups of people with psychosis for whom psychological therapies may be beneficial. A variety of promising new applications of these therapies are being developed. Barrowclough et al (31) have shown benefits for the important group of people with 'dual diagnosis' (co-existing substance misuse and psychosis) from a combined motivational interviewing, CBT and FI approach. In contrast to a focus on particular sub-groups, some CBT approaches have been successfully targeted on certain specific outcomes. For example, Mueser et al (32) have documented high rates of trauma and post-traumatic stress disorder (PTSD) in people with psychosis. They have subsequently piloted a modified CBT approach for PTSD symptoms in people with psychosis, which was demonstrated to be feasible and promising. Other specific targets for which CBT has been shown beneficial include medication adherence (33) and insight (34). One further aspect which is under development is the treatment of low self esteem and depression in psychosis (28,35,36). In this rapidly developing field, we can expect new findings over the next five to ten years, from treatment studies and from theoretical and empirical research into aspects of psychosis, which will offer an impetus for the further refinement of CBT and FI.

Training and dissemination

In general, CBT and FI were originally developed by qualified clinical psychologists and psychiatrists, often with considerable experience of clinical practice, therapy

and research in psychosis. In the research trials which have established efficacy, interventions have followed therapeutic manuals and supervision has typically been intensive. As these approaches have been disseminated more widely, other mental health professionals, with a variety of training backgrounds, have taken on this work. Formal training courses have been developed in some countries, although there is not as yet a clear consensus on required training. Furthermore, there is evidence that training alone may not be sufficient to ensure effective implementation (37). In consequence, Tarrier has argued that the organisation and management of training and services need to be planned and evaluated to ensure that staff are adequately skilled to offer systematic therapeutic interventions. It is also important to ensure that they have time to see patients regularly and receive skilled supervision.

While CBT for psychosis is a relatively new approach, only recently expanding beyond the confines of research settings, FI have been established as effective for over a decade, and services in many countries have attempted to disseminate the FI approach into routine practice. There has been considerable difficulty with this, at least in UK (38). In addition to the practical difficulties of delivering interventions with a family group, as opposed to individuals, another reason for this may be the changing nature of family structures in some countries. In urban settings in Northern European countries, there is growing evidence of fragmentation of family ties and higher levels of separation and isolation. In one multi-centre European study of the care of people with serious mental illness, between two thirds and one half of the patients in the Northern European centres lived alone (39). FI can be conducted with family members not living together, if in close contact, but may not be applicable when contact and care-giving is less. For these reasons, in certain cultures, individual therapies such as CBT may be more practicable in many cases.

CONCLUSIONS

The current evidence confirms that FI are effective at reducing relapse in psychosis and that CBT is effective for symptom reduction. A variety of other benefits and new applications are suggested by current research, and thus both approaches are likely to play leading roles as psychotherapies for psychosis in the future. There are many potential areas for development, most notably, perhaps, in the treatment of co-existing substance misuse and in the growing field of early intervention. However, other targets for these approaches should not be neglected, such as relapse prevention or the treatment of depression and trauma. There is no suggestion, in most of their applications (except perhaps with 'high risk' groups - see 40), that these psychological therapies will stand alone. There are a number of other important therapeutic elements, medication certainly, but also the provision of a range of social activity, leisure and work programmes. It is likely that CBT and FI will best meet the wider goals of improving outcomes for patients, in ways which are accessible and acceptable, when they are effectively integrated within comprehensive services.

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Psychiatry and primary care

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There is now almost universal recognition that primary care is the place where most mentally distressed people first present for help. However, the pace at which the health system has adapted to this reality varies greatly from country to country, depending on the amount of resource devoted to mental illness services, the way in which primary care physicians have organized their practice, and the inertia of the system. Here we present several models from developed and developing countries and address briefly the issue of training of health workers.

Key words: Primary care, general practitioners, community mental health teams, multi-purpose health workers, training

The de-institutionalisation of the mentally ill has partly been driven by humanitarian impulses, but partly by financial necessity. Developed countries, faced with an ageing population and the demands of high-tech medicine, have closed their large mental hospitals and mental subnormality hospitals; developing countries, faced with the realisation that basic medical services were not reaching much of the rural population, have looked for alternatives in the community as a way of providing basic mental illness services. The large mental hospital in the capital city, dating from colonial times, seems a poor way of doing this.

Whatever the reasons, the results have been the same. An increasing burden of care of those with severe mental disorders has fallen on primary care physicians. But there has also been another, powerful reason why this has been so. The public health burden on a population posed by common mental disorders far exceeds that of severe mental disorders, but it has only been in the past 50 years that this has been widely appreciated (1).

However, the pace at which some changes have occurred varies greatly from country to country, and this variation is partly determined by the amount of resource devoted to mental illness services, partly by the way in which primary care physicians have organised their practice, and partly, of course, by the inertia in any professional system.

CHANGES IN THE UNITED KINGDOM

Fifty years ago, most primary care physicians worked on their own, usually helped by a part-time secretary/ receptionist.

Today doctors work in groups of about six or eight, and they are assisted by many other staff: practice nurses, district nurses, health visitors, receptionists and a practice manager.

The government now looks upon primary care as the key player in deciding health expenditures, and most of the money for health care is given to groups of between 40 and 60 primary care physicians called 'primary care trusts' (PCTs). These have been given most of the resource for health care for the population registered with them. They must pay for all services in primary care, as well as purchase general hospital care and mental health care directly on behalf of their patients.

Even before these fundamental changes in funding, however, mental illness services were working much more closely than they previously did with primary care, and patients in the community with chronic, severe mental disorders would have their care shared between community mental health teams (CMHTs) and primary care.

As early as 1984, Strathdee and Williams (2) described the fact that 19% of English psychiatrists were providing clinics in primary care as "the silent growth of a new service", and by the following year Pullen and Yellowlees showed that 50% of Scottish psychiatrists were doing the same. More recently, Gask et al (3) have described four main ways in which psychiatrists can relate to general practitioners (GPs) in such clinics, and also described attachments by community nurses, clinical psychologists and social workers in primary care. The first is a close association with the CMHT with a single point of referral from primary care, and much closer integration of services between them. The second is the "shifted outpatients" model. The third is the attachment of various members of the CMHT to do clinics in primary care. Finally, the "consultation-liaison" model has the psychiatrist discuss difficult cases with members of the primary care team, and sometimes see patients with them - but the patients remain with the primary care team.

Jackson et al (4) described how CMHT services can relate directly to primary care, and carried out a cost-effectiveness analysis showing that patient satisfaction was greater in such clinics, and the mean cost per case was less. However, the new service resulted in four times as many patients with common mental disorders receiving treatment, so the overall costs of the new service were about the same (5).

The conventional CMHT relates to

primary care in an unsatisfactory way, since new patients are assigned to community nurses depending on which nurse has the smallest caseload, having regard to the degree of experience that the new patient requires from the nurse. This typically results in a system in which each community nurse looks after a set of patients who are under the care of many different GPs, so that a close working relationship between GP and community nurse is difficult to sustain.

Goldberg and Gournay (6) argued that most mental disorders should be looked after in primary care, with severe mental disorders (schizophrenia, bipolar illness and dementia) jointly under the care of mental health services with a "shared care" plan, and other disorders treated by primary care services unless they failed to respond to treatment from the GP. It was suggested that severely ill patients under the care of a particular GP should all, as far as possible, be cared for by the same mental health worker - who would therefore act as a "link worker" between the two services. It would be the responsibility of this worker to act as a culture carrier between the two services, and be responsible for keeping the shared care plans up to date.

In this changing context the Royal College of Psychiatrists (7) commissioned a survey of both PCTs and mental health trusts, asking to what extent they were working together, and how they saw services developing in the future. This revealed that about 68% of PCTs had 'shared care plans', and that GPs contributed to these plans in 84% of them. A shared care plan is drawn up for each patient with a severe mental disorder (schizophrenia, bipolar illness or dementia) treated by the CMHT in the care of the practice, and is jointly agreed by the two services. It states - among other things - the diagnosis, treatment plan, drugs prescribed and who prescribes them, alternative drugs, likely symptoms in relapse and name and contact details of the 'key worker' (or link worker) in the CMHT.

Of the 59 PCTs replying to the question, it was of interest that 11 had now altered their practice to the pattern of working with a single 'link' worker relating to each GP. Of these, 91% were satisfied with the collaboration, compared with only 54% who had the traditional arrangements (Fisher's exact p-value = 0.038).

The most striking finding of the survey was that over 90% of both PCTs and mental health providers predicted that the routine care of well controlled cases of schizophrenia and bipolar illness would pass to primary care in the future, with assistance only sought from the mental health services should need arise.

Closer collaboration between the two services can bring advantages to patients, to primary care staff and to mental health staff. In one study, patients reported much greater satisfaction with the service based in primary care compared with controls seen by the hospital based service, GPs were pleased to have specialised treatments made available to the patients who had failed to respond to first line treatment, and mental health staff were pleased to have access to a wider range of patients than the dangerous and disruptive psychotic patients that may form the bulk of routine referrals to a specialised service (5). Some studies have shown a reduction in admission rates to psychiatric inpatient beds as a result of closer working (8,9), but others have not found this effect (4,10).

Other ways of improving collaboration between the two services include shared care registers (11). These include all patients on prolonged psychotropic drugs as well as those with severe mental disorders, and the use of electronic referrals and transfer of information between the two services.

PATTERNS OF COLLABORATION BETWEEN PRIMARY CARE AND MENTAL HEALTH SERVICES

When group practice is the norm

In some countries, like Sweden, Denmark and the UK, and in health maintenance organisations (HMOs) in the USA, doctors work in group practices accompanied by many kinds of primary care workers: these include practice nurses, practice managers and a variety of other health technicians, which vary from place to place.

In these countries, with the smaller number of GP surgeries to serve, it becomes practicable for mental health professionals to work collaboratively with primary care workers on the practice premises. Thus, not only psychiatrists and clinical psychologists, but also community psychiatric nurses offer clinics as part of the primary care services. These developments are possible because a given community mental health service (CMHS) has a small number of group practices in the area that they serve.

Thus, closely integrated services have been described by Kates et al in Canada (12) and the benefits of closer working have been described by Katon et al (13) in an HMO in Seattle. Benefits of closer integration of services were only seen with more severe cases of depression, with usual care by the GP being just as effective with mild depression. Schulberg et al have shown real advantages of treatment by psychiatrists, albeit in a selected group of patients, and with more intensive psychiatric input (14).

Simon (15) has described various ways in which psychiatrists can supplement the work of primary care physicians, and argues for a 'minimal effective dose' of psychiatric intervention, targeted on the more difficult cases.

In Iran, an entirely different pattern of collaboration is represented by having a tier of service below primary care, with responsibilities for both physical and mental disorders. These are called 'health houses', and health workers manning them screen the people living near them for four common mental disorders (called minor mental illness), major mental illness, mental retardation and epilepsy, as well as recognising stress related conditions and using simple stress reduction methods. Cases are referred by them to the group prac-

tices in health centres, and cases given treatments are followed up in the health houses (16).

When single handed practice is the norm

In contrast, a close working collaboration is more difficult in countries where doctors work on their own, usually accompanied only by a receptionist, as there are too many of them for the CMHS to relate directly to all of them on the practice premises. In countries such as France, Germany and much of the USA, primary care services and CMHS are virtually independent services, which relate to one another by means of formal referrals.

Gersons (17), for example, has written of the intrinsically competitive relationship between mental health and family practice, since in a fee for service system they are both competing in the same market. Quoting Balestrieri et al's (18) earlier finding that mental health treatment only produces results that are 10% better than those in primary care, he writes "it is not surprising that a number of GPs doubt the need for special training by psychiatrists or for increasing their referrals to the mental health system".

However, in some countries with predominantly single handed practitioners there is now a movement towards closer collaboration, and this can take a number of forms. In Warrnambool, in Victoria, Australia, the CMHT prescribes only for patients while they are in the inpatient unit. All medical treatments are under the supervision of the GP, so that the mental health staff are only involved in psychological and social interventions, with the aim always being to make the patient independent of the service, so that any ongoing treatment is the responsibility of the GP. Patients are seen over a wide predominantly rural part of Australia, and GPs feel themselves intensely involved in the service.

In Bologna, Italy, because of the single handed working habits of GPs, it was not possible to introduce the kinds of within-practice clinics described in the earlier section: instead, the CMHS has set up a primary care liaison service (PCLS), that is based on the CMHC and has a staff of two psychiatrists and a psychologist who provide GPs with a prompt written report about patients referred to them. Shared care interventions include the initiation of pharmacological treatments, the provision, where necessary, of short-term psychotherapy and the availability of a telephone liaison service (19). Regular meetings are held with the GPs concerned with improvements to the service, and continuing education courses are provided. Most patients improved on 6 month follow-up, attendance at the GP's office tended to decrease, and 93% of the GPs expressed moderate or marked satisfaction with the service.

The developing world

The colonial era left many developing countries with only a small number of indigenous psychiatrists mainly concentrated on the capital city, and often served by a single large mental hospital. Such services left the majority of the population without access to any kind of mental health service, so that it became clear that an altogether new approach to the provision of services needed to be made. The World Health Organisation (WHO) set up such services in general medical clinics in four developing countries, with training to medical officers and multipurpose health workers in basic mental health skills, and support from interested local psychiatrists (20).

The supply of psychiatrists in developing countries is very much smaller than that in the developed world (typically below 0.4/100,000 versus 9-25/100,000 [21]), and virtually predicates that primary care must be the main provider of mental health care for all forms of disorder. However, many developing countries are not only short of psychiatrists - they are short of physicians. These shortages are especially acute in many African countries, some countries in the East Mediterranean Region, and some countries in South America (22).

This has meant that many countries - for example, Tanzania (23) - have found it necessary to train a cadre of assistant medical officers to carry out basic triage in primary care. The bulk of the additional mental health burden in most developing countries is taken up by multi-purpose health workers (MPHWs), who fulfil the function of community psychiatric nurses in the developed world, albeit with many additional functions in general health.

Shortly after the WHO had set up its first pilot project, the general model was proposed by Wig et al (24), and has since been introduced in most places where there are shortages of resources, and large numbers of the population have little or no access to psychiatric services (25).

Inevitably, the model has been adapted to fit local services, the availability of pharmacological agents, and the public health burden posed in each country. Wang et al (26) describe a three tier system in a rural area in China, with 'village health workers' at local level referring patients to medical officers in local clinics, with overall supervision from the county hospital. Services in South America are described by Levav et al (27), and Brazilian services are described by Iacoponi et al (28).

In both India and Pakistan, community mental health services are delivered at village level in primary care, but both governments have produced multiphase plans for the eventual provision of mental health services to the greater part of their vast populations. In India, Murthy (29) described that the major task is to implement district CMHS to provide cover and advice for the medical officers in the field, themselves supported by small psychiatric units in the local general hospital.

In Pakistan, Mubbashar (25,30) describes a well developed and highly ambitious system supported by major training initiatives. These extend well

beyond the basic need for medical officers and MPHWs, to the provision of training to lady health workers, to local religious healers and to public health physicians. Somewhat similarly to Iran, the lady health workers have a broad remit within mental and general health, and each have 100 local families to see annually in their house, which is re-designated as a 'health house'. They are trained to refer potential cases to the local basic health unit, where more experienced staff are available to offer treatments. The mental health service has also been extended to the schools, and research has demonstrated the effectiveness of this action (31). Mental health case finding in rural Pakistan is performed by MPHWs on their door to door visits, by local religious healers, and by school children alerted by the schools programme. It is also given a fair wind by public health administrators and the local mullahs.

THE WPA TRAINING PACKAGE ON DEPRESSION

The World Psychiatric Association (WPA) has produced a set of training packages on depression (8), and has recently added a skills learning package for general practitioners and physicians. This uses videotapes to model desirable behaviours using real general practitioners and role-played 'patients'. The videotapes are accompanied by an explanatory commentary, and followed by role-plays, where general practitioners have an opportunity to rehearse the behaviours they have seen on the tape. The videotapes supplied with the package were made by GPs in Manchester and London and deal with depression, unexplained somatic symptoms, psychosis, chronic fatigue and dementia. The intention is that teachers in other countries should make their own tapes, in the idiom of their own country.

The Virtual Group

Teachers in 13 countries have been recruited into a 'Virtual Group', which communicates by e-mail. These include Australia, Austria, Denmark, Holland, India, Italy, Pakistan, Romania, the Russian Federation, Singapore, Spain, the USA and the UK. The opportunity has been taken to discover the nature of changes in respect of mental illness services in each country. Teachers were asked to give details of the way in which mental health and primary care services related to one another in each country, and in particular whether cases of seven common mental disorders would be treated in primary care or would be referred to mental illness services.

In 11 of these countries mental health services were free at the point of delivery, but in Australia and the USA there is only partial reimbursement of fees.

Shared care between mental health services, reported by 68% of primary care trusts in the UK, was said to be 'sometimes' present by our respondents in Australia, Holland and Spain, and by some of the respondents in Denmark and the USA: it was rare or absent elsewhere.

It was evident that mental health staff are now working directly in primary care in many different places: only Austria, Italy, Romania, Russia, Singapore, Spain and some Danish respondents reported that no such clinics took place in their country. Psychiatrists were reported as doing clinics within primary care by Australia, Holland, Spain, the USA, the UK and by some Danish respondents; psychologists by Australia, Holland, Pakistan, the USA and the UK; psychiatric nurses by Holland, India, Russia, Singapore, the USA and the UK.

Home visits by mental health staff at the GP's request were reported as not available in India and by some of our respondents in Australia and the USA. Everywhere else they were available, usually by both psychiatrists and community nurses, but in Singapore and Spain only by nurses.

Respondents were asked whether cases of seven different disorders were usually treated in primary care, or would be routinely referred to the mental illness services. The seven conditions were acute episodes of depression, depression that has not responded to first line treatment, phobic illness, acute psychosis, chronic schizophrenia in stable clinical state, chronic bipolar illness in stable clinical state and drug dependence.

There was general agreement, in all countries, that new cases of acute psychosis, cases of drug dependence, and treatment resistant depression should be referred to mental illness services. Everywhere except in the Russian Federation and Romania acute episodes of depression would be treated in primary care.

However, there the resemblance ends. Cases of phobic illness, and bipolar illnesses in remission, are treated in primary care in five of the countries, and cases of well-controlled chronic schizophrenia are treated in primary care in the UK, Austria, Pakistan, Spain and some of our informants in USA, Denmark and Australia. Even if some of the informants have painted an over-optimistic picture, it is clear that the UK is not alone in transferring much routine care of chronic patients to primary care.

FINAL COMMENTS

There is now almost universal recognition that primary care is the place where most mentally distressed people first present for help, and also an acceptance that, even in physical disorders, the proper psychological management of distress is an important component of treatment. Most medical schools throughout the world do not provide enough instruction to future physicians in the management of common mental disorders, preferring to emphasise the much rarer major mental disorders. Those entering general medical practice therefore have an unmet need for supplementary training, and the speed at which the Virtual Group acquired enthusiastic members is testament to this need.

As has been emphasised, the training need goes well beyond the ranks

of physicians, and extends to community nurses and social workers in developed countries, and to MPHWs and health workers of various sorts in developing countries. The need is great, but is poorly met by the provision of textbooks backed up by didactic lectures, because clinical skills are not learned in either of these ways. Fortunately newer teaching methods can provide demonstrations of clinical skills followed by practice in role-played sessions. Other methods - such as asking a doctor to become their own most difficult patient, and getting another doctor to interview him or her in front of a class - are also very effective.

The prospects for the mentally ill have changed almost out of all recognition in the past 50 years, with the availability of more effective psychological interventions, as well as more powerful and less toxic drugs. The medical services are slowly availing themselves of more effective teaching methods, and widening the remit of providing care well beyond their own ranks. These changes, accompanied by the greater availability of self-help manuals, support groups and non-governmental organisations assisting in the provision of chronic mental health care, offer a future of unprecedented hope to those in mental distress. And hope is probably the most important of all therapeutic ingredients.

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Improving the filter between primary and secondary care for mental disorders

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Almost 25 years ago, Goldberg and Huxley described patterns of recognition and treatment for mental disorders using the concept of filters separating different levels of care (1). We might view David Goldberg's introductory paper in this Forum as a guide to improving the functioning of the filter or interface between mental health specialty services and primary medical care. This guide contains several principles for the optimal functioning of that filter.

First, the filter or border zone separating primary and secondary care should be broad - a gradual transition rather than a sharp boundary. In fact, the optimal border region might cover as much territory as the two nations it separates, the regions devoted exclusively to primary or secondary care. David Goldberg describes several models for primary care and specialty services to share responsibility for both common and more severe mental disorders.

Second, the filter should be sensitive to clinical need. The primary factor determining level of care should be severity of symptoms and degree of impairment. Because severity of illness varies considerably over time, regular monitoring of clinical condition is necessary for appropriate triage.

Third, the filter should be freely permeable in both directions. Given that clinical need varies over time, level of care should vary according to need - with relatively low barriers to transitions upward or downward.

Fourth, the filter should be relatively insensitive to non-clinical factors. Unfortunately, access to higher levels may be overly influenced by non-clinical factors such as insurance coverage, ability to pay, race, or social class. A well-functioning filter would ignore these factors and might, in some cases, actively work to circumvent barriers to appropriate care.

Fifth, the filter should be sensitive to local resources and constraints. Optimal criteria for specialty consultation or referral will vary widely depending on the availability of specialty services. In other words, the marginal benefit of specialty involvement may often be positive, but limited specialty resources must be reserved for situations in which they produce the greatest good.

Sixth, the filter should be sensitive to the particular strengths of primary and secondary care. In general, primary care has the advantages of easier access, long-term continuity of care, and coordination across multiple health conditions. Advantages of specialty care include greater expertise, focus, and (in some cases) efficiency due to a narrower scope of practice. The relative importance of these factors will vary between patients. For example, the advantages of primary care management might be greatest for a patient with comorbid chronic medical illness and a long-standing relationship with the primary care team.

Others have used the term 'stepped care' to refer to organized care adjusted according to severity of illness and response to initial treatment (2,3). David Goldberg's paper describes several promising stepped-care models for a range of health care environments.

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Can medical practice adapt to a changed world?

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In this issue of World Psychiatry, Sir David Goldberg outlines why, over the last fifty years, primary care has become the modal care setting for common mental disorders, and why it is likely to assume an increasingly important role in caring for persons with chronic, severe mental disorders. Like other common chronic medical conditions (e.g. diabetes, asthma, heart disease), there is an epidemiological imperative for care of most persons with common mental disorders to occur in the primary care setting (1). This is due to the sheer numbers of persons with these disorders, the relative accessibility of generalists versus specialists, and the preference of many individuals for care from their personal physician.

The last fifty years have witnessed revolutionary societal and technological changes that have accelerated community care of mental disorders in primary care settings. In the 1940s, the monthly cost of mental hospital care and of income maintenance programs for the disabled were roughly equal. Hospital care became prohibitively expensive relative to disability

payments in the ensuing decades, accelerating the trend towards community placement of the severely mentally ill. Effective drug treatments for schizophrenia, major depression and bipolar disorder were discovered mid-century, while the diversity of effective drug treatments for these disorders increased markedly in the 1970s and 1980s. Publicly financed health insurance emerged in the wake of the Second World War, and expanded rapidly thereafter, contributing to a rapid increase in use of medical services. The number and diversity of mental health professionals increased dramatically, insurance coverage for psychiatric treatment became common, and the general public became more accepting of mental health treatment. Over this fifty year period, effective drug treatments were discovered for a wide range of chronic conditions, making medical practice more complex and more essential for health maintenance of the chronically ill, including persons with mental disorders. We are now witnessing the emergence of consumerism in health care, including increased emphasis on shared decision-making, activated patients, patient-rights organizations, and (in the United States in particular) direct marketing of drugs and other treatments to the general public.

In the face of these revolutionary societal and technological changes that have transformed the context of health care, the practice of medicine has remained mired in traditional, ineffective practices. Physicians continue to embrace traditional ways of organizing and providing care despite extensive research showing that routine care is of embarrassingly poor quality (2). Patients prescribed medications for ongoing management of major chronic disorders typically take less than half of the prescribed dose (3). It is commonplace for less than half of the patients started on a new treatment regimen to carry out the treatment in a manner that satisfies evidence-based guidelines. Generalists and specialists remain wedded to the traditional medical encounter in which diagnostic evaluation and initial treatment selection are emphasized, while monitoring treatment over time is left to chance. Care is not organized to ensure active follow-up of chronically ill patients over time, to tailor treatment regimens to patient differences in treatment response or side effects, or to support patient self-management of complex therapeutic regimens (4).

To improve care of chronic conditions, primary care physicians need stronger support from specialists in managing complex cases, and from allied health professionals to ensure active follow-up and to fully engage patients in self-management of their illness (5). Unfortunately, specialty practice too often remains isolated from primary care in hospitals and specialty centers, with structural, cultural and economic barriers to closer collaboration with primary care physicians. Well organized care management services for patients with major chronic conditions remain the exception rather than the rule. David Goldberg points to progress in the integration of specialists and allied health professionals into primary care in the United Kingdom, but the scope of these changes is not yet in proportion to the magnitude of the problem. Innovations in care in the United States trail far behind developments in the United Kingdom, despite substantially greater per capita spending on health care in the United States.

It is only human nature that physicians are wedded to traditional ways of organizing and delivering care, despite abundant evidence that traditional ways of practicing medicine are seriously deficient. Changing deeply ingrained practices in professional organizations is difficult and slow. Traditional medical practice is failing to meet the needs of chronically ill patients, those with medical as well as those with psychiatric illnesses. If the health of chronically ill patients is to be maintained, fundamental changes in the organization of medical care are needed to ensure that patients are able to achieve the best long-term outcomes possible with available treatments.

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Five decades of research on psychiatric morbidity in primary care

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The extent and magnitude of minor psychiatric disorders in primary and general practice was first demonstrated by Michael Shepherd in the middle of the last century. At that time no research instruments were available in the field, psychotropics were unsafe and the doctor was much of the drug. David

Goldberg made the important contribution of leading the research teams that developed two main instruments to be applied in primary care: the Clinical Interview Schedule, a semi-standardized psychiatric interview, and the General Health Questionnaire, a short screening questionnaire for minor psychiatric disorders. Some years later, the World Health Organization supported the development of its own screening questionnaire, the Self Reporting Questionnaire (1). All these instruments were widely applied in general practice across the world, showing that minor psychiatric disorders have even more importance and impact than severe mental disorders. This is now well established and we owe this achievement to Shepherd, Goldberg and others, who were pioneers in the use of epidemiology for completing the picture of psychiatric morbidity in the community.

It was striking that research carried out in primary care in Brazil did demonstrate that 50% of patients attending general practices in the city of Sao Paulo present a minor psychiatric disorder (2). Moreover, general physicians were found to be the main prescribers of tranquilizers in a psychiatric morbidity survey in the city of Sao Paulo (3). All studies conducted in Brazil show that low income families have an excess of morbidity, and Lima et al (4) demonstrated an inverse relationship between level of income, schooling and prevalence of minor psychiatric disorders, but a positive relationship between income and consumption of benzodiazepines. The role of social inequality and social adversity in the development of a cluster of diseases, such as minor psychiatric disorders, post traumatic stress disorders, drug dependence, needs more attention and research as well as the development of efficacious interventions for reducing burden and suffering in developing countries.

How to integrate mental health community services with primary care physicians is still a matter of controversy. There are a variety of models described (5), but there has not been yet an agreement on what should be treated by whom. As mentioned by Goldberg, there is a certain agreement that acute psychosis, cases of drug dependence and resistant depression should be treated by mental health staff. The example of England, where psychiatrists started to provide clinics in primary care (6), sounds as a good model for interaction to be pursued anywhere in the world. However, it has not been demonstrated that such integration would produce a decrease of admission rates to psychiatric hospitals, and research on cost-effectiveness of such models is still incipient. Middle income countries like Brazil face the problems of scarcity of services and paucity of information as well as huge difficulties in health services management. Even in the richest state of the country, the State of Sao Paulo, it was shown that the majority of patients with schizophrenia remained untreated in a one year period (7). As recently pointed out by Kleinman and Han (8), the evaluation of intervention programs (i.e., of the development of new models of service delivery) is the most important direction for future research in developing countries.

The important role general physicians play in the mental health field is now more than evident, but epidemiological evidence solely has not had a major impact on medical education and physicians' attitudes. The treatment of minor psychiatric disorders in primary care and general practice is a relatively new field in medicine, despite the increasing research in the area. Indeed, models to teach physicians to deal with ordinary, psychosocial problems at the primary care level are still in their infancy and much has to be done for their implementation and testing.

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Integrating depression treatment into primary care for common medical illnesses

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Integrating psychiatric and psychological treatments into the bedrock of medical management for common chronic illnesses can increase access and enhance patient outcomes in general medical settings. As Sir David Goldberg highlighted in the introductory paper for this forum - primary care physicians (PCPs) have been shoulder-

ing an increasing burden of care for mental disorders over the last few decades. Yet, additional demands for PCP services are not limited to mental disorders. Primary care physicians are increasingly compelled to provide a higher volume of and more complex services to patients with common medical illnesses such as diabetes, heart disease, and arthritis. Care of patients with depression, the most common mental disorder in primary care, can help illustrate challenges and potentially efficient next steps to better serve patients who seek care in this interface of medicine and psychiatry.

Sir David Goldberg and colleagues helped launch the research discipline on common mental disorders in general medical settings over 25 years ago (1). Depression's toll on personal suffering, disability, medical and societal costs has been documented eloquently around the world (2,3). Recent research on older adults with depression in the US describes a population with many medical co-morbidities, significant disability and largely unmet mental health needs (4). Depression is more prevalent in patients with chronic medical diseases. Moreover, co-morbid depression is associated with worse medical outcomes (e.g. diabetic complications, mortality following myocardial infarctions) (5).

Unfortunately, a quality chasm separates depression care available in usual primary care from treatment guidelines for efficacious management of depression (6). Primary care physicians face competing demands such as comprehensive services for an increasing number of disorders, acute care, follow-up of chronic illnesses, and a mandate to be more productive and economical in their daily practices. It would be a wonder, if optimal depression care were routinely provided in general medical settings.

A chronic disease model was developed to guide re-organization of health care services for patients with chronic diseases, and to improve their well-being (7). Recent randomized trials to improve the quality of depression treatment in primary care demonstrated that patients who received interventions organized according to this chronic care model showed superior clinical and functional outcomes compared to their counterparts in usual care (4,8). In a study on late life depression, care manager collaborated with a primary care physician and/or psychiatric consultant to provide antidepressant pharmacotherapy or brief structured problem-solving treatment, patient activation and follow-up of clinical progress and treatment adherence (4). Care management interventions embedded in a chronic care framework have also improved outcomes of patients with diabetes, asthma, heart disease, and even reduced costs in some studies (9).

Current trends such as escalating medical needs of aging populations, and skyrocketing costs of hi-tech medicine can only magnify the pressures on PCPs to provide readily accessible, efficient and efficacious medical and psychiatric services in general ambulatory care settings. Care management for depression, though proven efficacious, cannot be delivered in isolation from treatment of co-morbid medical illnesses. In the US, competing demands for medical services, and tightening fiscal constraints have forced large numbers of health plans to refer patients with mental disorders out of primary care into 'carve-out' behavioral health services. A biopsychosocial approach, embedded into core medical services, may provide a viable way for better serving the psychological and physical health needs of patients.

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The burden of depression in primary care

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Primary care is where the majority of people with mental health problems are treated. It is also the key point in the pathway to mental health care in which interventions for the detection and management of depression have been focused. The last few decades have witnessed the increasing awareness that depression is not only a common and treatable illness, but also a potentially disabling, chronic and sometimes even fatal condition (considering the mortality

associated with both suicide and comorbid depression and physical illness such as coronary heart disease). Most people with depression, as David Goldberg indicates, are no longer only treated by psychiatrists, and fewer even become inpatients, but this has not so much to do with the trend towards deinstitutionalisation, but rather with the availability of effective medication than can be prescribed with confidence by a trained primary care physician.

Today, in developed countries, the majority of people with depression can be treated early and effectively in primary care, with drugs they can tolerate, in effective doses, by clinicians who feel confident that they understand what the effects and side effects of the treatment will be. Having antidepressants that can be taken on a long-term basis with minimal side effects has been a big step forward for people who suffer from depression. However, the newer drugs are much more expensive, and as yet are not widely available in the developing world for those who cannot pay for them. Furthermore, primary care physicians have still not come to understand that people with depression require proactive and perhaps even 'assertive' follow-up. People who are depressed may think that they do not deserve to take up the doctor's time or that it is not possible for doctors to listen to them or understand how they feel. The nature of the illness, and its impact on mental state, contributes further to ensuring that they do not obtain the treatment that they require. We may have spent many years trying to convince both the general public and primary care physicians that depression is an illness like any other, and even a 'physical' illness given that there is evidence of physical change in the brain. Yet, paradoxically these efforts to destigmatise depression also detract from a simple acknowledgment that depression affects not just the way we feel about ourselves and the world but also our need for help and treatment (1). People who are depressed don't always come back for more treatment and doctors don't necessarily tell them to.

Cynics might say that the discovery of depression in the latter part of the twentieth century had more to do with marketing of drugs by pharmaceutical companies than with public health, and I have some sympathy with this view. But there is no doubt, for those of us who see and treat people with depression every day, that these drugs are effective. And there is no doubt that depression is and will increasingly grow as a major contributor to the burden of disability in the world. Getting this message over to psychiatrists, particularly those in the UK, who, supported by government policy, confine their interest to people with 'severe and enduring' mental illness, is not always easy. I believe that the psychiatrist has a responsibility to take a public health perspective: to consider how his or her range of skills can most appropriately be utilised. This requires what Greg Simon (2) has described as taking a population view: stepping back and considering what his or her role must be to improve the quality of care provided in the system for all sufferers, as well as ensuring that those who are most severely ill, including many people with depression, get the care they need.

Mental health professional working in the level above primary care can provide support and supervision for those working in primary care to help ensure that not only do primary care workers feel supported, but also that they have back-up for when they feel out of their depth. In my experience as a trainer, it is essential to ensure that primary care staff understand pathways to more intensive care and support. Without this they may not feel confident to continue to use the new skills they have acquired. As doctors learn to explore patients' feelings, they uncover problems for which they feel unprepared. Training for primary care must go hand in hand with development of relationships between generalists and specialists. As psychiatrists, I believe we have a responsibility to take a leadership role in this task if we are serious about trying to help alleviate the increasing burden of depression.

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Managing the global burden of depression: lessons from the developing world

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Around the globe - be it Liverpool, Los Angeles or Lahore - primary care doctors (PCPs) are increasingly aware that depression is a prevalent condition associated with significant morbidity and mortality. With an estimated point prevalence of 2-4% in the community and 6-8% in primary care settings (1), depression is associated with levels of morbidity and dysfunction rivaling that of other chronic medical conditions (2). According to the World Health Organization, by 2020 depression is expected to be a

leading cause of disability worldwide, second only to cardiovascular disease (3). Because depression is typically detected and treated in primary care settings instead of the specialty mental health sector, health care systems are challenged to develop strategies that address both the mental and medical health needs of the patients they serve. David Goldberg's cross-national review in this issue of World Psychiatry describes a wide range of approaches to this problem. Weighing the relative merits and drawbacks of disparate paradigms, the reader is provided with an opportunity to learn from several innovative approaches, especially those used in developing nations.

Health care systems vary widely across the globe. They differ not only on the economic and societal constraints within which they operate, but also on the philosophical issue of whether mental and medical care should be delivered conjointly. At one end of the spectrum is the fragmented organization of care often found in the United States, where mental health care is 'carved out' from the rest of medical care; at the other end are more holistic models that address patients' broader needs. In the former example, reimbursement for mental health care is completely dissociated from primary care reimbursement, a system that actually prevents PCPs from receiving reimbursement for treating psychiatric illness, even when mental illness is the patient's primary medical problem (4). By contrast, in a Chinese model, 'village health workers' function at a local level to identify patients in need and refer them to medical personnel in local clinics. In Iran, health workers staff 'health houses', from which they screen local inhabitants for mental and physical illnesses, including stress-related conditions. Some psychosocial interventions (i.e., stress reduction techniques) are provided within the health houses; complicated cases are referred for more intensive treatment. In Tanzania, moderately trained physician-extenders meet both the general medical and psychiatric needs of the communities in which they are present. They are responsible for screening patients in primary care for mental and physical disorders, triaging cases by severity and offering interventions to less ill patients. These models from developing nations, all arising in response to physician shortages, rely on relatively inexpensive personnel to serve as the initial contact point for patients, thereby extending care to large numbers of patients despite limited resources.

It is striking that these models do not partition mental and medical health care. When initial triage is conducted by trained community members, even patients in rural settings have an opportunity to obtain care for both their medical and mental health conditions. In the face of limited access to specialized mental health services and antidepressant medications, several developing countries have evolved grass-roots systems of care that creatively overcome these apparent hurdles. In fact, the Chinese, Iranian, and Tanzanian solutions to this problem may offer important lessons to developed nations striving to evolve better methods for integrating depression care into their general medical settings.

While appealing, most of the models of care in developing nations have not been subject to rigorous systematic evaluation. Thus, David Goldberg's review points to the urgent need for more empirical cross-national comparison and outcome research on mental health services delivery around the globe. Indeed, several strategies developed in the so-called less developed world may prove equivalent to - or even better than - mental health care delivered in the developed world to patients in primary care settings.

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Mental health services in primary care in 'developing' countries

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It is important to acknowledge the vast, and growing, diversity among countries which are often lumped together by the adjective 'developing'. This diversity is especially relevant when considering models for the delivery of mental health care, particularly in the context of the tremendous changes taking place in the organisation of health systems. In some countries, such as in South East Asia, overall health indicators have shown remarkable improvements in recent decades. Among other factors, these improvements have been linked to political commitments to publicly-funded health care systems. Models that emphasize partnerships between specialists and primary care providers, such as those being implemented in many 'developed' countries, may be increasingly relevant. In other countries, where the political commitment

to public health has been much weaker - as in some South Asian, African and Latin American countries - primary care has come to constitute a heterogeneous set of providers. Traditional medical practitioners and private medical practitioners have become major players in primary care. Thus, the notion of primary care as being, principally, the first point of contact with a public funded health system is itself incorrect. In such countries, the emphasis may lie in creating greater involvement of these diverse sectors in a coherent public health policy targeting mental health problems. This may include incentives for private practitioners to provide care for mental disorders and joining a network of practitioners who refer difficult cases to specialists.

In the past year, two randomised controlled trials have demonstrated that there are efficacious treatments for common mental disorders and that they can be implemented in primary or general health care settings. One trial from India demonstrated the modestly superior efficacy of antidepressants in a placebo controlled design. This trial also demonstrated that those receiving antidepressants have significantly lower health care costs, compelling evidence that the efficacious treatment of common mental disorders is also cost-effective (1). Another trial from Chile - targeting low income women with common mental disorders - demonstrated significantly superior outcomes for women receiving a stepped care intervention that included psycho-education, group support and antidepressants (2). A third study, in one of the poorest and most resource poor settings in India, which relied to a large extent on locally recruited mental health workers, demonstrated the effectiveness of community-based rehabilitation in the management of severe mental disorders (3).

Thus, the evidence for the effectiveness of specific approaches to specific mental disorders in primary care and community settings is slowly, but surely, growing. However, there are likely to be many obstacles to the upscaling of specific interventions strategies to the health system level. There are many variables, unique to local health systems, which will profoundly influence the effectiveness of mental health interventions. These include markedly different priorities in public health (e.g., HIV/AIDS in some countries), varying levels of risk factors (e.g., violence), and the heterogeneous nature of primary health care provision and availability of health resources (4).

The acute shortage of mental health professionals and the relatively low levels of awareness about mental disorders implies that primary health care has been, is, and will remain the single largest sector for mental health care in low and middle income countries. While this notion has been a well-worn mantra of international mental health policy for decades, a recent review has found that there are precious few examples of the effective implementation of primary mental health care (4). Furthermore, discussions on the integration of mental health services into primary care have not taken the nature of primary care itself into consideration. A review of efforts to improve psychiatric knowledge and skills of primary care physicians found that the most effective models are likely to be those where there is an ongoing, interactive, contextually relevant continuing education which focuses not only on knowledge, but also on skills and attitudes of primary care physicians (5). The authors concluded that organizational and attitudinal issues may be equally or more important for educators to consider than the content or methods used.

The huge diversity between 'developing' country health systems would suggest that we have still much to learn about the effectiveness of different models of mental health care delivery in these settings. The strategies underlying these models must be based on three key assumptions: first, that the actual delivery of clinical services need to be provided largely by non-specialist health workers; second, that mental health specialists must be entrusted with the responsibilities of ongoing training, supervision, support and provision of referral services; and third, that the precise model of care will be heavily influenced by local health system factors, in particular, the state of the general health care system and political commitment to public health.

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Mental health and primary care in Nigeria

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Nigeria is a typical case of a developing nation. As rightly pointed out by David Goldberg, the country is generally short of physicians and,

with a population of over 120 million, has less than 100 psychiatrists. The majority of general practitioners are without postgraduate training and located in private practice, in most cases working on their own. This group of physicians, along with others in government owned institutions (general and teaching hospitals), offer primary care services. Unfortunately, these services are mainly located in urban areas, and most of the rural areas, where the majority of the populace (approximately 70%) reside, are deprived of health services. As part of the government's efforts in meeting some of this challenge, between 5 and 15 local health facilities have been established in each local government area (district) of the country. Specially trained individuals with or without medical background and with different educational levels run these facilities.

However, contrasting what David Goldberg points out for a few developing countries, in some other developing countries like Nigeria, the emphasis of the primary care has been geared mostly towards maternal and child care and, occasionally, treatment of minor physical ailments and infectious diseases. Recent findings (1,2) revealed that primary health care workers have very poor knowledge of mental disorders and virtually no mental health services are provided at the primary health care facilities studied. The mental health services offered at the private general practice and government owned hospitals seem to be the only hope for the minority of the populace. However, the level of capability and effectiveness in delivering these services is an area yet to be investigated. Judging by the level of mental health training received by primary health care workers (mainly from undergraduate schools), tied with deeply seated negative attitudes and superstitious beliefs on mental disorders, mental health services offered to the populace at the primary care level is likely to be minimal.

David Goldberg will agree that the roles of the traditional and religious healers in most developing countries, especially in Africa, cannot be ignored. Though orthodox psychiatric practice has expanded considerably in many developing countries, it is well documented that many psychiatric patients still seek primary help from the traditional healers and the syncretic churches. Traditional and religious homes probably look after the majority of mentally ill Nigerians. Traditional and religious healers are easily accessible to the people, and Africans, regardless of their level of education, adhere in varying degrees to the belief in the supernatural causation of mental illnesses (3). However, in most instances, people seek orthodox treatment when the efforts of these healers seem to have failed.

Comparing the scenario here to what David Goldberg describes, the gap between the developed and some (if not many) developing countries is pretty large. The needs and the challenges in this part of the world are diverse and much greater than what is depicted. First is the need to get the government convinced and committed to the importance of delivering adequate mental health care at the primary care level; then, the need to educate the populace on the nature of mental illnesses, to ensure the availability of effective treatment and the provision of adequate facilities and resources; then, the challenge of adequate mental health training of physicians and other health workers working at primary care level. Also, adequate and appropriate remuneration and conditions of service are needed, in order to halt brain drain. Furthermore, there is the need to design a suitable model of mental health care and linkage that will be cost effective, cutting through the primary and secondary care levels to the tertiary/specialist centres.

This discourse is quite timely, bringing to the fore the progress and areas of opportunities of mental health in primary care, especially in the developing nations, and highlighting the need for a concerted effort to meet the challenges fostered by underdevelopment in many nations of the world.

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Probing cortical dopamine function in schizophrenia: what can D1 receptors tell us?

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Schizophrenia is characterized by positive symptoms, negative symptoms and cognitive impairment. Positive symptoms may be related to excessive dopamine (DA) function, as suggested by the common antidopaminergic properties of antipsychotic medications, which are most effective at treating positive symptoms. Negative symptoms and impairment in higher cognitive functions are thought to be related to a dysfunction of the dorsolateral prefrontal cortex (DLPFC), possibly related to inappropriate stimulation of D1 receptors. In the last few years we have clearly demonstrated excess subcortical DA transmission and now have indirect evidence for cortical dopamine deficit. We studied 16 drug free patients with schizophrenia (7 drug naïve and 9 previously treated) and 16 matched controls, using positron emission tomography (PET) and [^{11}C]NNC 112, a novel radiotracer for PET imaging of the D1 receptor, and the n-back task, a test of working memory. We observed a significant upregulation in D1 binding in the DLPFC in patients with schizophrenia compared to controls. This increase was present in both drug naïve and previously treated patients and was regionally selective. Furthermore, the increase was correlated with poor performance on the n-back task (r^2=0.45, p=0.004). This upregulation of D1 receptors might be secondary to a sustained deficit in prefrontal DA function, as postmortem studies revealed deficits in DA innervation in the prefrontal cortex in schizophrenia.

Key words: Schizophrenia, dorsolateral prefrontal cortex, D1 receptors, dopamine, positron emission tomography

The classical dopamine (DA) hypothesis of schizophrenia proposed that hyperactivity of DA transmission was responsible for the 'positive' symptoms (hallucinations, delusions) observed in this disorder (1). This hypothesis was based on the correlation between clinical doses of antipsychotic drugs and their potency to block DA D2 receptors (2,3) and the psychotogenic effects of DA-enhancing drugs (for review see 4,5).

More recently functional brain imaging studies showed alterations in prefrontal cortex (PFC) function in schizophrenia associated with poor performance on frontally mediated cognitive tasks (for review see 6). At the same time, a wealth of preclinical studies emerged documenting the importance of prefrontal DA transmission at D1 receptors (the main DA receptors in the neocortex) for optimal PFC performance (for review see 7). Together, these observations led to a reformulation of the classical DA hypothesis postulating that the excess DA transmission is restricted to subcortical areas of the brain, rich in D2 receptors, and associated with positive symptoms of the illness, while a deficit in DA transmission at D1 receptors in the PFC might be implicated in the cognitive impairments and negative symptoms (8,9). This was supported by the lack of efficacy of D2 receptor antagonism in the treatment of negative and cognitive symptoms.

Over the last few years, the development of new brain imaging methods based on the principle of endogenous competition enabled direct measurement of DA transmission at D2 receptors in the striatum (for review see 10). These imaging studies, combined with studies of striatal [^{18}F]DOPA accumulation, have consistently demonstrated that schizophrenia is associated with increased presynaptic activity of DA neurons projecting to the striatum. Moreover, this increased activity is more prominent during episodes of illness exacerbation, and predicts fast response to antipsychotic drugs (for review see 11). Thus, the first arm of the dopaminergic imbalance hypothesis (hyperactivity in subcortical territory) has received strong support from imaging studies.

On the other hand, the second arm of this hypothesis (DA deficit in cortical projections) is still largely based on inferences from preclinical models or indirect clinical evidence. Patients with schizophrenia perform poorly on a number of tasks subserved, among others, by dorsolateral prefrontal cortex (DLPFC) circuitry (12). Postmortem (for review see 13,14) and in vivo functional studies (for review see 15) suggest alterations in the cytoarchitecture and function of the PFC in schizophrenia. Frontal lobe damage is frequently associated with lack of drive and motivation, core features of the negative symptoms domain in patients with schizophrenia (16). This DLPFC dysfunction may be related to impaired DA function. One postmortem study reported decreased DA terminals in the DLPFC in schizophrenia (17). Poor performance on working memory (WM) tasks has been associated in patients with schizophrenia with low cerebrospinal fluid (CSF) homovanillic acid (HVA), a marker for cortical presynaptic DA activity (18) and with the high activity associated polymorphism (Val allele) of the DA metabolism enzyme catechol-O-methyltransferase (COMT) gene (19). Patients with drug induced or idiopathic Parkinson's disease also present deficits on these tasks (20,21). In patients with schizophrenia, amphetamine and apomorphine administration is associated with improved performance on frontal tasks (22,23). Animal models also support this view (for

review see 14): monkeys with selective DA lesions in the DLPFC present prefrontal cognitive dysfunction reminiscent of impairments observed in patients with schizophrenia (24).

As the majority of DA receptors in the PFC are of the D1 subtype (25,26), evaluation of prefrontal D1 receptor function in schizophrenia is important to understand the relationship between prefrontal impairment and DA function in this condition. A wealth of preclinical data shows that appropriate activation of cortical D1 receptors is essential for WM processing in rodents and nonhuman primates (27-30). Iontophoretic application of D1 antagonists in the DLPFC impairs WM performance in monkeys (27). In aged monkeys and in catecholamine depleted monkeys, infusion of the full D1 agonists A77636 and SKF81297 partially reverses deficits in spatial WM (28,31).

A recent positron emission tomography (PET) study with [^{11}C]SCH 23390 reported decreased density of D1 receptors in the PFC in 17 male patients with schizophrenia compared to age matched controls. This study used V3" as an index of receptor density. This outcome measure is the ratio of binding potential in a region of interest to the non-specific binding in a region of reference. In other terms, V3" does not correct for potential between-subjects differences in nonspecific binding.

Because of the limitations of [^{11}C]SCH 23390 to study prefrontal D1 receptors with PET, our group selected the newly developed tracer [^{11}C]NNC 112 for this investigation. D1 receptors have been visualized with several radiotracers. The first PET radiotracers for the D1 receptor to be introduced were the benzazepines [^{11}C]SCH 23390 (KD = 0.4 nM) and [^{11}C]SCH 39166 (KD = 3.6 nM) (32-35). Both radiotracers displayed relatively low specific to nonspecific ratios, which impaired the accuracy of the D1 measurement in the PFC (36-38). Moreover, [^{11}C]SCH 23390 has a poor selectivity for D1 receptors, especially in the cortical region, where it also binds to 5-HT2A receptors (39). More recently, two new benzazepines have been evaluated as PET radiotracers: [^{11}C]NNC 756 (KD = 0.17 nM) and [^{11}C]NNC 112 (KD = 0.18 nM) (34,40-42). Both radiotracers provide high specific to nonspecific ratios. The disadvantage of [^{11}C]NNC 756 compared to [^{11}C]NNC 112 is a low selectivity against 5-HT2 receptors (in vitro selectivity about 20:1) (41,43). Thus, [^{11}C]NNC 112 is the best D1 radiotracer presently available (44).

METHODS

We studied with [^{11}C]NNC 112 and PET 16 patients with schizophrenia and 16 matched controls. Patients fulfilled DSM-IV criteria for schizophrenia or schizophreniform disorder (provisional confirmed on follow-up) and were off antipsychotics for at least 21 days and depot neuroleptics for one year (45). We excluded any other lifetime axis I diagnosis, including alcohol or substance abuse or dependence (with the exception of nicotine), a significant medical or neurological condition, and pregnancy.

Controls were matched for age (± 5 years), gender, race, parental socioeconomic status, and nicotine smoking. They also had to be free of any psychiatric, medical or neurological conditions. The study was approved by the Columbia Presbyterian Medical Center and New York State Psychiatric Institute Institutional Review Boards as well as the Radioactive Drug Research Committee of Columbia University.

Diagnosis was assessed with the Structured Clinical Interview for DSM-IV (SCID) (46) for patients and the SCID non-patient version (SCID-NP) for controls. Clinical assessment included the Positive and Negative Syndrome Scale (PANSS) (47).

WM assessment was performed with the n-back test during the neuroleptic free period (48). The n-back task used here requires subjects to monitor a series of letters presented sequentially on a computer screen, and to respond when a letter is identical to the one that immediately preceded it (1-back condition), the one presented two trials back (2-back), or three trials back (3-back). The n-back paradigm engages WM because it requires subjects to maintain information about the previous stimuli, as well as to manipulate this information (i.e. to make a comparison with the current stimulus). Sixty letters were presented in each condition. Each presentation lasted 500 msec, with 2500 msec intervals (blank screen). A total of 12, 10 and 10 targets were presented for the 1, 2 and 3-back conditions, respectively. The hit rate (HR) was calculated as the number of correct responses divided by the number of targets. The error rate (ER) was calculated as the number of errors divided by the number of nontargets. The adjusted HR (AHR) was calculated as HR minus ER and d' was calculated for 2- and 3-back as inv(HR) minus inv(ER), where inv is the inverse of the standard normal cumulative distribution.

Executive function was tested with the Wisconsin Card Sorting Task (WCST) in patients and controls.

Measurement of [^{11}C]NNC 112 binding potential (BP) was obtained as previously described (44) except that data were obtained on the new ECAT EXACT HR+, which provides a superior resolution compared to the ECAT EXACT 47 used in the feasibility study. Because of the slightly better reliability of BP compared with V3", and because BP, but not V3", corrects for potential between-subjects differences in nonspecific binding, BP was selected a priori as the outcome measure.

RESULTS

Sixteen patients and sixteen controls completed the study. The groups were matched for age, gender, race, parental socio-economic status and nicotine smoking. Of the 16 patients with schizophrenia, 7 patients were first episode/neuroleptic naïve, and 9 were neuroleptic free for at least 21 days (average of 164 days). In patients, PANSS

positive symptoms, negative symptoms, and general pathology subscale scores were 19 ± 7, 18 ± 6 and 34 ± 7, respectively.

There were no significant between-group differences in injected dose (ID), specific activity at time of injection (SA), plasma clearance of the parent compound, plasma [^{11}C]NNC 112 free fraction (f1), cerebellum total distribution volume and DLPFC gray matter volume.

DLPFC [^{11}C]NNC 112 BP was higher in patients (1.63 ± 0.39 mL g^{-1}) compared to controls (1.27 ± 0.44 mL g^{-1}, p = 0.03). The increase in DLPFC D1 receptors in patients with schizophrenia was also noted when V3" was used as an outcome measure. To assess the regional specificity of the upregulation of DLPFC D1 receptors in patients, distribution of [^{11}C]NNC 112 BP was also compared in other regions. Patients tended to show higher [^{11}C]NNC 112 BP compared to controls in all neocortical regions, but this difference reached significance only in the DLPFC. Striatal, limbic, paralimbic, and thalamic regions showed no change between groups.

There were no differences in DLPFC [^{11}C]NNC 112 BP between drug naïve (1.62 ± 0.53 mL g^{-1}) and previously treated patients (1.65 ± 0.53 mL g^{-1}), suggesting that the upregulation of D1 receptors in DLPFC was not a long-lasting side effect of previous neuroleptic medication. Furthermore, studies in primates documented that exposure to antipsychotic drugs induces downregulation of D1 receptors in the DLPFC (49,50).

In patients, DLPFC [^{11}C]NNC 112 BP was not associated with severity of positive or negative symptoms on the day of the scan (r^2 = 0.01, p = 0.35; r^2 = 0.10, p = 0.21, respectively).

WM assessment with n-back was obtained in 14 out of 16 patients and 15 out of 16 controls. Patients with schizophrenia performed above chance level in all three conditions (chance level would correspond to an AHR of 0), but significantly worse than control subjects. Results of the n-back were analyzed with repeated measure ANOVA, with WM load (1-, 2- and 3-back) as repeated measure and diagnosis (controls versus schizophrenics) as cofactor. There was a significant effect of WM load (p < 0.0001), and diagnosis (p = 0.003), and no significant diagnosis by load interaction (p = 0.37). No association was present between age and WM performance.

Among patients with schizophrenia, no differences were noted in AHR at any level of the test between first episode patients never previously exposed to antipsychotics (n = 7, AHR at 1-, 2- and 3-back of 0.90 ± 0.10, 0.64 ± 0.28, and 0.49 ± 0.31, respectively) and chronic patients previously treated with antipsychotics (n = 7, AHR at 1-, 2- and 3-back of 0.85 ± 0.20, 0.57 ± 0.33, and 0.52 ± 0.26, respectively).

Severity of positive, negative or general symptoms measured with the PANSS subscales were not predictive of performance at 1-back, 2-back or 3-back conditions (r^2 < 0.15, p > 0.05 for all correlations).

At WCST, patients performed worse than controls, but this difference did not reach significance: number of categories achieved was 5.0 ± 1.3 in controls and 4.0 ± 1.7 in patients (p = 0.09). Perseverative errors were 15.1 ± 10 in controls and 21.8 ± 14 in patients (n = 0.18).

We tested the hypothesis of an association between D1 receptor availability in DLPFC and n-back performance. When analyzing both groups together, we observed an association between low WM performance at 1-, 2- and 3-back and high DLPFC [^{11}C]NNC 112 BP. This effect was accounted for by the patients with schizophrenia (Figure 1). Within the control group, there was no relationship between performance on the n-back and D1 receptor availability. In patients, low performance at 2-back and 3-back were significantly associated with high D1 receptor availability. In patients, high DLPFC D1 receptor availability was associated with low 2-back AHR (r^2 = 0.31, p = 0.03) and low 3-back AHR (r^2 = 0.45, p = 0.008). Similar results were obtained using d'. In contrast, WCST performances were not correlated with D1 receptors availability (categories, r^2 < 0.01, p = 0.84; perseverative errors, r^2 < 0.02, p = 0.69).

DISCUSSION

This study suggests that [^{11}C]NNC 112 in vivo binding might be upregulated selectively in the DLPFC in drug free patients with schizophrenia, and that this upregulation is predictive of poor performance at the n-back test. The in

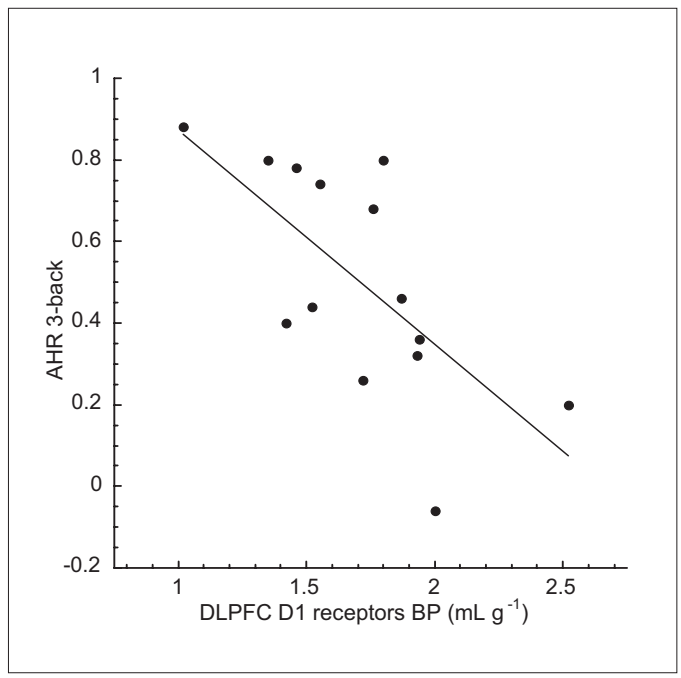

Figure 1 - Relationship between upregulation of D1 receptors in the dorsolateral prefrontal cortex (DLPFC) of untreated patients with schizophrenia and performance at working memory task (3-back adjusted hit rate, AHR; lower values represent poorer performance). BP - binding potential.

vivo binding of [11C]NNC 112 is not affected by acute changes in endogenous DA. It is therefore reasonable to assume that the increased [11C]NNC 112 binding observed in this study reflects increased concentration of D1 receptors in DLPFC of patients with schizophrenia. Our results did not replicate the findings of Okubo et al (38) of decreased [11C]SCH 23390 binding in the frontal cortex. Several factors may explain this discrepancy: the signal to noise ratio of [11C]SCH 23390 in the PFC is relatively low and may not allow reliable quantitative analysis (51). The PET camera used by Okubo et al (38) was a 7 slices device, with limited field of view and limited resolution. [11C]SCH 23390 displays a relatively low selectivity against 5-HT2A/2C receptors, and it is possible that a decrease in 5-HT2A receptors in the PFC in schizophrenia may have affected the results. Indeed, Okubo et al (52) recently reported a trend-level decrease in PFC 5-HT2A receptor density measured with [11C]NMSP in 10 previously treated patients originally included in their [11C]SCH 23390 cohort. Finally, the relationship detected in both studies between D1 binding and cognitive impairment suggest that these tracers may be detecting differentially potential receptors related trafficking changes induced by low DA tone, although in our data we have no relationship between D1 BP and performance on the WCST, suggesting that this task is less tightly related to cortical D1 function.

Due to the lack of direct measurement of presynaptic DA function in the PFC, the interpretation of this finding is inherently speculative. We postulate that an increase in DLPFC D1 receptors is a compensatory response to a deficit in presynaptic DA function. The observation that, in rodents, chronic DA depletion is associated with increased in vivo binding of [11C]NNC 112 in the PFC supports the plausibility of this interpretation of the PET findings (53). This interpretation is consistent with several other indirect lines of evidence suggesting that schizophrenia might be associated with a deficit in prefrontal DA function, and with the performance deficits at delayed-response tasks observed in nonhuman primate models of prefrontal DA deficiency. These deficits are reversed by indirect DA agonists and D1 agonists (24,28,31,54). This view is also supported by the preclinical observations that chronic phencyclidine exposure, which induces in humans symptoms reminiscent of schizophrenia (for review see 55), is associated with impaired WM performance, decreased DA turnover in the PFC (for review see 56), and upregulation of in vivo [11C]NNC 112 binding in the PFC (57). This interpretation suggests that WM function in patients with schizophrenia might be improved by DA agonists, and by the prefrontal DA enhancing effects of atypical drugs.

Our proposed model is hypothetical, and it could be argued that our findings are consistent with alternative explanations or models. The second model postulates that an increase in DLPFC D1 receptors is a primary phenomenon and the alteration in WM performance seen in these patients results from increased post-synaptic sensitivity to DA released in the DLPFC during performance of the task (58). This interpretation would predict that administration of D1 antagonists should improve WM function in patients with schizophrenia. While no studies specifically evaluated the effect of D1 receptors antagonists on WM function in schizophrenia, limited therapeutic trials with selective D1 receptor antagonists in schizophrenia showed a lack of efficacy or even worsening of clinical conditions (59-62).

Another potential model combines elements of the first and second models. This third model proposes that a persistent decrease in prefrontal DA activity might induce upregulation of D1 receptors. The upregulation could in turn lead to increased sensitivity to agonists, resulting in an overstimulation of these upregulated D1 receptors in conditions associated with DA release such as stress or cognitive challenges. This third model predicts that the 'optimal stimulation window' in schizophrenia is too narrow, and that the threshold between too little and too much D1 receptor stimulation is immediately exceeded during prefrontal DA engagement. An attractive feature of this model is that it might reconcile some apparently conflicting effects of antipsychotic drugs. By providing partial blockade at DA receptors acutely and leading to receptor downregulation chronically, antipsychotics might acutely protect against the effects of D1 receptor hyperstimulation. Raising baseline prefrontal DA activity is another mechanism by which atypical antipsychotics might correct, at least partially, the deficit in prefrontal DA that caused the problem. This model would predict that acute administration of a D1 receptor agonist alone might be detrimental, while repeated administration of a D1 agonist at low doses might lead to desensitization of the receptors and thus have long term therapeutic effects.

Proper elucidation of the role of PFC DA transmission at D1 receptors in the pathophysiology of cognitive impairment will thus critically depend not only on the development of an imaging method suitable to assess presynaptic function, but also on the development of D1 receptor agonists available for clinical investigation.

The pathogenesis of a putative deficiency in prefrontal DA function in schizophrenia is at present unknown. Elucidation of the genetic bases and mechanisms of development of the mesocortical DA system would provide important clues regarding possible origins of alterations in prefrontal DA neurons. Furthermore, alteration of DA function in schizophrenia might not be due to a primary problem of DA systems, but rather a consequence of more generalized neurodevelopmental abnormalities. However, it is an important consequence, to the extent that it is implicated in a cascade of events leading to the emergence of symptoms and persistent disability. An improved understanding of the origin of this DA phenotype will offer important leads as to potential neurodevelopmental

mechanisms that might be implicated in the illness, and open new therapeutic avenues.

Acknowledgements

This work was supported by a United States Public Health Service Grant (NIMH 1 ROI MH59144-01), a Charles A. Dana Foundation grant, NARSAD and the Lieber Center for Schizophrenia Research.

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Symptom dimensions and outcome in schizophrenia

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Since Kraepelin, outcome has been one of the most frequently used criteria for testing the validity of diagnosis in psychiatry. Factor analytic methods have showed, however, that the symptomatology of psychiatric patients can be divided into symptom dimensions, which also correlate with outcome. The aim of the present study was to explore how diagnostic sub-categories and symptom dimensions correlate with outcome in first-episode and chronic patients with schizophrenia. In samples of first-episode schizophrenia patients (n=156) and chronic schizophrenia patients (n=1571), symptom variables were factored and the five symptom dimensions obtained were correlated with outcome variables. In both samples, symptom dimensions were more powerful in explaining variance of outcome than categorical sub-diagnoses. Thus, a dimensional approach seems to be valuable not only in describing the illness picture, but also in predicting outcome in schizophrenia.

Key words: Dimensions, categories, schizophrenia, outcome, factor analysis

According to Kraepelin (1), the characteristic features of dementia praecox were emotional dullness, lack of interest and apathy. Kraepelin's view was strictly categorical and the main principle in making the diagnosis was the outcome. Bleuler (2) gave priority to the clinical picture in establishing a diagnosis of schizophrenia and considered the fundamental symptoms to be affective and thought disturbances, ambivalence and autism. Accessory symptoms, such as hallucinations, delusions and catatonic symptoms, were seen in other psychoses as well. The primary disturbance in schizophrenia, however, was the loosening of associations, which preceded both fundamental and accessory symptoms.

The clear-cut distinction between schizophrenia and other disorders rapidly began to lose its strength. Kasanin (3) showed that there are patients who display both schizophrenic and manic or depressive symptoms and suggested the concept of schizo-affective psychoses. Hoch and Polatin (4) described pseudoneurotic forms of schizophrenia with the main features being pan-anxiety, pan-neuroticism, pan-sexuality and brief and limited psychotic episodes (micro-psychoses). Schneider (5) introduced the concept of first-rank symptoms, which were reliably detectable in all cultures and very frequently seen also in patients with schizophrenia. However, first-rank symptoms were not specific to schizophrenia but also seen in other severe psychiatric disorders.

In the 1930s, Langfeldt (6) tried to solve the problem of differentiating between dementia praecox and schizophrenia concepts by dividing schizophrenia into nuclear schizophrenia, corresponding to Kraepelin's dementia praecox, with poor prognosis, and schizophreniform psychoses, with an acute onset and good prognosis. In the late 1950s, Garmezy and Rodnick (7) made a distinction between process and reactive schizophrenia. Process schizophrenia was associated with poor premorbid psychosocial development, neurological findings and poor clinical outcome, while patients with reactive schizophrenia showed a good premorbid development, the onset of illness often being preceded by distressing life events, and a relatively good outcome.

In the current classifications of diseases (DSM-IV and ICD-10), schizophrenia, as well as other disorders, is seen as a (mixed) categorical entity including both clinical (symptoms) and outcome (duration) items. However, because the definition of schizophrenia requires only a certain number of items without any preference, it is usual that two patients with the same diagnosis have almost totally different symptomatology, while outcome within the schizophrenia diagnosis varies considerably.

At the same time as the revision of classifications of disease and along with the development of statistical methods, also the dimensional approach began to gain ground. Crow (8,9), adopting a dimensional view, proposed two syndromes in schizophrenia. Type I consisted of positive symptoms such as delusions and hallucinations; these are often seen in the acute phase of the illness, they respond well to neuroleptic drugs, and they might be associated with a pathology of dopaminergic transmission. The type II syndrome is more or less chronic and is characterized by negative symptoms, such as flattening of affect, poverty of speech and loss of drive; these symptoms are related to poor outcome, poor response to neuroleptic drugs, and structural pathology in the central nervous system. A confirmatory factor analysis by Lenzenweger et al (10) lent support to Crow's independent model of positive and negative symptoms in schizophrenia.

Andreasen and Olsen (11) accepted the concept of positive and negative symptoms, but considered them as categorical characteristics of two different types of illness. In their sample of hospitalised schizophrenic patients, there was a negative correlation between positive and negative symptoms. A factor-analytic study by Liddle (12), with a more homogeneous but chronically ill sample of schizophrenic patients selected for persistence of symptoms, yielded three syndromes: psychomotor poverty, disorganisation, and reality distortion. Each of the three syndromes was associated with a specific pattern of perfusion in the

paralimbic and associative cortex, and in the related subcortical nuclei (13). Later, Andreasen and co-workers (14,15) agreed that the categorisation of symptoms in schizophrenia required more than two distinct dimensions: negative, psychoticism and disorganisation. Of these three dimensions, in a longitudinal study, negative symptoms were rather stable, while psychoticism and disorganisation tended to be less stable (16). Peralta et al (17) also failed to find support for the classification of schizophrenic symptoms into positive and negative syndromes; their results supported Liddle's three-syndrome model as well as the findings of other researchers (18).

Several later studies have supported this model of three syndromes (19), but the model has also been criticised. Kay and Sevy (20) found seven factor dimensions. The first four factors (positive, negative, excited and depressed) were retained and included in a four-factor pyramid model. Three other components (cognitive dysfunction, suspiciousness and stereotypic thinking) were discarded. Other factor analyses (21,22) have produced five factor dimensions: negative, positive, excited, cognitive and (anxious)/depressive.

The instruments used in assessment and the way of rating have important effects on the results of factor analyses. For example, Toomey et al (23) found that the analysis of global ratings revealed three factors: negative, positive and disorganisation, but that the item-based analysis produced two negative factors (diminished expression and disordered relating), two positive factors (bizarre delusions and auditory hallucinations), and a disorganisation factor. Within the negative dimension, Carpenter has made an important distinction between primary or deficit and secondary or reactive negative symptoms (24).

Independent of the clinical picture, we have no criteria such as a laboratory test for diagnosing schizophrenia or its subtypes. Therefore, since Kraepelin, outcome has been one of the mostly used independent criteria for testing the validity of diagnostic procedure in psychiatry. The literature referred to above suggests that, in addition to categorical diagnoses, the dimensional approach may also be associated with patient's outcome, possibly even more strongly than the categorical one. Thus, the aim of the present study was to explore associations between symptom dimensions and outcome factors in samples of first-episode and chronic schizophrenia patients.

METHODS

First-episode patients

The first-episode sample consisted of 156 (75 men and 81 women) consecutive 15-44-year-old (mean age 27.1 years) DSM-III schizophrenia patients (hebephrenic, catatonic, paranoid, undifferentiated, residual, schizoaffective and schizophreniform), who during one year (March 1983 - February 1984), contacted the public psychiatric services for the first time in their life for schizophrenic symptoms in six mental health districts in Finland. The patients were examined at their first treatment contact and two and five years thereafter by the psychiatric teams responsible for their hospital or community treatment.

The basic examination was conducted as soon as possible after the initial contact. It consisted of questions concerning the patient's premorbid development, psychosocial life situation, duration of symptoms, age at onset of first psychic symptoms and acuteness of the illness.

The teams produced evaluations of the patients' friendships, hobbies, heterosexual relationships, and amount of useful work (25); the Global Assessment Scale, GAS (26); the assessment of psychotic and depressive symptoms, insight, maintenance of grip on goals of life (27) and subjective life satisfaction. These ten variables were transformed so that their means in the whole sample were 1, and the sum scores of all 10 variables were calculated for each patient to describe his/her global psychosocial situation at each examination.

The assessment of psychiatric symptoms was based on a shortened version of the Comprehensive Psychopathological Rating Scale, CPRS (28). The variables of the CPRS were factored for each examination separately. After the principal-component solution, an orthogonal rotation of five factors (eigenvalue > 1) was calculated and the rotated factor scores were transformed (mean = 0 and SD = 1). Pearson's product moment correlations were calculated between the symptom dimensions (factor dimensions) and the variables describing the patient's psychosocial situation. The variance of clinical dimensions was explained by the variables of the psychosocial situation, and the variance of the global psychosocial outcome by symptom dimensions in regression analyses. Further methodological details can be found elsewhere (29,30).

Chronic patients

The sample of chronic patients consisted of 1571 (841 men and 730 women) consecutive DSM-III-R schizophrenia patients in the age range 15-64 years (mean age 40 years and mean duration of illness 15 years), who had been discharged from the psychiatric hospitals of 20 health care districts in Finland in 1990 and 1994 and interviewed three years later. The patients fulfilling the criteria of disorganised, catatonic, paranoid, residual or undifferentiated schizophrenia were included. Schizophreniform and schizoaffective psychoses were excluded. In a reliability study, all study patients were correctly classified as schizophrenia patients; the sub-grouping was correct in 72.5% of cases and kappa was 0.62.

Data were collected on the patients' background, psychiatric history, including the year of the first hospital admission, living partner and living situation, psychiatric care after discharge, use of psychiatric hospital and outpa-

tient services during the three-year period prior to the index discharge and during the three-year period after the index discharge.

The patients were interviewed by each district's psychiatric teams responsible for their treatment three years after their hospital discharge. The interview consisted of questions concerning physical health, global assessment of psychotic, depressive and neurotic symptoms, the GAS (26), useful work (25), number of close interpersonal relationships, subjective life satisfaction, and restrictions of daily social functioning (31).

The assessment of psychiatric symptoms was based on a shorter version of the Positive and Negative Syndrome Scale, PANSS (32). The symptom items were factorised according to the principal axis method, an orthogonal rotated solution was calculated for the five first factors (eigenvalue > 1) and the rotated factor scores were transformed (mean = 0 and SD = 1). Further methodological details can be found elsewhere (33).

Table 1 Factor dimensions in first-episode and chronic schizophrenia patients

First-episode patients (CPRS)	Chronic patients (PANSS)
Baseline examination	*At follow-up*
F01 Negative	F01 Negative
F02 Delusional	F02 Positive
F03 Depressive	F03 Depressive
F04 Manic grandiosity	F04 Hostile
F05 Hallucinations	F05 Disorganisation
Second year	
F21 Depressive/negative	
F22 Delusional	
F23 Auditory hallucinations	
F24 Visual hallucinations	
F25 Disorganisation	
Fifth year	
F51 Depressive	
F52 Negative	
F53 Disorganisation	
F54 Hallucinations	
F55 Delusional	

CPRS - Comprehensive Psychopathological Rating Scale; PANSS - Positive and Negative Syndrome Scale.

RESULTS

First-episode patients

Five factor dimensions at each stage

In the factor analysis of the CPRS, five symptom dimensions were found at baseline and at both follow-up examinations (see also 29). They are shown in Table 1. There was only one significant difference between genders: at the time of initial examination, delusions were more prevalent in men than in women (p=0.01). Delusional symptoms were less prevalent, but negative symptoms more prevalent, in younger patients. Single patients had more negative symptoms at all examination stages (p<0.05).

Premorbid development

Poor or lack of relations with the opposite sex during the premorbid period predicted the negative dimension at every examination (r=0.32, r=0.24, r=0.24, respectively) and disorganised behaviour at the second year follow-up (r=0.27). Premorbid withdrawal had similar but smaller correlations than poor heterosexual development. Asocial premorbid behaviour predicted auditory hallucinations (r=0.21) and disorganisation at the second year follow-up (r=0.28). Chronic onset of illness predicted the negative dimension in the later course of the illness (r=0.24, r=0.20). Regression analyses emphasised the significance of premorbid heterosexual development and withdrawal, as well as early and chronic onset of illness, especially in explaining the variance in the negative dimension.

Psychosocial outcome

Correlations between the psychosocial situation and symptom dimensions were lower at the baseline examination than at follow-ups (Table 2). The factors including the negative dimension (at all examinations) and the depressive dimension (at the second and fifth year follow-up) were closely and comprehensively associated with the patient's current psychosocial situation.

Heterosexual relationships, work situation and grip on

Table 2 Statistically significant (p<0.05) correlations (multiplied by 100) between psychosocial variables and clinical symptom dimensions

	Clinical symptom dimensions														
Psychosocial variable	Baseline examination					Second year					Fifth year				
	F01	F02	F03	F04	F05	F21	F22	F23	F24	F25	F51	F52	F53	F54	F55
Social relationships	20					49		23				25			18
Hobbies	19					45					30	26			
Sexual	25					34				21	20	32			
Work	26					48		18		17	33	36			23
Grip	40					60				17	46	41			18
GAS	29					64	27	16			38	32	17		19
Insight	26						25			23		44	19	21	
Satisfaction	22					39		24			44				23

Dimensions are those listed in Table 1. GAS - Global Assessment Scale

goals of life at the baseline examination predicted the negative dimension at the second and fifth year follow-up. In regression analyses, of the baseline examination variables, poor grip, lack of heterosexual relations and good insight predicted the depressive/negative dimension at the second year follow-up (R=0.50), while poor grip and GAS and frequent social relations predicted disorganisation at the second year follow-up (R=0.28), and poor work history and lack of heterosexual relations predicted the negative dimension at the fifth year follow-up (R=0.42). Few social relations, poor work history and good satisfaction at the second year follow-up predicted the negative dimension at the fifth year follow-up (R=0.45). Asocial behaviour, poor work history and poor satisfaction at the second year follow-up predicted the depressive dimension at the fifth year follow-up (R=0.39).

On the other hand, symptom dimensions strongly explained the variance in the global psychosocial situation at various stages (Table 3). Of the baseline dimensions, only the negative one was significantly associated with the current global psychosocial situation; at later examinations, all dimensions except visual hallucinations entered the regression function, and the power of the model was strong. Thus, the patients' current psychosocial situation was broadly associated with their clinical dimensions. In the predictive design, a lack of negative dimension but a great deal of depression and manic grandiosity at the baseline examination predicted a good psychosocial situation at the second year follow-up; depression even until the fifth year. The depressive and negative dimensions as well as auditory hallucinations at the second year follow-up predicted poor psychosocial situation at the fifth year follow-up.

Chronic patients

Five factor dimensions

In factor analysis, five factors were interpreted (see also 33) and named as shown in Table 2. The factor structure of the chronic sample resembled that of the first-episode patients at five-year follow-up. Negative, depressive and disorganisation factors were found in both samples. The positive factor was more global in the chronic sample than in the first-episode sample, in which it was divided into hallucinatory and delusional factors.

Men had higher negative (p=0.000) and women higher depressive scores (p=0.000). Age at discharge had no consistent association, but age at first admission was associated linearly with hostility (p=0.019) and disorganisation (p=0.000): both were more prevalent in the patients with early onset of illness. Single patients had higher, and presently or ever married patients had lower scores on the negative (p=0.000) and disorganisation (p=0.013) dimensions. Single men had the highest scores in negative symptoms (p=0.000).

Clinical diagnosis and history

The diagnostic subtype was associated significantly with all factor dimensions except hostility. Disorganised patients had the highest scores on negative, positive and disorganisation dimensions (Table 4). Catatonic patients also had high negative scores. On the other hand, para-

Table 3 Variance in global psychosocial situation explained by clinical symptom dimensions in regression analyses of the first-episode schizophrenia patients

Psychosocial situation	Symptom dimensions		Model R2
Actual interconnections			
At baseline examination	F01	Negative	0.199
At second year	F21	Depressive/negative	0.484
	F25	Disorganisation	0.567
	F22	Delusional	0.586
	F23	Hallucinatory (auditory)	0.600
At fifth year	F51	Depressive	0.231
	F52	Negative	0.446
	F54	Hallucinatory	0.515
	F53	Disorganisation	0.540
	F55	Delusional	0.557
Predictions			
At second year	F01	Negative	0.044
	F03	Depressive (-)	0.079
	F04	Manic (-)	0.103
At fifth year	F03	Depressive (-)	0.066
	F21	Depressive/negative	0.161
	F23	Hallucinatory (auditory)	0.179

Table 4 Symptom dimension scores by diagnoses in the chronic sample of schizophrenia patients

	Negative	Positive	Depressive	Hostile	Disorganisation
Diagnosis					
Disorganised (n=248)	0.193	0.231	-0.073	-0.127	0.260
Catatonic (n=54)	0.173	-0.135	-0.336	0.048	-0.075
Paranoid (n=538)	-0.097	0.149	0.011	0.048	-0.146
Residual (n=129)	0.124	-0.273	0.025	-0.085	0.083
Undifferentiated (n=602)	-0.035	-0.158	0.044	0.023	0.012
p	0.000	0.000	0.018	0.052	0.000
GAS at discharge (score)					
1-3 (n=415)	0.244	0.186	0.023	0.058	0.139
4-5 (n=882)	-0.054	-0.043	-0.000	-0.012	-0.024
6-9 (n=180)	-0.293	-0.245	-0.061	-0.107	-0.179
p	0.000	0.000	0.551	0.079	0.000

noid patients had the lowest scores on negative symptoms. Long duration of illness meant higher positive (p=0.000) and disorganisation (p=0.000) scores. Poor GAS at discharge was associated, as expected, with high scores on negative, positive and disorganisation dimensions.

Psychiatric treatment and psychosocial situation at follow-up

Prescription of antipsychotics correlated with the positive and disorganisation dimensions, while prescription of antidepressants and anxiolytics correlated with the depressive dimension. Having a physical illness correlated with depressive symptoms. Both GAS scores and number of restrictions in functioning had rather high correlations with all factor dimensions, being highest for negative, positive and disorganisation dimensions (Table 5). Life satisfaction correlated negatively with all factor dimensions, and number of confidants with all factor dimensions except disorganisation.

Categorical vs. dimensional diagnosis

As a stepwise logistic regression analysis was performed in the chronic sample, the four major symptom dimensions, together with duration of illness, significantly explained the variance in GAS scores (Table 6). Diagnosis did not enter into the equation. When negative, positive and disorganisation dimensions had been entered, the association between diagnosis and GAS became non-significant.

The first-episode sample analyses produced basically similar results. At each stage, the negative dimension entered into equations (at baseline: OR 0.52, 95%CI 0.36-0.74; at 2nd year: OR 0.15, 95%CI 0.08-0.30; at 5th year: OR 0.54, 95%CI 0.37-0.80). At 2nd year, also the delusional (OR 0.31, 95%CI 0.17-0.55), auditory hallucinatory (OR 0.61, 95%CI 0.39-0.98), and disorganisation (OR 0.53, 95%CI 0.30-0.94) dimensions, and, at 5th year, the depressive (OR 0.51, 95%CI 0.34-0.75) and disorganisation (OR 0.57, 95%CI 0.37-0.91) dimensions entered into equations. Diagnosis did not enter into the equations at any stage.

Table 6 Logistic regression analysis of GAS scores

Variable	p	OR	95%CI
Negative	0.000	0.230	0.179-0.295
Positive	0.000	0.292	0.230-0.370
Disorganisation	0.000	0.390	0.295-0.515
Depressive	0.001	0.650	0.507-0.834
Duration of illness	0.035	0.978	0.959-0.996

DISCUSSION

The factor analyses of both studies produced five major dimensions. The negative, positive, depressive and disorganisation dimensions were found in the first-episode and chronic samples. Negative, positive and disorganisation dimensions have also been found in other studies (e.g. 18). Additionally, although patients with schizoaffective disorder were excluded from the chronic sample, a depressive dimension emerged. This is in line with findings in various, more widely defined samples of schizophrenia patients (e.g. 19). Thus, in addition to the negative, positive and disorganisation dimensions, the depressive dimension belongs to the symptomatology of schizophrenic disorders.

In a sample of first-episode schizophrenia patients, the negative and depressive dimensions were not consistently separated from each other during the first two years of follow-up, but were clearly separated at the fifth year of follow-up. Thus, during the first years of schizophrenia, the distinction between negative and depressive symptoms is not clear yet, but becomes more distinct in later phases of the illness.

It is also important to note that, in the first-episode sample, hallucinations and delusions formed two separate dimensions, which in the earliest phase of illness had no correlation and later rather few correlations with the concurrent psychosocial situation. In the chronic sample, both delusions and hallucinations loaded on the same positive dimension, which had strong associations with social outcome factors. These findings support the conclusion that delusions and hallucinations are distinct symptom dimensions (23), which in selected chronic samples of schizophrenia patients are merged together.

In the chronic sample, all symptom dimensions were associated with outcome variables; the higher the symptom score in any of the dimensions the poorer the outcome. The negative, positive and disorganisation dimensions had the highest associations, but high depressive and hostile scores also meant poorer outcome. In the first-episode sample, depressive symptoms at a later stage of illness also predicted a poor psychosocial situation, while

Table 5 Significant correlations (multiplied by 100) between factor scores and treatment and psychosocial situation at follow-up

	Negative	Positive	Depressive	Hostile	Disorganisation
Antipsychotics	8	12			15
Antidepressants		-10	15	-6	-6
Anxiolytics			21	-6	10
Physical illness			24		
GAS	-41	-36	-15	-10	-26
Functioning	47	29	10	20	23
Confidants	-22	-8	9	-13	
Life satisfaction	-12	-7	-27	-14	

their occurrence at an early stage of illness was a predictor of a good prognosis. Additionally, it is worth noting that, at baseline, there was a manic symptom dimension, which also predicted a positive psychosocial situation at the second year. Thus, affective symptoms (both depressive and manic) in an early phase of illness are predictors of a good outcome, as also found in earlier studies (34-36).

The symptom dimensions were associated with patients' socio-demographic background, but these associations were stronger in the chronic than in the first-episode schizophrenia patients. In the chronic sample, men, in particular single men, had more negative symptoms. The high prevalence of negative symptoms can partly explain why male schizophrenia patients have poorer outcome than females (34,35,37-41). On the other hand, women had higher scores in the depressive dimension, as also reported in the general population (42). Thus, being depressed seems to be a general symptom dimension related to the female gender.

The depressive dimension was also the only dimension of schizophrenia which was associated with comorbid physical illness. Among outpatients of general practitioners, physical illness is one of the most important risk factors for occurrence of depressive symptoms (43). Thus, among long-term schizophrenia patients, depressive symptoms have the same physical and social associations as is the case in the general population (42).

Being single was associated with the occurrence of the negative dimension. In the first-episode patients, the negative dimension was associated with premorbid psychosexual development from the onset of illness until the fifth follow-up year, supporting the social selection hypothesis. Patients with poor premorbid psychosexual adaptation are predisposed to remain single, as shown in other studies (35,41), and also to suffer concurrently from negative symptoms. It is also possible that family life tends to prevent the development of negative symptoms. Living without a close relationship also means lower social stimulation, which has been associated with the clinical poverty dimension (44).

In logistic regression analysis, symptom dimensions proved to be more powerful in explaining variance of outcome than categorical sub-diagnoses. This offers rather convincing proof in favour of the dimensional approach in describing symptomatology in schizophrenia. In the chronic sample, antidepressants and anxiolytics were prescribed for patients with high depressive scores more often than others, while patients with high negative, positive and disorganisation symptoms received higher doses of antipsychotics. Clinicians' treatment practice was thus in accordance with patients' symptom dimensions.

Overall, the findings of the present study support the view that the dimensional approach to phenomenology in schizophrenia is valuable both from a scientific and a clinical point of view. Symptom dimensions of schizophrenia patients are closely associated with patients' premorbid development, sociodemographic background, clinical history and conditions, as well as with outcome and the treatment patients receive. A dimensional rather than a categorical diagnostic approach can thus offer an informative method for evaluating the life situation of schizophrenia patients in various phases of their illness.

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Integration initiatives for forensic services

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Poorly implemented mental health reform policies are often given as reasons for the growth in demands for forensic psychiatric services and the steady increase of mental patients in prison systems. However, in this paper, additional reasons are advanced to explain the growth of forensic psychiatry, such as an expansion in the types of "psychiatric defences" in courts of law; public concerns about violent behaviour attributed to the mentally ill; the community management of paraphilias, especially pedophilia; the development of risk assessment methodologies and the halo of super-specialization. The net result of these developments is that patients who receive a label of "forensic" enter into a mental health ghetto with little connectivity or integration with the general mental health system. The forensic label increases the stigma and decreases opportunities for reintegration and full social recovery. The paper provides guidelines to reverse these trends.

Key words: Forensic psychiatry, mental health services, mental health reform, reintegration

Deinstitutionalization, the closure of mental hospital beds and changes to commitment laws were highly touted initiatives that made the backbone of mental health reform policies implemented in many countries in the second half of the last century. These initiatives, however, have often been given as reasons for the increasing demands for forensic psychiatric services and the steady increase in the numbers of mental patients in prisons (1-5). However, the real problem is likely to be the inadequate follow-up and the lack of social structures in the community at the time hospital beds are closed. Were adequate community systems in place, they could prevent the backward drift of mental patients into a more pernicious form of institutionalization (6,7).

At a different level, in some jurisdictions, the growth of demands for more forensic services threatens the stability and funding for regular mental health services, because the overcrowding in forensic units makes it necessary to 'download' forensic patients to regular mental health beds, or because, as happens in some jurisdictions, the judiciary tends to overuse 'hospital orders' (8). Furthermore, given that forensic admissions unbalance ecological funding distributions (9), staff in the regular mental health system feel that funds are inappropriately funneled out of hospitals and community care to treat 'criminals' in forensic units or in prisons. A separation of ways, therefore, seems to have taken place between two sections of what ought to be a single and wholly encompassing system of care for the mentally ill. Clearly, better information and a closer integration between forensic services and the general mental health system seem required. This paper will review issues pertaining to the development of forensic psychiatry and its impact on general mental health services, and provide some general guidelines for better integration within a continuum of behavioural health services.

THE FIELD OF FORENSIC PSYCHIATRY

Several reasons have been advanced to explain the growth and the seemingly overwhelming reach of forensic psychiatry over the past two decades. They can be summarized as follows.

Courtroom work

Although the field of forensic psychiatry has a long history (10), its growth can be traced back only to the 1800s, when concerns about legal decisions involving mentally ill defendants as per their level of criminal responsibility were aroused out of the celebrated McNaghten case in England in 1843 (described in detail by East) (11). Ever since, the literature on the relationship of mental illness to criminality and criminal responsibility has grown exponentially, so that it is impossible to summarize it in a paper of this nature. There is, for example, a large number of publications on the matter of criminal psychopathology, that started in the first half of the last century with the psychoanalytic writings emphasizing the role of neurosis in sexual perversions (12-14) and phenomenological descriptions of psychopathology underlying a variety of criminal behaviours (15,16), and that continues to this day with highly technical, multi-authored, publications on the same subject (17,18).

Forensic court work, through the introduction of 'psychiatric defences', has expanded from clearly defined areas where serious psychopathology, usually caused by severe mental conditions, was the only reason to exempt an accused from criminal responsibility (defence of the insane or not criminally responsible because of a mental disorder), as in the case of McNaghten, to include a variety of conditions including 'partial' and 'temporary insanity' related to inability to control the passions, and which may lead to findings of diminished responsibility because of lack of intent; the impacts of childhood traumas (19) and related memory syndromes (20,21), and most recently, cases of drugs or alcohol intoxication and psychogenic dissociations and automatisms (22). The growth in the numbers and types of psychiatric legal

defences and the high relevance given to the evidence provided by mental health professionals has started to arise concerns about the quality of the science and the ethical standing of forensic clinicians (23-25). Yet, the more mental health evidence is heard in courts, the more it seems that criminal law can no longer be dissociated from forensic psychiatry, to the point that an expert is now required for matters that in the past were left entirely in the hands of the Judge or the jury. Furthermore, the watering down of the insanity threshold, as has happened in Canada, where it was reduced from 'beyond reasonable doubt' to 'on the balance of probabilities' (26), instead of being of help to patients, has led to an increase in the levels of criminalization of behaviour that in the recent past was usually dealt with via hospitalization.

Mental illness and violence

The media coverage of sensational crimes allegedly committed by mental patients (27) has aroused concerns about the safety of the public, so that a backlash against further implementation of deinstitutionalization initiatives and a tightening of legal controls on the mentally ill has already started, as exemplified by the proposed reform to the Mental Health Act in the UK, section on 'high risk patients' and the implementation of community treatment orders (outpatient commitment legislation) in some jurisdictions in USA and Canada, also proposed more recently in England and Wales. Forensic psychiatrists, as the ones who most often deal with high risk patients, have developed an increased expertise in the management and knowledge of violent behaviour. By extension, the public concerns about mental illness and violence have further accrued the importance of forensic psychiatry and need for its practitioners.

Paraphilias

Another area of much public concern is the management of persons suffering from paraphilias, especially pedophilia. Much has been written recently about the positive prospects for the treatment of sexual offenders (28,29). Although most of these therapeutic approaches take place in prisons, eventually sexual offenders are released to the community where their predatory behaviour may start anew. This has led to demands for further community treatment or mental hospitalization (30). Yet, despite the introduction of newer and stronger antiandrogenic medications such as cyproteron acetate and leuprolide acetate, and the newest, triptolerin, the success of treatment for pedophilia still remains uncertain (31). On the other hand, community demands to reinstitutionalize pedophiles by committing them to mental hospitals after their release from prison, a practice referred to as 'gating', has created pressures on the few remaining mental hospital beds in many jurisdictions (32) along with many legal and ethical concerns (33).

Risk assessment

Super-specialized forensic psychiatrists have practically cornered the market on risk assessment to the exclusion of every other psychiatrist or mental health specialist, excepting some equally super-specialized forensic psychologists. Esoteric as the science seems to be (34-36), it is no more than a set of psychological scales infused with the mystic belief that only the initiated can do it, and the other, some would say naïve belief, that prediction science has gone far enough to offset the good or bad imponderables of human behaviour. The controversy in this respect centres around whether *static* risk factors (also called *actuarial* or *statistical*) are as good as, or better than clinical factors (also called *dynamic*) for the prediction of dangerousness (i.e. are technicians as good or better than clinicians). It is not uncommon nowadays to hear forensic psychiatrists explaining that an offender has a probability of, say, 70 or 90% of reoffending violently, based on the probabilities worked out through the help of any of the scales produced to predict violent behaviour. The way the science of prediction is moving, it would not be too far from the predictions of the infamous Texan Dr. Grigson, also known as Dr. Death (37), a forensic psychiatrist that used to go to courts to pronounce that he was *100% certain* that an offender (whom sometimes he would not have examined or examined only for a few minutes) will commit homicide again. This mechanistic approach to the understanding and management of human behaviour has already been highly criticized on ethical, social policy and scientific grounds (38-40). Yet, many forensic psychiatrists and psychologists still hold to the position that these instruments are infallible, instead of accepting the more conservative view that they are only aids to diagnosis and that not even that plus a superb clinical assessment (41,42) could give but approximate answers to violence risk prediction and management.

Super-specialization

The more the impression that forensic psychiatry is the purview of only a few super-specialists, the more difficult it is to reintegrate forensic psychiatric patients into the mainstream of the mental health system and, ultimately, into society. The mumbo-jumbo legalese language coupled to the cloak of pseudo-scientific pronouncements (43) has scared away many other mental health specialists, who now refuse to manage forensic patients, rather deferring to the knowledge of the super-specialists and refusing to accept these patients even in the more highly specialized assertive community treatment teams. Forensic psychiatry has apparently become a ghetto, "once forensic, always

forensic", from where forensic patients cannot leave. The forensic label identifies, stigmatizes and perpetuates the difference of forensic patients. And yet many of these patients are the same mental patients whose lot has been to commit an offence, many times a minor one (44). The super-specialization aura of forensic psychiatry may have helped the subspecialty, but it might have worked to the detriment of mental patients.

INTEGRATION THRUSTS

Making it Happen (45), the basic compendium of mental health reform in Ontario, Canada, enunciates seven principles for a complete restructuring of mental health systems, from hospital beds to community tenure, to rehabilitation and recovery as well as including advocacy, promotion and prevention for good mental health in the population:

- The consumer is at the centre of the mental health system
- Services will be tailored to consumer needs with a view to increase quality of life
- Consumer choice will be improved while access to services will be streamlined
- Services will be linked and coordinated so the consumer is able to move easily from one part of the system to another
- Services will be based on best practices
- Mental health funding will continue to be protected
- There will be continued investments/reinvestments in mental health services to support mental health reform and increase the overall capacity of the mental health system.

While on the surface these principles appear self-evident, it is precisely the lack of clarity about the principles and the goals of previous attempts at mental health reform, besides the financial neglect, that doomed those attempts to failure and caused so much damage to the mentally ill. Previous attempts dealt only with the most obvious flaws of existing systems, but neglected the rehabilitation needs of consumers and the steps required towards successful reinsertion in the labour market along with other social needs such as adequate housing and recreation. In short, that consumers have to be provided with all the supports required to a full recovery and reestablishment in the social structure of the community. In fact, knowing quite well that it has been the implementation that has failed, *Making it Happen* stipulates the implementation goals (46) of the new system by detailing that core mental health services and supports:

- Are provided within a comprehensive service continuum developed to meet client needs and based on best practices
- Are well integrated with the broader continuum of care provided by health and social services
- Are organized and coordinated based on a "levels of need" structure, to ensure that consumers have access to the services that best meet their needs
- Are appropriately linked to other services and supports within geographic areas
- Facilitate a shared service approach to meeting the needs of individuals with serious mental illness who have multiple service needs
- Achieve clear system/service responsibility and accountability through the development of explicit operational goals and performance indicators
- Are simplified and readily accessible to the consumer's needs.

In essence, quality of interventions, tailoring to needs, comprehensiveness, integration, seamlessness, accessibility and accountability are, among others, the key concepts to make the system work and be responsive to the needs of the patient.

From these perspectives it can be surmised that conceptually, organizationally, administratively and financially, forensic psychiatry cannot be a system independent from the main stream of the general mental health system; at best, it could only be a subsystem. The sooner this premise is accepted the better for forensic patients and the more integrated the total system should be. Several steps should be taken in order to reach this point, but two assumptions have to be accepted prior to developing steps for integration. First, that there are not too many differences between the regular psychiatric patient and forensic patients, and second that, with appropriate rehabilitation approaches, forensic patients have the same possibilities of re-adaptation and reintegration as regular mental patients (47). In addition, modification of two social perspectives will have to be accepted. The first, that, not all abnormal behaviour, aberration, perversion, or criminal behaviour are mental illnesses amenable to treatment and rehabilitation within a modern, community oriented mental health system and the second, that forensic specialists should demystify their profession and make their technical skills and knowledge more accessible to other mental health workers.

Once these basic premises are accepted, it remains to develop points of convergence and similarities where the two subsystems would interface. In the Province of Ontario in Canada, 20 key juncture points within the justice-correctional system have been identified in which mental patients can be diverted to the general mental health system. These points go from the moment of detention to the moment of release from prison and subsequent probation encompassing prevention, treatment and rehabilitation - from the moment of detention when a police officer could take the person to a psychiatric emergency instead of proceeding with arrest and detention within the

justice system to the moment the patient-inmate leaves the prison so that relapses and recidivism could be averted.

In regard to expectations on personnel and systems, staff in assertive community treatment teams (48) in charge of managing the most difficult patients in the community in lieu of hospitalization should be trained in the assessment and management of violent behaviours among their patients (49). Similarly, the development of mental health courts in USA and Canada, where the thrust of judicial action is to mobilize community resources so that the mentally ill is given another chance to remain in the community within the general mental health system instead of being channeled into the forensic system, has reduced the number of fitness assessments and decreased to some degree the need for more beds within the forensic system. These courts depend heavily on court mental health workers (50) whose role, while closely aligned to the forensic system, is to help and implement court diversion schemes, thus forming a bridge between the legal and the general mental health system (51). Furthermore, they as well as forensic psychiatrists should become educational resources for the rest of the mental health personnel, so that expertise on forensic psychiatry becomes the knowledge of the majority of the workers, who will then feel comfortable and at ease in the management of forensic patients. Easy and direct contacts between the regular mental health system and mobile outreach community forensic teams will foster the development of 'share-care models' whereby the consumer, regardless of the complexity of the condition and legal issue, is managed by both the basic service or primary mental health care worker and the consultant. These models are to be favoured over direct taking over of the case by the consultant. This way the consultant forensic psychiatrist becomes an on-going teacher and supervisor of the less knowledgeable colleagues in the system. Only under extreme circumstances that threaten the safety of the public will the consumer be removed from community tenure. It is only through this integration of forensic psychiatrists and the forensic system into the general stream of mental health that we can expect to curb the growth of forensic psychiatry and achieve better reintegration of forensic patients into society.

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Chronic cognitive impairment in users of 'ecstasy' and cannabis

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MDMA use is commonly accompanied by use of other substances, most notably cannabis. Both MDMA and cannabis have probable effects on cognition. This paper reviews research into long-term effects on cognition which are likely to represent neurotoxicity. Research is hampered by numerous confounds and methodological difficulties. With recent cannabis use there is both an acute and a residual effect on cognition, making it important to have a significant abstinence period from cannabis when studying effects of MDMA in recreational users of both substances. It would appear that MDMA does indeed have subtle long-term effects on complex memory and executive functions that are independent of cannabis and may remain with abstention. This is consistent with evidence of disruption of the serotonin system in animal and human studies. Chronic effects on cognition due to cannabis are less consistently demonstrated, but more sensitive tests including electrophysiological measures have revealed long-term deficits in attention.

Key words: 3,4-methylenedioxymethamphetamine, 'ecstasy', cannabis, cognitive performance, neurotoxicity

The controversy surrounding the risks posed to society and to the mental health of individuals by the use of illicit psychoactive drugs continues unabated. 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and cannabis are perhaps the most controversial drugs. Despite much research, many of the long-term risks related to the use of these drugs have not been clearly defined or quantified, but remain central to the debate over their legal status. Furthermore, the use of these drugs remains widespread, with approximately 10% of adults in the UK aged between 15 and 29 having tried 'ecstasy' (1), and 20% of university students having cannabis weekly or more frequently (2).

There has been stronger evidence of chronic effects of MDMA on cognitive functions and in this review we will focus on these, as well as on the less well documented confounding role played by cannabis, the illicit drug most widely used by MDMA users, and on the effects on cognition of cannabis per se.

EARLY STUDIES ON MDMA AND COGNITION

Taking MDMA leads to an acute massive neuronal release of serotonin (5-HT), followed by a period of depletion before levels return to normal. More chronic toxic effects appear also to involve primarily the 5-HT system, with the demonstration of serotonergic degeneration in several animal species, including non-human primates (3). 5-HT is thought to play a prominent role in memory function and marked toxic effects of MDMA have been observed in the hippocampus and frontal cortex - areas crucial to memory and other cognitive functions (4). This suggests that MDMA may have long-term effects on cognition.

Important difficulties are faced by researchers investigating the effects of MDMA on humans. First and foremost, there are ethical and legal proscriptions to repeatedly administering an illicit and potentially toxic drug in controlled laboratory conditions. This means that studies are mostly restricted to recreational users, with the possible consequence of inaccurate self-report of the amounts of MDMA used. Furthermore, 'ecstasy' tablets bought on the black market contain a variable amount of MDMA (5), and may contain a variety of other substances, including the closely related 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxyethylamphetamine (MDEA), caffeine, ephedrine, selegiline, amphetamine, ketamine, and LSD (6,7). Thus, amounts of MDMA consumed by experimental subjects are estimates and extraneous substances may affect findings. Then there are difficulties in finding suitable MDMA naïve control groups to match user groups. MDMA is primarily used in the dance/'rave' scene, and there are very few individuals who share this lifestyle - including for example the sleep deprivation associated with all night raves - who have not taken MDMA. Premorbid differences between users and controls in intellectual, cognitive or psychological functions also need to be addressed. Furthermore, most MDMA users take other psychoactive drugs, including alcohol and illicit drugs, and these may have their own effects on cognition. Importantly, acute and chronic effects are often masked by too short an abstinence period for both MDMA and cannabis, especially the latter when the focus is on MDMA.

One of the first indications of chronic cognitive deficits resulting from MDMA came in 1992 (8). Impairment of initial and delayed paragraph recall was described in 9 subjects compared to age-matched normative values. Subjects had taken an average of approximately 130 'ecstasy' tablets. They reported abstinence from MDMA for an average of about 66 days prior to testing and from all psychoactive drugs for 3 weeks. Performance on other cogni-

tive tests was unimpaired. Results were, however, limited by the small number of subjects, the past use of other psychoactive substances, the fact that they were given a tryptophan infusion prior to testing and the lack of a control group. Furthermore, some of the subjects had psychiatric histories.

Parrott et al (9) then compared three groups: 10 regular MDMA users who had taken MDMA on more than ten occasions, 10 novice MDMA users (< ten occasions), and 10 age-matched control subjects who had never taken MDMA. The period of abstinence was undefined, so that possible lingering effects following recent MDMA or other drug taking were not excluded. The MDMA groups were significantly impaired on immediate and delayed word recall, but not on other cognitive tests (information processing speed, sustained attention). An important flaw was that details of other illicit drugs were not recorded. This study was noteworthy for finding deficits in light users.

A study looking at slightly heavier consumption compared 24 MDMA users (> 25 times) and 24 MDMA naïve controls after an abstinence period from all psychoactive drugs of 2 weeks (10). No significant differences in memory function were found between the two groups. However, impairment in immediate verbal and delayed visual memory was found in the heavier MDMA users when estimated monthly dose of MDMA was included in regression models. Both subjects and control groups had taken other illicit substances, thus achieving some control for this potential confounder. However, levels of use were much greater in the MDMA group.

Shortly after the above studies, in 1999, we instigated a study of MDMA recruiting participants via advertisements in the popular press (11). The sample size of 36 was relatively large for the field and MDMA use was greater than in most preceding studies (estimated mean 235 tablets). Subjects were identified for whom MDMA was the primary drug and who reported using other drugs only irregularly. They had not consumed any illicit drug for a mean of 78 days prior to the testing. Thus, impairments were unlikely to represent either acute MDMA effects, which last approximately 3-5 hours after a dose (12), or lingering effects which may last several days and may reflect the time course of regeneration of 5-HT.

We found discrete deficits in memory and learning compared to drug naïve controls, which were both verbal (immediate recall of words from a list, digit sequence learning) and non-verbal (face recognition and spatial associative learning). Other cognitive functions were intact, including executive/frontal lobe functions, attention and verbal and non-verbal working memory. Both sides of the brain were implicated and the patterned deficit profile excluded explanations based on non-specific factors such as subjects' motivation. Mood, as assessed by the Beck Depression Inventory, also did not affect results. Cannabis was clearly identified as the next most commonly used illicit substance; however, none of the deficits showed any correlation with frequency or amount of cannabis used. Nevertheless, the difficulty in identifying a pattern to the MDMA deficits prompted a second study looking more closely at the role played by cannabis.

In this second study (13), a group taking cannabis but not MDMA (n=18) was introduced and compared with a group that took both cannabis and MDMA (n=11) and controls who had not taken MDMA or cannabis (n=31). Both user groups performed more poorly than controls on tests of verbal and visual memory, verbal fluency, speed of processing and manual dexterity. However, there was little difference between user groups on any of the tests. Thus, deficits appeared more closely related to cannabis than MDMA. It should be noted, however, that the size of the cannabis+MDMA group was comparatively small and the mean MDMA usage was about 42 tablets, far lower than in our previous study, whereas cannabis use was heavy, with mean estimates of about 11000 and 7800 total joints in the user groups. Recent cannabis use may have affected findings, as the requested abstinence period from cannabis was 48 hours and a number of subjects reported even less than this.

Notwithstanding these findings, MDMA has continued to be implicated in contemporaneous research, and further work in our department with electrophysiological measures highlighted residual effects that were independent of cannabis. Croft et al (14) focussed on the suspected neurophysiological correlate of MDMA-related cognitive impairment, namely depressed 5-HT function. 5-HT in the primary auditory cortex is thought to operate as a protective mechanism by attenuating the cortical response to loud auditory stimuli, and this was employed as an electrophysiological index of 5-HT function. It was found that long-term predominantly MDMA users exhibited 5-HT dysfunction relative to both predominantly cannabis users and drug-naïve controls. The 5-HT impairment was strongly related to total MDMA consumption, but was independent of frequency of MDMA use, suggesting a causal relationship, i.e. that MDMA caused the 5-HT impairment. This follows the argument that, if the relationship were reversed, such that impaired 5-HT predisposed an individual to 'risky behaviour' including MDMA use, then frequency of MDMA use and not total tablets consumed would be more closely related to the 5-HT deficit. The total number of tablets consumed would be determined by the stage of the subject's MDMA 'career' when recruited to the study. This study also found that cannabis was not related to the 5-HT deficit.

Now in the new millennium there have been a plethora of studies on the cognitive effects of chronic MDMA use. Before reviewing these, the cognitive effects of cannabis will be considered. Cannabis is a popular drug of choice in the rave subculture and is also taken by MDMA users to ameliorate the low mood and irritability of the 'coming down' period after MDMA use.

CANNABIS AND COGNITION

The neuropsychological effects of cannabis can be divided into acute and residual (15). Acute effects are those associated with intoxication. Residual effects may be 'drug residue' effects from cannabis accumulation in the CNS in the hours/days after acute intoxication, or a chronic residual toxicity that persists after the drug has left the body representing CNS alteration effects.

Considering first acute influences, cross-sectional studies experimentally administering cannabis to subjects have indeed supported the existence of a syndrome of acute intoxication, with mood change, perceptual changes and characteristic cognitive impairments in memory and attention, motor skills, reaction time and skilled activities (16). After the period of acute intoxication, it takes some time for performance to return to pre-dose levels, suggesting a drug residue effect. For example, performance on a flight simulator was impaired for up to 24 hours in aircraft pilots after smoking cannabis (17). In light users there has been evidence of a drug residue effect for 12-24 hours following a dose, but no clear evidence of a deficit persisting for more than 48 hours.

Investigation into the chronic residual/toxic effects of cannabis has focussed on 'naturalistic studies' of individuals who have taken the drug more heavily or over longer periods than could be ethically duplicated in the laboratory. Users have been tested after a period of abstinence to exclude acute or drug residue effects, although the length of this period has varied from study to study. In the 1970s and 1980s studies were roughly equally divided with respect to positive and negative results. Most had serious methodological flaws. In general abstinence periods were less than 24 hours or unrecorded, thus drug residue effects may easily have explained findings.

Two early reports of chronic deficits resulting from cannabis were subject to limitations. In groups that were small and not well matched for gender and use of other drugs, Schwartz et al (18) compared 10 cannabis dependent users after 6 weeks of supervised abstinence with control groups of polydrug users and non-users. Visual retention and verbal memory for prose passages were found to be impaired. A larger scale study importantly matched 144 users and 72 non-using controls in intellectual ability prior to onset of cannabis use (19). Heavy cannabis users (7+ times weekly) showed modest deficiencies in mathematical reasoning and verbal expression as well as selective impairments in the memory retrieval process. Light and intermediate use was not associated with deficits. The user group had, however, experienced other drugs far more extensively and there was only a 24 hour unsupervised abstinence period.

In more rigorous studies, a consistent theme has been attention impairment as a result of heavy or long-term use, as well as memory impairment. A study comparing groups of heavy and light cannabis users with a supervised abstinence period of 19 hours before testing found impairments in mental flexibility (attentional set shifting) in heavy users (20). Learning of word lists was also impaired. The group differences remained after some statistical control of potential confounding variables, such as estimated levels of premorbid cognitive functioning and use of alcohol and other substances. In a Costa Rican sample having an abstinence period of 72 hours verified by urinalysis, subtle deficits in selective and divided attention associated with working memory and in verbal memory were disclosed that were specific to long-term users (21).

The most recent report (22) found that long-term cannabis takers (mean of 24 years use) performed significantly less well on verbal memory than shorter-term (mean 10 years) and non-user controls. Impairments were not severe, but learning, retention and retrieval were all affected following a median self-reported abstinence period of 17 hours. There was some suggestion of attention impairment, although executive tasks were generally unimpaired. Problems with this study include the fact that the cannabis users recruited were seeking treatment for dependence due to concerns including that of subjective cognitive impairment and may thus not be representative of cannabis users in general. The abstinence period was short and groups differed in use of other drugs; however, attempts were made to control these factors statistically. Performance measures on several tests correlated significantly with the duration of cannabis use, suggesting a chronic neurotoxic effect. Interestingly, apart from a time estimation task, no deficits were shown in shorter-term users with a mean use of 10 years and who were using cannabis daily.

Although the studies described so far used abstinence periods of 12-72 hours, it is still not clear if the deficits found were neurotoxic effects or whether they were due to a residue of cannabinoids in the brain. The principal active component of cannabis, delta-9-tetrahydrocannabinol, accumulates in fatty tissue, and has a tissue elimination half-life of about 7 days (23). In heavy users cannabinoids may remain in the body for more than two months after cessation (24). This prompted a study by Pope et al (25) in 108 long-term heavy users of cannabis throughout 28 days of monitored abstinence confirmed by urinalysis. Deficits were found on memory of word lists detectable at least 7 days after discontinuation of the drug and which were related to initial urinary cannabinoid concentration. These appeared to be reversible phenomena associated with recent drug exposure - attributable either to cannabinoids lingering in the CNS or to withdrawal from abruptly stopping use. An association between cumulative lifetime use of cannabis and cognitive deterioration was not found. After 28 days of abstinence, users showed virtually no differences from control subjects on a battery of 10 neuropsychological tests. Thus, impairments were related to recent cannabis exposure and were reversible with abstention. These findings are compatible with studies that found no significant long-term effects on IQ measures

and the Mini Mental State Examination (26,27). A meta-analysis of 13 of the more methodologically sound studies also found no significant evidence for chronic deficits in 7 out of 8 neuropsychological ability zones, with a possible small effect in only one domain, namely learning (28).

Finally, looking at electrophysiological evidence of attention impairment, Solowij et al (29,30) examined cortical event related potentials for anomalies of processing negativity in an auditory detection task. The ability to focus attention and filter out irrelevant information was impaired progressively with the number of years of cannabis use and only partial recovery was evident in former heavy users after a mean of approximately 2 years abstinence.

In summary, there is clear evidence that cannabis has a residual effect on cognition that lasts 12-24 hours after even a single episode of smoking. This needs to be considered when investigating effects of MDMA. Frequent smoking may lead to an accumulation of CNS cannabinoids and a drug residue effect may persist for much longer and may be continuously present. It is likely to include impaired focussed attention and working memory as well as impaired visual and verbal memory. There is less evidence for chronic neurotoxic effects following cannabis; however, there may be more subtle deficits influencing attention, such as those demonstrated electrophysiologically which appear to be related to duration of cannabis use. Studies into MDMA should aim for periods of abstinence from cannabis of some weeks rather than days, to avoid or minimize residual effects, particularly if cannabis is taken frequently. It also has to be borne in mind that withdrawal effects - characterised by insomnia, restlessness and irritability - in heavy cannabis users may affect cognitive performance. However, a more complex effect with MDMA and cannabis potentiating or diminishing the impact of the other on cognition cannot be ruled out.

RECENT RESEARCH INTO CHRONIC EFFECTS OF MDMA ON COGNITION

In an attempt to address the fact that past use of other psychoactive drugs may confound MDMA results, Morgan (31,32) compared polydrug taking controls who had never taken MDMA with MDMA+polydrug users and nonusers. The MDMA group had consumed an average of 50 tablets and reported being MDMA free for an average of 9 weeks. Participants were only required to abstain from taking other psychoactive drugs on the day of the study, so that effects from their recent use were not excluded. The MDMA group had impaired immediate and delayed prose recall compared to both control groups. Performance on other cognitive tests, including executive function and working memory, was unimpaired.

Focussing more specifically on controlling for past cannabis taking, Gouzoulis-Mayfrank et al (33) compared groups of non-drug controls with cannabis and cannabis+MDMA users (average about 94 tablets). Abstinence from MDMA was reported to be more than 21 days; however, subjects were asked to refrain from cannabis only on the day of the study. The MDMA+cannabis group performed significantly worse than both other groups on tests involving complex attention (but not basic alertness), visual learning, problem solving and strategic planning, suggesting that MDMA was primarily responsible. No significant deficits were associated with the cannabis groups, but of note was that in the MDMA group heavier use of cannabis was associated with stronger cognitive deficits. A similar design was used by Rodgers (34) to investigate lighter MDMA users (average of 20 times) after 2 months abstinence from MDMA and 1 month abstinence from cannabis, although this was not confirmed by drug screening. Deficits associated with MDMA were found on delayed recall of visual and verbal paired associates.

Then in order to minimise differences in psychosocial factors, Verkes et al (35) used MDMA naïve controls who were also rave party visitors, and compared them with 'moderate' frequency MDMA users (mean about 169 tablets), and 'heavy' frequency MDMA users (741 tablets). Abstinence from all psychoactive agents for one week was checked by urine drug screening. MDMA groups were impaired on memory span and word and figure recognition. The MDMA groups had consumed more cannabis, cocaine and amphetamines; however, deficits remained after some statistical control for this had been introduced.

Thus, while there is a growing consensus that memory deficits remain when past use of other drugs and psychosocial factors are considered, none of the recent studies are free from methodological confounds. MDMA has inevitably been taken with other drugs, and while our review suggests that cannabis may not produce memory deficits as a long-term residual effect, synergistic effects cannot be ruled out, but even more pertinently abstinence periods have been poorly controlled. For example, with an abstinence period from all drugs of only 24 hours, Bhattachary and Powell (36) found impaired immediate and delayed prose recall and executive function (verbal fluency). Similarly, Fox et al (37), although requesting participants to be free of MDMA and other illicit drugs for at least 2 weeks, only requested them to be free of cannabis for 1 day prior to testing. They reported deficits in verbal learning that were more related to storage and/or retrieval than problems associated with capacity. Long-term (>8 years) users showed some evidence of selective executive problems. Then with an abstinence period from all drugs of 2 weeks confirmed by drug screening, but with no control group and with polydrug use in the MDMA group, a longitudinal study found that continued use of MDMA over one year was associated with decline in immediate and delayed prose recall (38).

Consensus is also emerging for deficits in working memory and central executive functions in heavier MDMA users, though with less consistency across reports

compared with deficits of long-term memory. Furthermore, these studies remain fraught with the same methodological confounds. With no defined abstinence period for other drugs and limited statistical control for their past use and with no definition of an MDMA-free period in current heavy MDMA takers (about 1200 tablets), Wareing et al (39) found impairment in aspects of central executive functioning (random letter generation) along with impaired accuracy of information processing. A study designed to avoid effects of recent psychoactive drug taking included abstinence periods from all recreational drugs of at least three weeks with confirmation of drug-free status by drug screening (40). Heavy MDMA polydrug users (mean of about 584 tablets) were subtly impaired on computerised tests of sustained attention, complex attention/working memory and logical reasoning as well as delayed memory compared to MDMA naïve polydrug controls. However, MDMA subjects had used more recreational drugs than controls and this may have contributed to cognitive impairments.

Requiring participants not to have smoked cannabis for three days and not to have consumed other drugs for 24 hours, both relatively short abstinence periods, Heffernan et al (41) investigated the central executive functions involved in prospective memory (i.e. remembering to do something in the future). Heavy MDMA users were impaired in self-rated prospective memory, as well as in verbal and semantic fluency tasks compared to a MDMA naïve polydrug group. Impairments remained significant when a measure of statistical control was used for consumption of cannabis and other drugs; nevertheless use of other drugs was much greater in MDMA groups. This limitation also applied to the carefully designed studies of Fox et al (42,43), both of which used MDMA naïve polydrug controls. In the first study, subjects with subjective problems attributed to MDMA (mean of about 372 tablets) were compared with MDMA users without these problems (mean of about 357 tablets) and controls (42). Deficits were disclosed on executive planning and spatial working memory which related to total MDMA consumption and were not related to subjective problems, suggesting that damage may occur without conscious appraisal. However, the second study (43) provided somewhat conflicting results whereby participants were unimpaired on most measures of prefrontal functioning. Here less heavy MDMA polydrug users (mean of about 172 tablets) were compared with controls. The MDMA group showed deficits in memory tasks sensitive to involvement of temporal structures or in a manner similar to patients with temporal pathology. Results remained significant when measures of drug use which differed between subjects and controls were used as covariates. In both these studies, subjects were requested to be free of psychoactive drugs for 2 weeks, but this was not tested. The discrepancy regarding executive functions was attributed to lower total doses and shorter duration of MDMA taking in the second study.

Executive function was subtly impaired in a recent study of heavy users that looked more closely at duration of toxic effect with abstinence (44). Subjects had consumed averages of 93-577 tablets across the different groups and included a group of ex-MDMA users who had been abstinent for at least 6 months. Participants were required to abstain from cannabis for 24 hours and other illicit drugs for 1 week. Deficits in the MDMA groups which persisted when measures of other illicit drugs were used as covariates involved story recall and working memory/executive function. Subtle executive impairment was again described in what was predominantly an EEG study (45). In subjects abstinent from all drugs for at least a week, a test of executive function (rule shift card test) correlated negatively with MDMA use in the past year. Interestingly, MDMA use also correlated with EEG coherence, a measure of synchronisation of firing, in posterior brain sites overlying visual association pathways, possibly indicating dysfunctional local connectivity.

Correlations between reported total MDMA exposure and measures of cognitive impairment suggest that deficits are primarily associated with MDMA and support evidence of chronic toxicity in heavier users. Estimated lifetime consumption of MDMA has been found to correlate with verbal memory functions (33,36,37,44), and with working memory and executive function (33,36). However, the fact that MDMA exposure calculations are based on self report and that the amount of MDMA in a tablet may vary considerably make such calculations problematic. Furthermore, the fact that individuals with higher lifetime MDMA consumption tend also to have higher levels of consumption of other drugs needs consideration when assessing regression or correlation analyses. It also has to be considered that MDMA induced neurotoxicity may not simply relate to cumulative dose, but that patterns of use may be important and single high doses of MDMA may represent a particular risk, although this has not been widely studied in humans.

Morgan et al (44) suggested that cognitive impairment resulting from MDMA might be a long-lasting phenomenon. Deficits in verbal recall and working memory persisted for at least 6 months and for an average of 2 years after cessation of use. Wareing et al (39) also found that working memory impairment persisted for at least 6 months and Reneman et al (46) reported that verbal recall remained affected at 1 year after stopping use. There has been, however, tentative evidence of some recovery of memory in a small group of 3 MDMA users who had abstained for more than 6 months (32).

Some of the studies mentioned have provided evidence of an association between cognition and indirect biological evidence of 5-HT disruption. Decreased cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA - a metabolite of 5-HT) has been positively correlated with memory decline (10). Memory span has been found correlated with cortisol response to a serotonergic challenge

(35). On the other hand, although finding significant decrements in CSF 5-HIAA in MDMA users, a correlation with cognitive deficits was not found by McCann et al (40).

In a single photon emission computed tomography (SPECT) study, Reneman et al (47) found post-synaptic cortical 5HT2A receptor binding positively correlated with verbal recall in a group of 5 heavy MDMA users. Reneman et al (48) found impairment in verbal delayed recall to be associated with prefrontal cortex neuronal loss or dysfunction as indicated by altered N-acetylaspartate to creatinine ratio on magnetic resonance spectroscopy. Subjects were 8 heavy MDMA users who had been abstinent for a week. These studies were supportive of relationships between 5-HT disruption and cognitive dysfunction, but were small and not controlled for use of other substances.

A larger SPECT study by Reneman et al (46) did not, however, find brain pre-synaptic 5-HT transporter densities in the cortex to be associated with cognitive measures. Receptor density was significantly lower in MDMA users compared to controls, but not in ex-MDMA users who had stopped at least one year before the study, suggesting that the effect was reversible. By contrast, verbal recall remained impaired in ex-MDMA users. Similarly, a SPECT study by Semple et al (49) found reduction in 5-HT transporter densities in the cortex of heavy MDMA users after about 18 days abstention. They did not report a correlation between receptor binding and neuropsychological measures. Transporter reduction in many regions was inversely correlated with time since last dose, suggesting again that this may represent a reversible effect.

CONCLUSIONS

MDMA is almost never taken without other drugs, most notably cannabis. Studies of cannabis without MDMA have provided clear evidence of acute and short-term effects on attention and memory with possibly the only long-term effects being on frontal attentional networks. In contrast, there is evidence that MDMA does chronically impair complex memory tasks (hippocampus) and, in heavier users, higher executive information processing (frontal cortex) as well. Much of the evidence is compromised by the fact that short-term residual effects of cannabis and sometimes even acute effects cannot be ruled out. Furthermore, synergistic effects of cannabis and MDMA may explain effects on cognition. Circumstantial evidence correlating total lifetime dose of MDMA with cognitive measures does imply that MDMA is more likely to be the culprit than interaction with cannabis, but in the absence of evidence from pure groups this cannot be known for certain.

The cognitive impairment associated with MDMA and cannabis is not large relative to normal cognitive variability among individuals. Nevertheless, it may be sufficient to affect scholastic performance or those embarking on intellectually challenging careers and may become more manifest as neuronal reserve diminishes with age. Conversely, impairments may resolve with prolonged abstinence. If deficits in MDMA users are indeed a clinical manifestation of serotonergic dysfunction, as some biological studies would suggest, this is cause for concern that users may have increased risk of other psychiatric conditions with strong serotonergic aspects, including depression, schizophrenia, anxiety, impulsivity, aggression, and obsessive-compulsive disorder.

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The WPA website

Roger Montenegro
WPA Secretary for Education

WPA Online (www.wpanet.org), the website of the WPA, has been created to become an efficient means to achieve an active, fluent and dynamic communication among WPA components (Executive Committee, Zonal Representatives, Council, Standing and Operational Committees, Member Societies, Affiliated Associations, Scientific Sections) and members of the WPA Educational Liaisons Network (ELN), as well as governmental and non-governmental organizations and the media.

It was originally developed by the WPA Secretary General and Secretary for Education. Now the Education Coordination Center (ECC) is in charge of its constant upgrade and update. This process is based on excellent technical resources and, most important of all, on our human resources, the group of people who make up the ECC, who are in contact with more than 1,000 colleagues from all over the world, sending them news from the WPA and answering their queries. Such intense work has made the website a useful informational tool which receives almost 8,000 visitors per month.

Since March 2003, the ECC is producing a monthly WPA Electronic Bulletin, to inform WPA components of the latest productions of the WPA available in WPA Online. The latest issues of World Psychiatry, the official journal of the WPA, of WPA News, and of the Sections' Newsletter are always present in our Bulletin, plus a list of the latest inclusions regarding publications, institutional and educational programs, meetings, and contributions from the Sections and WPA ELN members. Also, thematic and institutional forums, whose topics change every month, encourage the participation of WPA members.

Zonal Representatives actively cooperate in the dissemination of the Bulletin in their zones, the Chairpersons of the Scientific Sections circulate it among their members, and Member Societies have been asked to propagate it among their members and translate it into their own language, to facilitate the communication with individual members. For example, the first issue of the Bulletin was translated into Spanish by a WPA ELN member, and was sent to all Spanish-speaking member societies and ELN members.

The Bulletin has multiplied the visibility of the productions of the WPA, making colleagues around the world aware of the material they have at their disposal. Besides, it gives everyone the chance to share their publications with the rest of the professional community.

Here is a sketch of some of the contents of WPA Online.

Home page

- Next World Congress
- World Psychiatry
- WPA News
- The Sections' Newsletter
- Jean Delay prize
- What's new (latest inclusions in WPA Online)
- WPA E-Bulletin
- Site map
- Search engine
- Free email (offer for WPA components)

General Information

- WPA Leadership
- WPA Secretariat
  - WPA News past issues
  - WPA News latest issue
  - Invitation to bid for the Permanent Secretariat of the WPA
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- Statutes and Manual
  - WPA statutes and bylaws
  - WPA manual of procedures
- WPA members
  - Member societies
  - Affiliated associations
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- Ethics and psychiatry
  - Madrid declaration on ethical standards
  - Historical note on WPA work on ethics
  - Declaration of Hawaii
  - WPA statement and viewpoints on the rights and legal safeguards of the mentally ill
  - Declaration on the participation of psychiatrists in the death penalty
  - Forums on ethics
  - Statement on review procedures

Sectorial activities

- Institutional programs
  - Core curriculum in psychiatry for medical students
  - Core training curriculum for psychiatry
  - Against stigma and discrimination because of schizophrenia
  - Service for member societies in Sub-Saharan Africa and Central Asia
  - Program to promote the professional development of young psychiatrists
  - Institutional program for Eastern Europe and the Balkans (under development)
  - Other WPA programs
- Consensus statements
  - Psychiatric rehabilitation
  - Neurasthenia
  - Preventive psychiatry
  - The use and usefulness of second generation antipsychotic medication
  - Disasters and mental health
  - Reducing stigma and discrimination against older people with mental disorders
  - Globalization and mental health
- WPA educational activities
  - Committee on Education
  - WPA educational liaisons network (WPA ELN)
  - WPA network of consultants to the Education Committee

WPA educational programs
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WPA institutional program on the core training curriculum for psychiatry
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Volumes originating from world congresses and regional meetings
Journals and volumes produced by WPA Sections
Other publications
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Public Information

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- Info services for patients and families
Information and orientation regarding mental disorders and health care services
Advocacy groups for patients and relatives
- Links
International organizations
Informational and specialized organizations
University departments of psychiatry

News from the WPA Secretariat

JOHN COX
WPA Secretary General

On the move: the Interim Secretariat

The WPA Secretariat is now back in Manhattan. In the middle of May we moved to the third floor of the Metropolitan Hospital on 35th Avenue and a few days later the welcome ceremony took place. This move was made possible by the astute leadership of Ahmed Okasha with the assistance of Harold Eist and the commitment of Joseph English. The arrangement has been facilitated by Ronnie Swift, who had given up her own office to make the necessary space for the WPA: five rooms and an ample reception area. The doors open onto the Department of Psychiatry, which is committed to establishing community services, and the windows look out onto a courtyard where patients gather. The WPA Secretariat is close to the real world of mental health service provision.

The WPA is indebted to Juan Mezzich and his colleagues at Elmshurst Hospital, who have housed the Secretariat until the present time. This accommodation had, however, become insufficient for the expanding needs of the Secretariat, but we shall miss the immediate assistance from the President Elect and his students who helped so much to establish the Secretariat after its move from Madrid in 1996.

My experience to date is that the Secretariat *can* satisfactorily continue its work with the Secretary General in another country thanks to electronic communication and occasional visits. Sustaining this effort may be more difficult unless there is substantial increase in the Secretariat staffing to cope with increased responsibility, less supervision from the Secretary General and an increased workload.

Please look in when you visit New York. Ronnie Swift and her colleagues are hopeful for educational and research collaborations, and we expect the new premises will facilitate meetings and conferences. There may be some teething troubles yet to emerge, but the WPA is strengthened considerably by this move whilst we await the decision about the site of the Permanent Secretariat.

The Permanent Secretariat

Preliminary bids for the Permanent Secretariat have been received by the agreed deadline of August 15. Shortlisted centres will be asked for further clarification and the Executive Committee at its first meeting in 2004 will make a recommendation to be ratified by the 2005 General Assembly in Cairo.

Other Secretariat news

Responses to the President's requests for information to update the World Health Organization/WPA Atlas are not yet complete. Could Member Societies who have not yet completed their returns please do so!

The forms for the General Survey will be sent to WPA components in Autumn and will provide member societies with a chance to comment on the extent to which the WPA is fulfilling its goals and to suggest new ways of fulfilling our responsibilities.

Zonal Representatives

WPA should be enormously proud of the work that Zonal Representatives undertake in all corners of the world. The forum meeting in Vienna was one of the best attended ever: 11 of 18 Zonal Representatives were able to gather. There will be a Board meeting in Florence in November 2004, following the one taking place in Caracas, October 2003.

Acknowledgement
This publication has been supported by an
unrestricted educational grant from Eli Lilly,
which is hereby gratefully acknowledged.

€ 16,67 per issue
Printed in Italy by Rotolito Lombarda, via Roma 115/a - 20096 Pioltello, Milan