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The World Psychiatric Association (WPA)

The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 135, spanning 117 different countries and representing more than 200,000 psychiatrists.

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

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

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World Psychiatry

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The new impact factor of *World Psychiatry*

MARIO MAJ

President, World Psychiatric Association

World Psychiatry recently received its new impact factor, 4.375. It is now in the top 10 of journals of general psychiatry and in the top 20 of all journals of clinical psychiatry, biological psychiatry and psychopharmacology.

The journal is now published in five languages: English, Spanish, Chinese, Russian and French. Selected articles or abstracts are also translated in other languages, such as Japanese, Polish and Romanian, and posted on the website of the WPA and/or relevant WPA Member Societies. All issues of the journal can be freely downloaded from PubMed Central (www.ncbi.nlm.nih.gov/pmc/journals/297) and the WPA website (www.wpanet.org). The paper version of the journal reaches more than 33,000 psychiatrists in 121 countries, being for many thousands of them the only accessible international psychiatric journal.

In compliance with a decision made by the WPA Executive Committee in 2001, the journal does not contain advertisements.

The publication of *World Psychiatry* has two main objectives, which make it different from most, possibly all, other international psychiatric journals. The first objective is to reach as many psychiatrists of the various countries of the world as possible, disseminating information on recent significant clinical, service and research developments in a language that can be assimilated by the vast majority of them. Relevance to everyday clinical practice of the average psychiatrist and usefulness to foster his/her professional growth are the two main criteria by which an article submitted to *World Psychiatry* is evaluated. In addition to this, the style of the paper must be simple and clear.

The second objective is to give voice to psychiatrists of all regions of the world, encouraging submission of research papers, commentaries and reports on innovative service modalities. Among the articles published in *World Psychiatry* in the last two years, 21% had at least one author from a low or middle income country, including seven with at least one author from Africa.

Is there the need for a journal like *World Psychiatry*? Are there, at present, problems with the dissemination of information on clinical, service and research developments to psychiatrists worldwide, with the contribution by psychiatrists from non-Western countries to international psychiatric journals, and with the clinical relevance of part of the scientific research which is published in psychiatric journals? I think that each of these questions can be answered positively.

The access of the average psychiatrist to international psychiatric journals is becoming more and more difficult. This is not only due to financial reasons (the vast majority of psychiatrists of the world cannot afford a personal subscription

to even one international psychiatric journal, and many academic centers are now reducing the number of journals to which they subscribe), but also to the objective difficulty in understanding the language, the concepts and the technical details of several articles, and the lack of motivation to read papers which do not have an obvious clinical relevance. The traditional gap between the small circle of researchers and the multitude of psychiatric practitioners is becoming wider and wider.

That only very few psychiatrists from non-Western countries are able to contribute to international psychiatric journals has been repeatedly documented. In addition to problems with language and research traditions, the fact is that research in psychiatry is becoming an increasingly complex and expensive activity. The contents of our main scientific journals increasingly consist of sophisticated papers reporting on neuroimaging, genetic, or molecular biology research carried out in well-resourced academic departments of a limited number of Western countries. The traditional gap between developed and developing countries in conducting psychiatric research is becoming wider and wider.

The gap between the issues addressed by part of published psychiatric research and those perceived by clinicians as relevant to their everyday clinical practice is probably also increasing. Biological research in psychiatry is crucial for the advancement of knowledge and for the development of new treatment modalities. However, we have been probably too liberal in the last few decades in accepting biological research papers for publication in international psychiatric journals. A look at some papers published 10 or 15 years ago may be, in this respect, instructive: the message they conveyed is now completely obsolete, not so much because new technologies have developed in the meantime, but because the findings themselves (usually, a small although statistically significant difference between a sample of patients with a psychiatric diagnosis and a sample of healthy controls, with respect to the mean values for one or more biological variables) were of no actual scientific and clinical relevance.

Given the above-mentioned two objectives, it is understandable that the ingredients and the overall flavor of each issue of *World Psychiatry* are different from those of other international psychiatric journals. An important ingredient is represented by the forums, which are particularly appreciated by our readership and usually attract several quotations in the international literature. Among the most successful forums we published in the past few years are those on the concept of mental disorder (1), on conflicts of interests in psychiatry (2), on steps, challenges and lessons in developing community mental health care (3), on the role of functional

impairment in the diagnosis of mental disorders (4), on the lessons learned from pragmatic trials of psychotropic drugs (5), and on early intervention in psychosis (6). Each of these forums included participants from all continents. Another special ingredient is represented by the mental health policy papers, providing information on innovative experiences in mental health care from various regions (7,8), or addressing issues, such as psychiatric brain drain (9) or burnout in psychiatrists (10), which are rarely covered in international psychiatric journals.

Among research reports, we give priority to international and national multicenter studies providing data on epidemiology of mental disorders in various countries or testing innovative modalities of mental health service delivery or psychosocial interventions. In the past few years, we hosted for instance two of the main reports on the World Mental Health Survey Initiative (11,12); the first community study of the prevalence and correlates of mental disorders in Iraq (13), which attracted the attention of the International Herald Tribune, the Washington Post and the New York Times; and the first controlled trial of a classroom-based intervention for children and adolescents exposed to war experiences in the Middle East (14).

Our review articles are all invited and deal with issues of great interest to psychiatrists worldwide. Among the articles which were most appreciated by our readership in the past few years, are those on grief and bereavement (15), on cultural factors in psychiatric diagnosis (16), on self-stigma in people with severe mental disorders (17), on neurobehavioural sequelae of traumatic brain injury (18), and on diagnosis and treatment of attention-deficit/hyperactivity disorder in adults (19).

The forum of one of the latest issues of *World Psychiatry* was entitled "Are psychiatrists an endangered species?" (20). Indeed, we and our profession are stigmatized in many countries of the world. This is certainly related to our difficulty to convey the new image of psychiatry: the image of an integrative discipline, which deals with a broad range of disorders, including some that are very common in the population, using interventions that are at least as effective as those available to most other branches of medicine. However, it would not be fair to state that psychiatry has just a problem with promoting more successfully its new image. It has to be acknowledged that our profession also has a problem, in several contexts in many countries, with matching up to this new image in the reality of clinical practice, research and training.

Our hope is that the dissemination of *World Psychiatry* will contribute to upgrade the image and the reality of psychiatry in as many countries of the world as possible.

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WPA guidance on how to combat stigmatization of psychiatry and psychiatrists

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In 2009 the WPA President established a Task Force that was to examine available evidence about the stigmatization of psychiatry and psychiatrists and to make recommendations about action that national psychiatric societies and psychiatrists as professionals could do to reduce or prevent the stigmatization of their discipline as well as to prevent its nefarious consequences. This paper presents a summary of the Task Force's findings and recommendations. The Task Force reviewed the literature concerning the image of psychiatry and psychiatrists in the media and the opinions about psychiatry and psychiatrists of the general public, of students of medicine, of health professionals other than psychiatrists and of persons with mental illness and their families. It also reviewed the evidence about the interventions that have been undertaken to combat stigma and consequent discrimination and made a series of recommendations to the national psychiatric societies and to individual psychiatrists. The Task Force laid emphasis on the formulation of best practices of psychiatry and their application in health services and on the revision of curricula for the training of health personnel. It also recommended that national psychiatric societies establish links with other professional associations, with organizations of patients and their relatives and with the media in order to approach the problems of stigma on a broad front. The Task Force also underlined the role that psychiatrists can play in the prevention of stigmatization of psychiatry, stressing the need to develop a respectful relationship with patients, to strictly observe ethical rules in the practice of psychiatry and to maintain professional competence.

Key words: Stigmatization, psychiatry, psychiatrists, general public, media, medical students, patients and relatives, ethical rules

(World Psychiatry 2010;9:131-144)

One of the goals included in the WPA Action Plan 2008-2011, adopted by the WPA General Assembly, is an improvement of the image of psychiatry and psychiatrists in the eyes of health professionals, the general public, health decision makers and students of health professions (1,2). In the pursuance of this goal, the President of the WPA established a Task Force and entrusted it with the development of a guidance on how to combat stigmatization of psychiatry and psychiatrists.

This paper provides a review of the current knowledge in the area and lists a series of recommendations about what can be done to address the problem.

METHODS USED TO REVIEW PUBLISHED EVIDENCE

The Task Force conducted a review of the literature to identify publications dealing with the image of psychiatry, psychiatrists, psychiatric institutions and psychiatric treatment. The search algorithm selected was applied to Social SciSearch/Social Science Citation Index, PsycINFO, Embase, Somed (joint search via the meta-search engine Dimdi, title only) and Medline (titles and abstracts).

The review aimed at providing a comprehensive account of stereotypes of psychiatry and psychiatrists. However, there are several topics related to attitudes towards psychiatry and psychiatrists (e.g., help-seeking behaviour, compli-

ance) that could not be included completely, and are thus only contained as far as they appeared to be of relevance for our review.

The search was conducted in July 2009, was not limited to any specific year and identified articles published in English and German. The members of the Task Force contributed suggestions about publications in other languages of which they were aware. The initial search yielded 8,217 articles, of which 7,296 remained after duplicates were excluded. After screening titles and abstracts, we identified 398 papers as potentially relevant. A further review of references identified additional publications. A total of 503 potentially relevant studies were considered in detail and form the basis for this review.

RESULTS OF THE REVIEW OF KNOWLEDGE

We defined stigma broadly, to encompass the negative stereotypes and prejudicial beliefs that people may hold, as well as discriminatory or inequitable practices that may result. Further, we recognized that stigma and discrimination may occur at the level of the individual, through interpersonal interactions, as well as at the level of social structures by virtue of unfair policies, practices, and laws (3). We first consider the stigmatization of psychiatry (and psychiatric treatments), then the stigmatization of psychiatrists.

The stigmatization of psychiatry

The general public

The public opinion about psychiatric facilities has been consistently negative during the past decades. The image of a “psychiatric hospital” has been typically that of a large-scale institution with a custodial character (4), locked doors, and located on the outskirts of the community (5,6). In a representative survey of German respondents (4), 25% believed that patients were not let out, and 50% believed that straightjackets were still in use.

Some positive changes could be observed during the 1970s, with the development of community mental health care (7). However, community care was also met by resistance from community residents, referred to as the NIMBY (not in my backyard) syndrome. For example, in one study, while 81% of Americans rejected the idea that “the best way to handle the mentally ill is to keep them behind locked doors”, significantly fewer (31%) would actually welcome an outpatient mental health centre in their neighborhood (8). Reasons for this resistance included concerns about declining property values, the safety of children, and personal safety (9-12).

Public opinions about psychiatric treatment have been found to be mixed. While some studies revealed that respondents considered psychiatric treatment to be helpful (13-15), in others, respondents expressed concern about the quality and efficacy of treatment (16-18), and in some, respondents considered psychiatric treatment to be harmful (19-21).

Selecting from a range of treatment options, psychotherapy was usually preferred over psychotropic medication (6,20,22-33). However, the framing of the questions seems to influence the results. A forced choice among treatment options seems to yield a preference for psychotherapy, but if the acceptance of a certain kind of treatment is assessed, studies usually find high rates of acceptance for both psychotherapeutic and psychopharmacological treatment (34-37).

The general public tends to overestimate the effectiveness of psychotherapy, recommending it as the only treatment even for conditions such as schizophrenia where scientific evidence suggests that psychopharmacological treatment is indicated (22,38). In contrast, negative effects of psychotropic medications are perceived as severe, whereas the positive effects are underestimated (31,39,40). In some cases, despite agreeing that they are effective, the majority of respondents would not be willing to take psychiatric medications (41).

Five misconceptions about psychotropic medications were found to be prevalent in the general population. They are perceived as being addictive (30,31,39,42-44), a “sedation without curing” (30,38,39,44-46), an “invasion of identity” (39), merely drugging patients (40), and ineffective in preventing relapse (30). These misconceptions are represented also in Africa, where traditional healers are trusted more than Western trained doctors (47,48).

Negative attitudes about electroconvulsive therapy (ECT) were often observed. In an Australian population study, for example, only 7% perceived ECT as helpful, whereas 70% perceived it as harmful (22).

Medical students

Among medical students, results are mixed, sometimes contradictory. While the overall status of psychiatry as a discipline is low, some studies also report positive changes in attitudes, either over the course of time (49,50) or after completion of psychiatric training during medical school (51-71), although improvement in attitudes seems to be transient (72-75). In other studies, no improvement in attitudes was noted (76-83). Despite positive attitudes, the proportion of medical students indicating they would choose psychiatry as a career is often low (84-91).

Perceived low prestige and low respect among other medical disciplines have been among the main reasons mentioned for not choosing psychiatry as a career (49,87,92-111). In a recent survey of US medical students on medical specialties perceived as the object of bashing, psychiatry ranked third (39%) after family medicine and general internal medicine (112).

When there was an attraction to psychiatry, it appeared to be based primarily on its being interesting and intellectually challenging (77,101,110), and providing a career that promises job satisfaction with good prospects (101,113,114). Medical students often do not view psychiatry as an (intellectually) challenging career choice (101,115-117) and see it as a profession with low job satisfaction and limited fulfillment (109). Psychiatry was, however, in other studies, ranked as most attractive as far as intellectual challenge was considered (92,118,119).

A further influential aspect is the impact of students’ families on their attitudes and their decision to aim for a career in psychiatry. Stereotypes such as specializing in psychiatry being “wasted time” are widespread among the families of medical students (94,120), although students do not necessarily feel discouraged by their family (100,104). Nevertheless, this attitude reflects an image of psychiatry as not being “real medicine” (109).

Financial aspects, such as low pay (49,87,92,99,106,107, 109,116,121-124) and lack of government funding (103, 125-129), also play a role in forming the image of psychiatry as a discipline. These financial drawbacks have an impact on attitudes of medical students in both clinical and research settings.

Medical students also perceive psychiatry as lacking a solid, authoritative scientific foundation (92,97,101,109, 117,119,130-135). This attitude is partly based on uncertainty concerning the nosology and diagnosis of mental illnesses, which is mentioned among the reasons for medical students not to enter psychiatry (109,136,137). The classification of mental disorders in the DSM and ICD categories

has been subject to criticism because the majority of these diagnostic categories are not validated by biological criteria (138-141), thus reinforcing the image of psychiatry as not being “real medicine”. One aspect of this discussion includes the question as to whether research using diagnoses that are not validated as inclusion criteria “is equally invalid” (142).

Results concerning medical students’ opinion about psychiatric treatment and its outcome have been mixed. Medical students often viewed psychiatric treatment as ineffective (115,143) and considered psychiatry to be “too slow moving” (133).

Medical students were often less skeptical than the general public towards psychotropic medications (144,145). However, psychotropic drugs were criticized for not targeting the actual cause of the illness (146). Psychotherapy was rated more positively in some instances (147).

Medical students’ attitudes towards ECT have been also mixed. Most of the respondents viewed it as a form of punishment (148,149), only to be used as a last resort (150). In contrast, the majority of medical students in a Nigerian study disagreed with the idea of ECT being misused as a punishment (151). UK students reported no fears of abuse of ECT by psychiatrists, unlike some 30% of their counterparts in Iraq and Egypt (152). Negative attitudes towards ECT may be attributable to mass media and movie depictions (148,153), whereas the UK students were more likely to have observed actual cases treated with ECT (152,154).

Health professionals

Family physicians’ attitudes toward psychiatry have been explored in some studies. Two reasons for non-referral were identified (155): concerns about the effectiveness of psychiatric treatment and stigma for the patient. Psychotropic drugs were often considered necessary, but psychotherapy and combined approaches were also recommended (156,157).

The image of psychiatry from the perspective of psychiatrists has not been studied extensively. A study evaluating how a sample of psychiatrists and pediatricians felt about their specialty found that satisfaction was rated high among psychiatrists (158), with no differences in satisfaction compared with pediatricians. Lambert et al (136), assessing the reasons why doctors left the specialty they had initially chosen, report that the main reasons mentioned by psychiatrists included the specialty’s poor public image, the perceived lack of respect among other doctors, and the perception of under-resourcing. Only 71% of psychiatrists in a British study reported a general willingness to take antipsychotics themselves in the case of a schizophrenic disorder (159).

Student nurses and nurses have been found to have positive attitudes toward psychiatry (160-166). The same applies to pharmacy students (167).

Health professionals’ attitudes towards specific psychiatric treatments appear to coincide with those of the general population and medical students. Thus, depot medication

was often perceived as coercive and compromising patient autonomy (168,169), psychotherapy was preferred over antidepressants (170), and psychotropic drugs were often accepted only as a last resort (171). Social workers, however, had a positive attitude towards psychotropic medications (172,173). Only 35% of non-medical mental health professionals reported that they would consider taking antipsychotics themselves in the case of a schizophrenic disorder, whereas 85% would recommend them to relatives (159). Mental health nurses recommended ECT only in cases of extreme depression (174). Involuntary treatment methods elicited strong emotions among nurses (175,176).

Patients and relatives

Among patients who did not comply with a referral to a psychiatrist, the most frequently mentioned reason was the fear of mental illness stigma, rather than negative expectations about the treatment and its quality (177). Patients usually expect that treatment will be helpful (178,179), and most outpatient clients in a community mental health centre were satisfied with the treatment they received (180,181). However, expectations that treatments such as ECT will be painful, and that medications may be administered without their consent are often reported by patients (26,182).

Regarding specific forms of psychiatric treatment, patients and their relatives harbor the same stereotypes about psychotropic medications as are found in the general public. Thus, these medications are often rejected because they are thought to be addictive (32,183-185), not to target the actual causes of the illness (32), to induce personality changes (179,186) and to suppress normal feelings (184). Some studies show a clear preference for psychotherapy over pharmacological treatment (19,26,187,188) and patients often do not expect psychotropic medication when first beginning treatment (178,179,189). Psychiatric treatment was often seen as being either slow in taking effect or completely ineffective (190).

However, compared to the general population, psychiatric patients and their relatives have been found to have slightly more positive attitudes towards psychotropic medications (191-195), and some studies report that satisfaction with this form of treatment is high (196-198). Previously hospitalized patients showed more positive attitudes towards psychiatric treatment (199-201).

While ECT has often been viewed by patients as an effective treatment method (202,203), most patients expected severe side effects (204,205), often leading them to consider it as a treatment of last resort. However, this was not the case in patients who had already undergone ECT (206-208). Similarly, while most patients reported that they were not in favor of compulsory treatment, because it would limit their autonomy, most evaluated their actual experience with compulsory treatment as helpful (197,209-218).

The media

The general depiction of psychiatry in the news and entertainment media is predominantly negative. In a media commentary, psychiatry was portrayed as “a discipline without true scholarship, scientific methods, or effective treatment techniques” (219). Newspapers and movies have often conveyed a negative picture of psychiatric hospitals (220,221). These images were quickly generalized and contributed to the negative image of psychiatry overall (222,223). Modern community mental health centers have been rarely depicted in the media (224).

The depiction of psychiatric treatment is also often negative, with images of ineffective and punitive electroshocks (225), forced confinement, or psychoanalytical treatment (224,226,227) prevailing. The “Hollywood mythology of psychiatry” (228) conveys the idea that successful treatment is not based on medication and gradual progress, but on a single cathartic session. Newspaper reports on psychotropic drugs have been substantially more critical than reports on cardiac drugs, more often emphasizing negative side effects while omitting information on beneficial effects (229,230). Reports on ECT have been frequently negative and biased (231). Several newspapers repeatedly criticized the relationship between psychiatry and the industry (232).

The stigmatization of psychiatrists

The general public

The public image of psychiatrists is largely negative and based on insufficient knowledge about their training, expertise and purpose. For example, it is not widely known that psychiatrists are medical doctors, and the duration of their training is underestimated (6,182,233-235). They are ascribed a low status among physicians (236), academicians (235), and mental health professions (237). Many studies report an insufficient differentiation between the various mental health professions, in particular between psychiatrists and psychologists (233,237,238). Only two studies reported that respondents were able to differentiate between the professions (6,235). Psychiatrists are accused of relying too much on medications (239). In the presence of a mental health problem, help from a confidant (25,27,34) or a family physician (241-242) is often recommended instead of treatment by a psychiatrist. Nevertheless, only a small minority of the general public endorse the stereotype that “psychiatrists are useless” (22,236,237,243).

There are competing stereotypes concerning the professional roles of psychiatrists (244,245). On the one hand, they are often perceived as “agents of repression” whose purpose it is to guarantee conformist behavior (244) and who can “see into people’s minds” (18). It is sometimes suggested that psychiatrists do not really want to understand their patients and are hostile towards them (6,107). On the

other hand, psychiatrists are sometimes perceived as oracles, diviners or loving saviors, with exaggerated expectations about treatment success and healing (244).

Another misconception about psychiatrists concerns their role in courts as experts who testify about the mental health of defendants. Their explanations for a defendant’s behaviour are often misunderstood as “creating loopholes for criminals” (246,247). In this context, respondents also expressed low confidence in psychiatrists’ ability to detect legal insanity. Similarly, it has been suggested that the testimony of forensic psychiatrists is not based on professional expertise but motivated by financial interest (219,248,249). Nevertheless, the majority of lawyers and judges rejected the low-competence stereotype (250).

Three additional stereotypes describing psychiatrists can be found in the literature, referring to madness, oddness and abusiveness. Arguably, the most common is that of the psychiatrist who suffers from mental health problems (18,233, 239,251). However, we have not found a single study that gave direct empirical evidence that the public actually endorse this stereotype. In a population survey (236), the majority described psychiatrists as helpful and trustworthy, and only a small minority perceived them as quirky or intransparent. But, given the choice between various mental health professionals, the participants in an Australian survey felt least comfortable talking to psychiatrists and rated them highest on perceived oddness (237). Finally, psychiatrists have been viewed as dangerous and manipulative abusers (107,252), who exploit their patients and abuse their power (51), even to the extent of trying to obtain sexual favours.

Medical students and health professionals

Medical students often report overhearing negative, disparaging remarks about psychiatrists by teachers in medical school and during clerkship (112,120). Based on the notion that “psychiatrists must be crazy because they are able to deal with crazy people” (244) or that “working with crazy people will make you crazy” (120), medical students sometimes perceive psychiatrists as more emotionally unstable or neurotic than other health professionals (65,94,97,253). Medical students may also see psychiatrists as peculiar, fuzzy, confused thinkers who are complex and difficult to understand (79,94,253,254).

Within the medical community, the status of psychiatrists is usually described as low. Some authors suggest that there is a “lack of respect among the medical community” (120), which stereotypes psychiatrists as “unsure, ineffective, useless and incomprehensible” (244). This perception of psychiatrists as “not real doctors” is also reflected in the fact that referral letters from family physicians to psychiatrists rarely contain information about physical symptoms (255). Nevertheless, medical doctors acknowledge that psychiatrists can help people with mental disorders and possess relevant expertise (256). They also report that they value and

desire the advice of consultant psychiatrists (257-259), although they do not want to have them as treatment providers on a long-term basis (250,261). Despite these positive attitudes, 35% of non-psychiatric doctors see psychiatrists as less emotionally stable than other physicians, and 51% as neurotic (256).

On the other hand, psychiatrists rated themselves as more introspective, less authoritarian, more cultured and mature than their medical colleagues and 77% disagreed with the idea that they were more neurotic. Psychiatrists are, however, well-aware of their negative image (246,256,262).

Psychiatrists appear to be generally well accepted by other mental health professionals (263,264). Psychologists, nurses and social workers rated psychiatrists as equal to other professional groups in competence, although they consistently evaluated them as less warm (265).

Patients and relatives

Attitudes of patients and their relatives to psychiatrists are ambivalent. Satisfaction with psychiatrists' performance tends to be high (196,198), with attitudes becoming more positive during hospitalization (161). An often expressed concern is about the time pressures that exist within psychiatric care facilities and the associated lack of time for intensive conversations (196,266-269). Some patients have described psychiatrists as controlling (267) and some relatives have perceived them as arrogant (268). Strehlow and Piesur-Strehlow (270) found that lack of knowledge about the expertise of psychiatrists and negative attitudes led parents to choose psychiatrists only as a last resort for their children with mental health problems.

The media

Many of the stereotypes that are prevalent among the general public can also be found in the way psychiatrists are portrayed in the media. For example, psychiatrists are depicted as unhelpful, not providing effective therapy (128, 224), and unable to explain or predict their patients' behaviour (271). Furthermore, derogatory and colloquial terms for psychiatrists are frequently used (107). The depiction of a malicious, controlling psychiatrist (272), a functionary of the oppressive state (227), was typical for the first half of the last century (228). In the ensuing years, different subtypes of psychiatrists have evolved. For example, Schneider (273) differentiated Dr. Dippy, Dr. Wonderful and Dr. Evil, representing the stereotypes of the mad psychiatrist, the super-healer and the exploitative, boundary-violating psychiatrist. A similar classification has been proposed on the basis of a movie analysis (226). Typically, positive attributes of psychiatrists include them always being available to their patients (228). A review of American movies (274) found that psychiatrists were depicted as helpful and friendly in about

one half, and as malicious and boundary-violating in the other half, of the analyzed movies.

INTERVENTIONS TO COMBAT THE STIGMATIZATION OF PSYCHIATRY AND PSYCHIATRISTS

Our review of the literature on the stigmatization of psychiatry and psychiatrists revealed a scarcity of research on the development and evaluation of interventions to combat stigma. The results of these few studies are presented separately for the stigma toward psychiatry and that toward psychiatrists.

Interventions to combat the stigmatization of psychiatry

Concerning the stigma towards psychiatric treatment, there is some evidence that improving people's knowledge about mental disorders during a "mental health first aid course" improves concordance with generally recommended therapies (275). There is also some evidence that attitudes towards community-based facilities could be improved by providing information about mental disorders and their treatment as well as contact with persons who suffer from those disorders (276). Battaglia et al (277) found that a presentation given by a psychiatrist on mental health issues for high school students not only improved knowledge about mental health, but also improved help-seeking attitudes and appreciation of psychiatrists, possibly due to greater familiarity.

Changing the depiction of psychiatry in the media is an important prerequisite for changing public opinion, particularly by promoting realistic expectations about treatment modalities and their success (234,239). Stuart (278) suggests that mental health professionals as well as patients should be more present in the media, in order to provide a more accurate picture of psychiatric treatments and their consumers. Media training for mental health professionals may improve their credibility and the acceptability of their message. A specific intervention that aims at improving the relations between psychiatrists and the media is described by Kutner and Bresin (279). Based on the idea that insecurity in a media interview situation can come across as arrogance, they developed a specific media training program. In workshops with groups of six psychiatry residents, information about the media and its functioning is provided and communication and presentation skills are practiced in role-playing. Even though no formal evaluation was reported, the authors claim positive experiences with the training.

Most interventions aimed at modifying medical students' attitudes towards psychiatry centered on changes in teaching modalities and the curriculum in medical school. Studies comparing different styles of teaching (e.g., traditional versus problem-based teaching) failed to show an advantage of one method over another (55,67,72). According to a study by Singh et al (67), the acquisition of knowledge, an aware-

ness of the therapeutic potential of psychiatric interventions and direct patient contact can improve attitudes and enhance psychiatry's attractiveness as a career choice.

One specific approach to correcting the misperception of psychiatric treatment as ineffective is described by Coodin and Chisholm (280). A psychiatry seminar on recovery in persons with schizophrenia, co-taught by a consumer and a professional, led to more favourable perceptions of treatment for mental illness. Lambert et al (136) argue that tackling the negative image of psychiatry should start in medical school and continue in junior doctor training, in order to retain psychiatrists in their jobs. Moreover, in order to avoid mismatches, they recommend that interested medical students have the opportunity to gain more experience in psychiatric internships before pursuing a long-term career in psychiatry.

Interventions to combat the stigmatization of psychiatrists

We were unable to identify any studies describing interventions specifically targeting the stigmatization and discrimination of psychiatrists. However, there were several recommendations on how to change their negative image, most of which focused on developing a positive relationship with the media. This includes active participation of psychiatrists in the flow of information (233) and provision of expert knowledge on mental health issues (281) and forensic cases (282).

The Quebec Psychiatric Association developed recommendations on how to improve the image of psychiatrists with the help of a communication firm. Their strategies include becoming more visible in the media, responding to public needs and critical events, and increasing the visibility of psychiatrists in the community (283). They further argue that psychiatrists should react publicly to criticism of their profession. Higher visibility and better community orientation are also recommended by Felix (284) and Davidson (285), who suggest that community volunteering is an important approach to better public recognition.

In the interest of reducing stigma within the medical profession, it is recommended to address stigma in psychiatric education (120), providing medical students with a more accurate picture of psychiatry as a discipline and offering positive role models (94,176,286). To form positive relations with trained doctors, consultation-liaison relationships with a psychiatrist are recommended (287). In that regard, it is important that the psychiatrist remains "a physician first and a specialist second", with sound medical knowledge (176,288). Spiessl and Cording (289) suggest an easily accessible psychiatric liaison service for family physicians in order to reduce delays in referrals. Moreover, they suggest practice-oriented seminars for family physicians, informing them about mental illness but also about psychiatric facilities, as well as continuing education in the context of the psychiatric liaison service.

RECOMMENDATIONS

Our review of the literature on stigmatization of psychiatry and psychiatrists produced only a very small number of articles on research concerning the development and evaluation of interventions aimed at reducing such stigma. The main results indicated the importance of close collaboration with the media. In this regard, the improvement of public relations, the inclusion of psychiatrists in the media as experts on psychiatric issues, as well as workshops for psychiatrists on how to interact with the media, have proven to be effective in reducing the stigma of psychiatry and psychiatrists. Moreover, the media play an important role in providing information and correcting misconceptions about psychiatric treatments, facilities and the job of psychiatrists. The second main result concerns the improvement of the image of psychiatry and psychiatrists through a combination of knowledge and contact with people with mental illness. Specific approaches concerning medical students' attitudes include addressing stigma and misconceptions about psychiatry during medical training, and improving teaching in psychiatry.

Also on the basis of the experience of its global programme on reducing the stigma and discrimination toward schizophrenia (290-293), the WPA recommends the following actions to combat the stigmatization of psychiatry and psychiatrists.

Recommendations to national psychiatric societies

National psychiatric organizations should define best practices of psychiatry and actively pursue their application in the mental health care system.

In addition to the publication of appropriate guidelines about best practices, psychiatric organizations should find ways to introduce their contents into the medical curricula and make training in their use an essential part of postgraduate education in psychiatry. The fact that best practice guidelines exist and that they are being applied should be public knowledge.

Psychiatric organizations should ensure rapid action in instances of human rights violations in the practice or research related to psychiatry and clearly report on the effects of such action. They should place emphasis on the development of techniques that will facilitate the control of quality of psychiatric practice, and on the wide use of such techniques. They should regularly report on scientific achievements and successes in the provision of care for people with mental disorders in communications with governments. They should work toward full transparency of their relationship with health related industries.

National psychiatric organizations, in collaboration with relevant academic institutions, should revise the curricula for undergraduate and postgraduate medical training.

There is evidence from a number of countries that medical students have a poor opinion of psychiatry and that a decreasing number of them choose psychiatry as a specialty upon graduation. As our review showed, this is in part due to the influence of teachers from other medical disciplines who hold such views and in part to the way in which psychiatry is presented and taught in medical schools in most countries. A variety of teaching methods that could make the subject of psychiatry more attractive exist, but are not widely used. These include the intensified instruction about skills (that can be used in dealing with mental illness as well as in the practice of medicine in general), contact with people who have been treated for their psychiatric illness and recovered, the involvement of family members as teachers about the routine management of mental illness and impairment in the community, exposure to successful community care for the mentally ill, use of summer schools and exchange programs to increase the attraction of psychiatry, and a better integration of the teaching of psychiatry with that of neurosciences and behavioral sciences.

Skills of presentation and communication, for work with the media and governmental offices, are of considerable importance in the development of mental health services as well as in any effort to change the image of psychiatry. At present, these skills are taught only exceptionally. Postgraduate training should also include education about the origins of stigma of mental illness and about the methods that can be used to combat it.

National psychiatric societies should establish closer links and collaboration with other professional societies, with patient and family associations and with other organizations that can be involved in the provision of mental health care and the rehabilitation of the mentally ill.

The image of psychiatry and of psychiatrists depends, to a large extent, on the opinion of other medical specialists and on the perception of the discipline by those who use psychiatric services. Psychiatric societies often have very poor links to other professional societies and to organizations of patients and relatives, with which the relationship is often adversarial. The conduct of joint projects (e.g., research on comorbidity of mental and physical disorders) and collaboration with patient and family organizations in the production of guidelines and practice standards might diminish the gap that currently exists and contribute to the improvement of the image of psychiatry.

Collaboration with patient and family organizations can also contribute to the effort to make psychiatric services more efficient and user-friendly. The experience that some countries have in this respect (e.g., in the joint selection of an "ombudsman" who can help to resolve problems emerg-

ing in mental health services and the introduction of regular meetings of representatives of patient and family organizations and leaders of mental health programs) may reduce the number of conflicts and provide opportunities for contact and collaboration.

Collaboration with schools and teacher associations as well as organizations such as the Rotary Club can also be helpful in reducing the stigma of psychiatry.

National psychiatric societies should seek to establish and maintain sound working relationships with the media.

The role of the media in shaping attitudes of the general public is of increasing importance. The information which media have about the practice of psychiatry is often incomplete or obsolete. National psychiatric societies should consider different ways of providing up-to-date information and developing working relationships with media representatives, including workshops, regular informative bulletins and press releases, the involvement of media representatives in planning services and other ways appropriate for the country.

Recommendations to leaders of psychiatric services and individual psychiatrists

Psychiatrists must be aware that their behaviour can contribute to the stigmatization of psychiatry as a discipline and of themselves as its representatives.

The behaviour of psychiatrists in their clinical practice is of decisive importance for the image of psychiatry and psychiatrists. Its components that need to be given particular attention include: a) the development of a respectful relationship with patients and their relatives; b) staying abreast with advances of psychiatric research and practice and their implementation in clinical practice; c) strict observance of ethical principles in the provision of care and in the organization of services; d) collaboration with other medical specialists and health workers as well as with other professionals involved in the care for people with mental disorders.

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Resilience under conditions of extreme stress: a multilevel perspective

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Resilience has been conceptualized as a dynamic developmental process encompassing the attainment of positive adaptation within the context of significant threat, severe adversity, or trauma. Until the past decade, the empirical study of resilience predominantly focused on behavioral and psychosocial correlates of, and contributors to, the phenomenon and did not examine neurobiological or genetic correlates of and contributors to resilience. Technological advances in molecular genetics and neuroimaging, and in measuring other biological aspects of behavior, have made it more feasible to begin to conduct research on pathways to resilient functioning from a multilevel perspective. Child maltreatment constitutes a profound immersion in severe stress that challenges and frequently impairs development across diverse domains of biological and psychological functioning. Research on the determinants of resilience in maltreated children is presented as an illustration of empirical work that is moving from single-level to multilevel investigations of competent functioning in the face of adversity and trauma. These include studies of personality, neural, neuroendocrine, and molecular genetic contributors to resilient adaptation. Analogous to neural plasticity that takes place in response to brain injury, it is conjectured that it may be possible to conceptualize resilience as the ability of individuals to recover functioning after exposure to extreme stress. Multilevel randomized control prevention and intervention trials have substantial potential for facilitating the promotion of resilient functioning in diverse high-risk populations that have experienced significant adversity. Determining the multiple levels at which change is engendered through randomized control trials will provide insight into the mechanisms of change, the extent to which neural plasticity may be promoted, and the interrelations between biological and psychological processes in the development of maladaptation, psychopathology, and resilience.

Key words: Resilience, stress, developmental pathways, multiple levels of analysis, neural plasticity, resilience-promoting interventions

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From the perspective of developmental psychopathology, maladaptation and mental disorder are viewed as evolving from progressive liabilities in the organization of biological and psychological systems, resulting in the undermining of the individual's efforts to adapt effectively to stressful and adverse experiences (1,2). The dynamic interplay between risk and protective forces is conceived as influencing the developmental course through the impact it has on the quality of the organization of biological and psychological systems as the individual develops (3).

Developmental psychopathologists stress that there is multifinality in developmental processes such that the manner in which persons respond to and interact with vulnerability and protective factors at each level of the ecology (i.e., culture, community, family, and their transactions) allows for diversity in developmental outcomes (4,5). Individuals may begin on the same major developmental trajectory, yet exhibit very different patterns of maladaptation or adaptation. The pathway to either psychopathology or resilience is influenced by a complex matrix of the individual's level of biological and psychological organization, current experiences, active choices, the social context, timing of the adverse event(s) and experiences, and the developmental history of the individual (5).

Understanding the dynamic transactions between risk and protective factors plays a central role in building developmentally informed models of prevention. Through increasing the relative balance of protective processes over risk factors, the potential for righting the developmental course, attaining adaptive developmental pathways, and reducing the emergence of psychopathology may be achieved (4,6).

Just as deviations from the average expectable environment potentiate some individuals toward the development of maladaptation, others demonstrate adaptation in the face of the same challenges (7-9). Thus, it is equally important to comprehend the mechanisms that promote adaptation among individuals experiencing significant adversity as it is to investigate the developmental trajectories toward maladaptation. Research conducted on biological, as well as psychological, protective factors is critically important for discovering mechanisms and processes that contribute to the development of either the recovery of function or resilient adaptation in the face of significant adversity (10-12).

DEFINITION AND HISTORICAL CONTEXT

Resilience is conceived as a dynamic developmental process encompassing the attainment of positive adaptation within the context of significant adversity (8,13,14). There are two critical conditions that are implicit within this conceptualization of resilience: a) exposure to significant threat, severe adversity, or trauma; and b) the achievement of positive adaptation despite major assaults on the developmental process (8,14).

For four decades, researchers interested in children who develop well in the context of significant adversity have endeavored to enhance understanding of the diverse pathways to psychopathology, to elucidate the processes that eventuate in normal development, and to inform preventive interventions and social policies that could improve the lives of vulnerable children and families (7,15-18). Investigations in the

area of risk and resilience have led scientists to rethink their prior assumptions about the causes and course of psychopathology and have resulted in a reformulation of the deficit etiological models that characterized earlier viewpoints about the development of children who have experienced disadvantage and great adversity (9,19,20).

Studies conducted on individuals at high risk for psychopathology and on persons with mental disorders frequently portrayed the developmental course as deterministic, inevitably resulting in maladaptive and pathological outcomes. Investigations focusing on genetic and biological predispositions to psychopathology, assaults on development associated with inadequate caregiving, and traumatic occurrences within the home – such as child maltreatment and domestic violence, exposure to community violence, chronic illness, and catastrophic life events – graphically convey the multiplicity of risks that can eventuate in disordered outcomes. As researchers discovered that not all high-risk children manifested the dire consequences that extant theories of psychopathology predicted, comprehending the processes through which children at risk did not develop psychopathology became viewed as important for informing theories on the development of maladaptation and pathology.

Before investigations on resilience could be initiated, a significant and illustrious history of research detailing the precursors to, as well as the contemporary patterns of, stress resistance had to take place (e.g., 8,21). In many of these early studies, researchers had discovered evidence of adaptive behavior; however, the nomenclature for labeling these results as indicative of resilience had not yet emerged.

The historical roots of resilience can be traced to early programs of research on individuals with schizophrenia and on persons exposed to parental mental illness, extreme stress and poverty, as well as on the functioning of individuals who experienced traumatic occurrences earlier in their lives (7,15,22,23). Early investigations of severely disordered schizophrenic patients were focused primarily on understanding maladaptive behavior, and the subset of patients who showed relatively adaptive patterns were considered atypical and afforded little attention. By the middle of the 20th century, researchers had discovered that people with schizophrenia with the least severe courses of illness were characterized by a premorbid history of a relative competence at work, good social relations, marriage and the capacity to fulfill responsibility (see 23). In a parallel fashion, studies of children of mothers with schizophrenia played a crucial role in the emergence of childhood resilience as a major theoretical and empirical topic (16,19,24).

Additionally, Werner's longitudinal study (17,18), that systematically searched for protective forces that differentiated children with healthy adaptation profiles from those who were comparatively less well adjusted, was a groundbreaking investigation. Evidence that many of these children experiencing great adversity thrived despite their high-risk status led to increasing empirical efforts to understand individual variations in response to adversity. Early empirical efforts

were primarily focused on the personal qualities of “resilient children”, such as autonomy or high self-esteem (25). As work in the area evolved, however, researchers increasingly acknowledged that resilience may often derive from factors external to the child (8). Subsequent research led to the delineation of these sets of factors implicated in the development of resilience: a) attributes of the children themselves; b) aspects of their families; and c) characteristics of their wider social environments (8,25).

In recent decades, there has been a shift in the focus of empirical investigations; rather than searching for protective factors, researchers are increasingly striving to discover the mechanisms underlying resilient functioning (8). This focus on processes as opposed to identifying factors has enabled scientists to design prevention and intervention strategies that are developmentally sensitive for promoting resilience in persons experiencing significant adversity or trauma (26-28). Knowledge of the processes contributing to resilient functioning can enable prevention and intervention scientists to capitalize on periods of developmental change and transitions as unique opportunities for promoting positive adaptation during significant adversity or trauma (27,29). As S. Luthar asserted, “it is far more prudent to promote the development of resilient functioning early in the course of development rather than to implement treatments to repair disorders once they are already crystallized” (7). Randomized control trial (RCT) preventive interventions may be conceptualized as true experiments in altering the course of development (30), thereby presenting opportunities to test existing developmental theories as well as to provide insights into the etiology and course of positive adaptational outcomes in individuals experiencing significant adversity (8,31).

As research on resilience has evolved and transformed over the years, it has become clear that the attainment of positive adaptation in the face of significant adversity involves a developmental progression; new vulnerabilities and challenges and/or strengths and opportunities often emerge with changing circumstances over the life course (8). Resilience is not something an individual “has” – it is a multiply determined developmental process that is not fixed or immutable. Hence, it is important to conduct longitudinal studies of the determinants of resilient functioning. In this regard, longitudinal studies on resilience should focus not only on assessing the stability of the construct over developmental time, but also on the ability of formerly resilient individuals to “bounce back” or to recover positive functioning after experiencing difficult periods and achieve their prior resilient adaptation (32). Moreover, since resilient adaptation may be achieved at any point in the life cycle, there is a need for research on the achievement of positive outcomes at different points in development, including in adulthood and in later life (8).

A MULTILEVEL PERSPECTIVE ON RESILIENCE

Until the past decade, the empirical study of resilience pre-

dominantly focused on behavioral and psychosocial correlates of, and contributors to, the phenomenon and did not examine biological correlates or contributors (8,10,11). These studies were undertaken prior to the inception of modern techniques for examining the molecular genetic, neural, and biological correlates of human behavior and development.

Evidence from earlier variable-oriented and person-oriented investigations of resilience converge on a short list of attributes of child and environment that turn out to be well-established general correlates of competent adaptation and psychopathology. Although there were methodological flaws and limitations in the early studies (14), more contemporary investigations nonetheless continue to corroborate the factors associated with resilient functioning: a) close relationships with competent and caring adults in the family and community; b) self-regulation abilities; c) positive views of self; d) motivation to be effective in the environment (i.e., self-efficacy and self-determination); and e) friendships and romantic attachments with prosocial and well-regulated peers (12). Problem-solving skills, foresight in planning, and a future orientation (all linked to executive functions), active coping strategies, and the capacity to confront fears directly, minimizing denial, disengagement, and avoidant coping have all been associated with resilient functioning (7,12,14). Moreover, optimism, positive emotionality, perceiving stressful occurrences in less threatening ways and the ability to reframe adverse experiences in a positive vein, spirituality, and being able to find meaning amidst trauma have each been linked to resilience (33).

Undoubtedly, the relative neglect of biology as relevant to developmental theorizing on the unfolding of adaptive behavioral outcomes in the face of adversity was primarily due to the paucity of information that existed about the structural and functional organization of the brain (34-36). There simply was not enough knowledge about brain development and function to articulate their role in the genesis and epigenesis of normal and deviant mental processes, let alone in their contribution to the development of resilient adaptation (33).

Most of what is known about the causes, correlates, course, and consequences of resilient functioning in the face of adversity have been gleaned from investigations that focused on relatively narrow domains of variables (7,8). Yet it is apparent from the questions addressed by developmental psychopathologists that progress toward a process-level understanding of resilient adaptation will require the implementation of research designs and strategies that call for the simultaneous assessment of multiple domains of variables both within and outside of the developing person (11).

In the past decade, a number of scientists have urged researchers to incorporate neurobiological and molecular genetic assessments into their investigations of the developmental pathways to resilient functioning (10,11,37). Technological advances in molecular genetics, neuroimaging, magnetoencephalography, electroencephalographic (EEG) recording, and hormonal assay techniques have made it more feasible to conduct research on the development of resilience

from a multilevel perspective (11,12).

In addition, the advent of modern neuroscience, along with its many associated subdisciplines, represents an unprecedented opportunity to augment current conceptual and methodological approaches to the study of resilience. Regardless, it is critically important to keep in mind that biological domains do not function independently; rather, more commonly the functioning of one system influences the functional properties of one or more other systems, through a developmental cascade of bidirectionally influenced processes (38). Given this increasing recognition of the importance of considering many levels of interdependent processes simultaneously, in order to advance the understanding of a multifaceted phenomenon such as resilience, it is incumbent upon resilience researchers to meet the challenge of simultaneously incorporating multiple levels of analysis both across and within systems (39). Biological and psychological domains are both essential to include in basic research on resilience and in resilience-promoting interventions. Each level both informs and constrains all other levels of analysis. Moreover, the influence of levels on one another is almost always bidirectional.

Because different levels of analysis constrain other levels, as scientists learn more about multiple levels of analysis, resilience researchers conducting their work at each level will need to develop theories that are consistent across all levels. When disciplines function in isolation, they run the risk of creating theories that ultimately will be incorrect, because vital information from other disciplines has either been ignored or is unknown. Just as is the case in systems neuroscience (40), it is critical that there be an integrative framework that incorporates all levels of analysis about complex systems in the development of resilience (11,36).

Resilience in maltreated children: from single-level to multilevel investigation

Growing up under conditions of child maltreatment constitutes a profound immersion in severe stress that challenges and frequently impairs development across diverse domains of biological and psychological functioning (41). The ecological conditions associated with maltreatment represent a severe deviation from the average expectable environment. Maltreated children are likely to manifest atypicalities in neurobiological processes, physiological responsiveness, emotion recognition and emotion regulation, attachment relationships, self-system development, representational processes, social information processing, peer relationships, school functioning, and romantic relationships (41). Accordingly, maltreated children are likely to develop a profile of relatively enduring vulnerability factors, placing them at great risk for future maladaptation and psychopathology.

Nonetheless, not all individuals who have been abused and neglected succumb to the extreme adversity in their lives. Investigation of how some maltreated individuals cope adap-

tively despite experiencing significant stress and trauma offers an opportunity to discover processes at multiple levels of analysis that are likely to be germane to effective coping in the face of adversity, yet less readily detectable under more normative stress exposure (42). Discovering how maltreated children develop and function resiliently despite experiencing a multitude of stressors offers considerable promise for elucidating developmental theories of coping and for prevention and intervention.

In a longitudinal investigation of the pathways to resilience in maltreated children, we sought to ascertain if there were different pathways to resilient functioning in maltreated and non-maltreated children (both from comparable low socioeconomic backgrounds) and to explore whether there were differences between these groups in resilience, recovery of function, or decline in functioning over the 3-year period of the study (32). Maltreated children demonstrated greater dysfunction than non-maltreated children on several indicators of resilient functioning (e.g., competence with peers, behavior problems, school functioning, relationships with adult caregivers). Moreover, many of these deficits persisted across 2 or 3 consecutive years of assessment. Furthermore, across each of the 3 years, maltreated children exhibited a lower level of resilient functioning than did the non-maltreated children. Additionally, the continuity of maladaptive functioning displayed by maltreated children across the course of this longitudinal study was substantial. Taken together, these findings underscore the deleterious impact that maltreatment experiences exert on competent functioning and attest to the non-transient nature of their influence.

In this study, we also constructed pattern groups based on the three consecutive yearly assessments of resilient functioning in maltreated and non-maltreated children. Inspection of these pattern groups revealed that there was a significantly greater percentage of maltreated children than non-maltreated children in the low resilient functioning pattern group (40.6% vs. 20%). Furthermore, a greater percentage of maltreated (9.8%) than non-maltreated children (1.3%) displayed zero competence indicators, thereby reflecting an absence of resilient strivings across the 3 year study period. Garnezy (16,24) consistently emphasized that most children maintain the ability to display some resilience strivings in the presence of chronic and serious adversity. The complete absence of resilient strivings in nearly 10% of the maltreated children is cause for great concern, as self-righting tendencies are vital characteristics of all living organisms. The consistent absence of such strivings throughout the duration of the investigation is quite aberrant and alarming.

We also examined factors that contributed to the development of resilient functioning in the groups of disadvantaged maltreated and non-maltreated children. For the maltreated children, the major predictors of resilient functioning were the personality characteristics of ego overcontrol (i.e., the ability to monitor and control impulses and regulate affect) and ego resiliency (i.e., the degree of relative flexibility in regulating affect and behavior to meet situational demands),

and positive self-esteem. In contrast, for the non-maltreated children, positive relationships with their mother and other adult caregivers and ego resiliency played prominent roles in the prediction of adaptive functioning. Given the high percentage of insecure and disorganized attachments in maltreated youngsters (43), it makes sense that relationship factors would be more vital to the attainment of resilience in the disadvantaged non-maltreated children.

Personality characteristics and self-system processes were more important in achieving resilient adaptation in maltreated children. Specifically, the self-system variables of self-reliance and self-confidence, in concert with interpersonal reserve (i.e., ego overcontrol), appear to bode well for the development of resilient adaptation in maltreated children. Through adopting a more reserved, controlled, and rational way of interacting and relating (i.e., resilient overcontrol), maltreated children who function in a resilient fashion may be more attuned to what is necessary for successful adaptation in their adverse home environments. It is conceivable that their more overcontrolled style may protect them from being targets of continued maltreatment incidents. In contrast, the more affectively expressive style of resilient undercontrollers may not be well suited for successful adaptation in maltreating environments, because such styles may provoke attention and reaction from others that could result in greater risk for maltreatment (44).

Following the completion of this longitudinal investigation of the psychosocial processes underlying resilience in maltreated children, we initiated two multilevel studies. The ecological-transactional perspective that undergirds this research inherently takes into account multiple levels of analysis, and allows for combining biological and psychological mechanisms within the same framework (3,4). This perspective does not ascribe ascendancy to any level of analysis over another, and it encourages loosening of conceptual boundaries between nature and nurture and biology and psychology (45-47). This theoretical perspective thus provides a ready-made structure for the integration of a multilevel perspective into resilience.

In the first multilevel investigation of resilience, emotion regulation, and hemispheric EEG asymmetry in maltreated and nonmaltreated children from high-stress low socioeconomic backgrounds, we hypothesized that the positive emotionality and increased emotion regulatory ability associated with resilient functioning would be associated with relatively greater left frontal EEG activity (48). A large body of literature concerning the meaning and correlates of hemispheric asymmetries in EEG activity has suggested that this ubiquitous phenomenon indexes a neural system that has emotion-specific influences whereby the two hemispheres of the cerebral cortex have been found to be differentially involved in emotion (48). Specifically, the left hemisphere is associated with positive emotions/approach behavior and the right hemisphere is linked with negative emotions/withdrawal behavior. Emotions, and in particular positive emotion and good emotion regulatory abilities, have consistently been associated with re-

silient adaptation (18,49,50). Thus, the potential connection of hemispheric EEG asymmetry with resilience lies in their common linkages with emotion and emotion regulation.

EEG asymmetry across central cortical regions distinguished between children with high and low resilient functioning, such that left hemisphere activity characterized those maltreated children who were adapting resiliently based on our competence composite index (e.g., good peer relations, adapting successfully to school, low levels of depressive symptomatology, low externalizing and internalizing psychopathology) (51). Moreover, a behavioral measure of emotion regulation, based on 35 hours of observation of the children, significantly contributed to the prediction of resilience in maltreated and non-maltreated children.

The investigation of a neural-level phenomenon such as hemispheric EEG asymmetry in the context of resilient adaptation reminds us that there is certainly no one single characteristic that will be ascendant in the process of resilience over the course of development. Resilience is a dynamic, interactive process between multiple levels across time, none of which holds primary importance at any given moment. However, viewed across development, the relative importance of various biological and psychological processes, although inevitably interrelated, may also vary across development.

In another multilevel investigation conducted in our laboratory, resilient functioning in maltreated and non-maltreated low-income children in relation to the regulation of two stress-responsive adrenal steroid hormones, cortisol and dehydroepiandrosterone (DHEA), as well as the personality constructs of ego resiliency and ego control, was examined (52). The steroid hormones we chose to investigate as potential predictors of resilience are the two primary adrenocortical products of secretory activity of the hypothalamic-pituitary-adrenal (HPA) axis. The capacity of individuals to elevate cortisol levels in response to exposure to acute trauma is important for survival (2). DHEA exerts an impact upon a diverse array of biological actions, including effects on the immune, cardiovascular, endocrine, metabolic, and central nervous systems (53).

As in the previous single- and multilevel research on the pathways to resilient adaptation described above, we utilized a composite measure of resilience that included multi-method, multi-informant assessments of competent peer relations, school success, and low levels of internalizing and externalizing symptomatology. We found that ego resiliency and ego overcontrol and the adrenal steroid hormones associated with stress (i.e., cortisol and DHEA) made independent and non-interactive contributions to resilience. Although operating at different levels of analysis, behavioral/psychological and biological factors each made unique contributions to resilience.

Prolonged stress, as is often the case in child maltreatment, can lead to allostatic load, characterized by cumulative physiological dysregulation across multiple biological systems, through a cascade of causes and sequelae that can change the brain, organ systems, and the neurochemical balance that undergirds cognition, emotion, mood, personality, and behavior

(54,55). Allostatic load is thought to occur when the adaptation to stress necessitates that the responses must be maintained over sustained time periods. Allostasis and allostatic load can be conceived as embodying a general biological principle – namely that the systems that help the body adapt to stress, and serve a protective function in the short term, also may take part in the development of pathophysiological processes when overused or managed ineffectively.

We found that higher morning levels of cortisol were related to lower levels of resilient strivings for the non-maltreated children. High basal cortisol may indicate that non-maltreated children are experiencing greater stress exposure and, consequently, are constrained in their ability to adapt competently. Within the group of maltreated children, differences in cortisol regulation were found as a function of the subtype(s) of maltreatment experienced. Physically abused children with high morning cortisol had higher resilient functioning than physically abused children with lower levels of morning cortisol. The positive role of increased cortisol for physically abused children is divergent from the more general pattern of higher cortisol being related to lower resilient functioning as we discovered in the non-maltreated and sexually abused children in this study.

Prior research on neuroendocrine regulation has indicated that physically abused children generally exhibit lower levels of morning cortisol secretion (56). It may be that the subgroup of physically abused children who were able to elevate cortisol to cope with the life stressors was demonstrating a greater striving for resilient adaptation. In contrast, the larger subgroup of physically abused children with lower levels of morning cortisol may have developed hypocortisolism over time in response to chronic stress exposure (i.e., allostatic load) (57). As a result, for these children there may be a diminished capacity to mobilize the HPA axis to promote positive adaptation under conditions of ongoing stress. Additionally, we found that the very low level of resilience among sexually abused children with high basal cortisol may be a product of their different traumatic experiences and consequences of chronic excessive vigilance and preoccupation, with commensurate HPA axis hyperarousal (52).

Finally, we also discovered that maltreated children with high resilient functioning exhibited a unique atypical pattern of a relative DHEA diurnal increase. Maltreated children who have the capacity to elevate DHEA over the course of the day may be better equipped to cope with the demands of high chronic exposure to stress and to adapt competently. In contrast, the non-maltreated children who functioned resiliently did not exhibit the pattern of diurnal DHEA increase; instead they displayed the lowest levels of DHEA across the day.

Gene-environment interaction and the molecular mechanisms that promote resilient functioning in maltreated children

Recent years have witnessed a renaissance of interest in investigating the interaction between genes and environmen-

tal pathogens in the development of psychopathology and resilience (58-60). From a genetic perspective, resilience can be conceptualized as the extent to which persons at genetic risk for maladaptation and mental disorder are not affected (61). Additionally, there may be genetic contributors to resilient adaptation that protect some individuals in families where there is a high genetic loading for developing maladaptation and mental disorder from succumbing to these deleterious outcomes (58). Moreover, genes are likely to serve a protective function against environmental insults for some individuals. Thus, it is apparent that genetic influences on maladaptation and psychopathology operate in a probabilistic and not in a deterministic manner.

In gene-environment interaction (GxE), environmental experiences moderate genetic effects (or vice versa) on normal, psychopathological, and resilient developmental outcomes. For example, genetic effects on functioning outcomes may be observed only under certain environmental contexts or in conjunction with particular histories of experience; conversely, experience may only relate to outcomes among persons with specific genetic characteristics (62).

The majority of GxE studies have investigated polymorphisms in monoamine oxidase A (MAOA) and serotonin transporter (5-HTT), two of the primary genes implicated in the maturation of the early developing brain and in mood, behavior, and responsiveness to stress (58). The variability exhibited in children's responses to the environmental hazard of child maltreatment suggests that this heterogeneity may be within the hemisphere of genetic influence (59). The experience of child maltreatment has proven to be a strong environmental pathogen that has generated a number of provocative findings which have contributed to engendering interest in research on GxE (59,60; for meta-analyses, see 65,66).

Caspi and colleagues (62,63) demonstrated GxE effects in a large sample of adults who had experienced severe early child maltreatment. Specifically, Caspi et al (58) found that adult males who were maltreated early in development and who possessed the low activity allelic variant of the MAOA gene evidenced higher levels of antisocial and aggressive symptomatology than did those individuals who were maltreated early and who had the high activity variant of MAOA. The latter group demonstrated lower levels of antisocial and aggressive symptoms (62) than did maltreated adults with the low activity variant of MAOA. In a subsequent investigation, Caspi et al (63) discovered that adults who experienced severe maltreatment in childhood and who possessed the short (s/s) variant of the 5-HTT gene exhibited higher levels of depressive symptoms than did adults who had the long variant (l/l) of the 5-HTT gene and had been maltreated as children. In contrast, adults in the latter group had significantly fewer depressive symptoms than did maltreated adults with the short allele variants (63). Thus, it is conceivable that the high activity MAOA gene polymorphism and the long variants of the 5-HTT gene may confer protection against antisocial disorder and depression to adults who have been severely maltreated in their childhood.

In our laboratory, we conducted a multigenic study examining the interaction between polymorphisms of 5-HTT and MAOA genes in a large sample of maltreated children in relation to depressive symptomatology (67). Adolescents from low socioeconomic backgrounds with a history of child maltreatment or no such history were administered a semi-structured diagnostic interview for mental disorders; moreover, these adolescents provided buccal cells for genetic analysis. Heightened depressive symptoms were found among extensively maltreated youth with low MAOA activity. Among comparably maltreated youths with high MAOA activity, self-coping strategies related to lower depressive symptoms. The finding that self-coping strategies and high MAOA activity were related to lower depressive symptoms calls to mind results from a number of our studies on resilience in maltreated children. Specifically, self-reliance and self-determination were found to be predictors of resilient functioning in maltreated children (32). It is conceivable that the maltreated children with positive self-system characteristics who functioned resiliently also may have possessed polymorphic variants of genes (such as high MAOA activity) that served a protective function against maladaptation.

Sexual abuse and the 5-HTT short/short genotype predicted higher depression, anxiety, and somatic symptoms. This GxE interaction was further moderated by MAOA activity level. Specifically, we found that sexually abused adolescents with one or two copies of the 5-HTT short allele had significantly reduced levels of internalizing symptoms if they also had the high activity version of the MAOA gene (67).

We also have begun to decipher co-actions across multiple levels of analysis through incorporating genetic and multiple physiological measures in our multilevel research on pathways to resilience in abused and neglected children. For example, in a longitudinal investigation that is currently underway in our laboratory, we are employing a multiple-levels-of-analysis approach to examining the course of trauma-related psychopathology in maltreated children, as well as the multilevel processes that contribute to resilient outcomes. In addition to genotyping relevant candidate genes, we have incorporated multiple measures of neurophysiological responses to classes of emotion stimuli, and hormonal, neurocognitive and behavioral functioning. The field can no longer afford to continue the artificial distinction among genetics, neurobiology, and behavior in research on the determinants of resilience.

Neural plasticity and resilience: some potential linkages

Experience-expectant and experience-dependent mechanisms of neural plasticity are integral to the very anatomical structure of cortical tissue and cause the formation of the brain to be an extended malleable process (65-67). Developmental psychopathologists and neuroscientists can utilize this knowledge as an avenue for understanding the vulner-

ability and protective processes of brain development as contributors to the genesis and epigenesis of psychopathology and resilience. Moreover, because the mechanisms of plasticity cause the brain's anatomical differentiation to be dependent on stimulation from the environment, it is clear that the cytoarchitecture of the cerebral cortex is shaped by input from the social environment. Because the human cortex is only diffusely structured by the genetic plan, and because its eventual differentiation is highly reactive to the active coping strategies of the individual in a particular environment, it is highly likely that both normal, abnormal, and resilient outcomes of this process would encompass a diverse range of cortical network anatomies and individual personalities.

Analogous to neural plasticity that takes place in response to brain injury (68-71), resilience can be viewed as the ability of an individual to recover after exposure to adversity or trauma (9,32). According to this view, adversity is thought to exert a damaging effect on one or more neural substrates, and mechanisms of neural plasticity bring about recovery in an individual. This might lead to the conclusion that certain individuals, classified as resilient, may have some increased innate capacity (i.e., plasticity), above and beyond normative levels, to recover from environmental insults that impact the brain. This view of resilience conceives of adversity in the environment as "bad" for the brain, with recovery as an innate property of the brain itself. This perspective, however, does not consider the impact of a positive environment (e.g., presence of social supports), or of the individual's active attempts at coping, or of protective/plasticity genes, on such recovery.

Another conceptualization of resilience would be one of greater than normative resistance to the impact of environmental adversity on the brain, such that resilient individuals may not succumb to the potentially damaging effects that adversity may have on the brain and other biological systems. This view of brain-adversity interaction would not strictly be classified as involving neural plasticity. Thus, for these individuals, the term recovery of function may not apply, in that they did not "lose" function at all.

The rapid growth in sophisticated techniques that permit imaging of the brain directly has resulted in the availability of a variety of methodologies to developmental psychopathology researchers; many of these methods could be utilized to examine neural plasticity, as well as brain structure and function, in detail. These new tools make it possible to now undertake empirical investigations of the relation between neural plasticity and resilience, perhaps enabling an examination of the direct linkage of these two processes. Questions about how neural plasticity may play a role in the development and maintenance of resilient functioning could be addressed, as well as whether the mechanisms of neural plasticity may operate differently in individuals classified as resilient.

Among the compelling questions about resilient adaptation that could potentially be addressed utilizing brain imaging methodologies are: a) Is brain structure and function different in maltreated and non-maltreated children functioning resiliently, matched on experiences of adversity? b) Is the

brain structure and function of resilient individuals who have experienced adversity different from normal children reared in non-adverse environments? c) Are particular areas of the brain more likely to be activated in resilient than in non-resilient functioning during challenging or stressful tasks? d) What aspects of brain structure and function differentiate individuals who function resiliently, despite experiencing early adversity, from those who function in a non-resilient fashion and who encounter adversity early in life (i.e., what is the role of early experience?) e) Are there sensitive periods beyond which the achievement of resilience is improbable or is resilience possible to achieve across the life span? and f) Are there changes over time in brain structure and/or functioning in individuals classified as resilient that may reflect processes of neural plasticity? The inclusion of neuroimaging techniques to the existing predominantly psychological approaches to charting the pathways to resilience, along with the additional biological and molecular genetic methodologies discussed earlier in this paper, could result in many exciting discoveries about the complex processes that eventuate in competent outcomes despite the experience of significant adversity.

Aside from investigating the proximal relation between resilience and neural plasticity, there are several neurobiologically mediated processes (e.g., cognition, neuroendocrine functioning) that have a direct relation to resilient outcome (14,51). Although such processes exert an impact on resilient functioning, neural plasticity may, to some degree, be the common, underlying mechanism that mediates the relation between such processes and resilience.

Resilience-promoting interventions: a multilevel perspective

Research on resilience has substantial potential to guide the development and implementation of interventions for facilitating the promotion of resilient functioning in diverse high-risk populations that have experienced significant adversity (27,72). Such interventions should target protective and vulnerability forces at multiple levels of influence – culture, community, family, and the individual.

Although several of the interventions that have been implemented have employed a multifaceted approach in order to ensure sensitivity to the diverse transactions between children and their environmental contexts, to our knowledge there have been very few interventions that have included biological assessments as part of the pre-post evaluation battery. Because one of the primary objectives of the field of prevention science is to intervene in the course of development to foster the recovery of function and to promote resilient adaptation in individuals at high risk for psychopathology (6), it is now essential to utilize a multiple-levels-of-analysis perspective ranging from DNA sequences to culture in research evaluations aimed at assessing the efficacy of RCT interventions whose goal is to foster the development of resilient adaptation.

There are at least two reasons for the dearth of attention to biological processes in the evaluation of preventive interventions with children and adolescents. This lack of attention may partly originate from a tradition in developmental psychology of measuring biological processes as indices of heritable, constitutional individual differences reflecting the neurobiological bases of temperament (73). This tradition encourages beliefs that biological processes are either not malleable or are more refractory to positive change as a result of experience. Because there are bidirectional relations between different levels of biological and psychological organization, it is essential to recognize that experience also influences biology (68,74). Evidence for neurobiological reorganization in response to alterations in the environment may be less apparent in normative populations where there likely is greater stability in supportive milieus; however, investigations of individuals reared in extreme environmental conditions should enable us to more clearly isolate the components of these diverse systems, thereby shedding light on the bidirectional effects of experience and neurobiology.

Random assignment to adversity or trauma is not possible, but random assignment to intervention is. If biological systems recover in response to the intervention, then this provides support for arguments that the systems under study are sensitive to environmental input during development. Furthermore, if randomized interventions alter neurobiological systems associated with disorders, and it can be shown that they mediate changes in psychosocial and behavioral functioning, then this fosters a better understanding of the neurobiological bases of the disorder. Moreover, preventive interventions may contribute to recovery or repair of biological sequelae in ways that have only begun to be understood. Improved comprehension of the neurobiological processes that increase risk of maladaptive development may also suggest novel targets for preventive intervention. Thus, it is important for prevention scientists to investigate the means by which changes in experience and psychological functioning resulting from preventive interventions may modify biological processes.

Now that animal studies have demonstrated that experience can exert impacts on the microstructure and biochemistry of the brain (75), a vital role for continuing neural plasticity throughout epigenesis in contributing to the recovery from various forms of maladaptation and mental disorder may be suggested. There is growing evidence in the animal literature that efficacious interventions modify not only maladaptive behavior, but also the cellular and physiological correlates of behavior (76,77). Successful preventive interventions may alter behavior and physiology through producing alterations in gene expression that create a new structural reorganization in the brain (76). One important goal of preventive intervention research is to identify periods of development when a specific intervention may be more efficacious so that the intervention can be targeted to that period. A goal of preventive intervention work that includes measures of neurobiological processes is to better identify sensitive periods for intervention (78).

Determining the multiple levels at which change is engendered through RCT prevention trials will provide more insights into the mechanisms of change, the extent to which neural plasticity may be promoted, and the interrelations between biological and psychological processes in maladaptation, psychopathology, and resilience (79). Moreover, preventive interventions with the most in-depth empirical support, based on integrative multilevel theories of normality, psychopathology, and resilience, can be implemented in effectiveness trials in community or real-world settings to reach the broadest number of people and prevent, alleviate, and ultimately cure, suffering from mental disorders (80). Furthermore, the inclusion of biological assessments in evaluations of interventions designed to foster resilience will enable scientists to discover whether the various components of multifaceted interventions each exert a differential impact on separate brain systems. It is thus possible to conceptualize successful resilience-promoting interventions as examples of experience-dependent neural plasticity.

Finally, although the consensus is that resilience is a dynamic developmental construct that, theoretically, is possible throughout the life course, it nonetheless is important to ascertain whether the timing of resilience-promoting interventions is a crucial variable that merits consideration. Specifically, it will be extremely important to know whether resilience-promoting interventions are more effective when implemented in the early years of life. Likewise, are such interventions more likely to achieve their goal of promoting resilience if they are instituted as closely as possible to the identification of the adverse event(s) or experience? The incorporation of a multiple-levels-of-analysis perspective will enable scientists to learn whether, for example, resilience-promoting interventions implemented in the early years of life are better for brain development and functioning, even if improvement occurs in individuals who receive resilience-facilitating interventions later in life or receive their interventions further removed in time from their adverse event(s) or traumatic experiences.

CONCLUSIONS

It is important to note that the call for a multilevel perspective in resilience research and resilience-promoting interventions – that includes the criticality of conducting genetic and neurobiological, as well as behavioral, assessments – does not reduce resilience to biology, let alone to a single biological variable. The inclusion of a multilevel perspective on resilience should not hearken scientists and clinicians back to the time when some espoused the view that they were “invulnerable” children. The incorporation of a multilevel perspective into research on resilience still requires adherence to a dynamic, transactional view that respects the importance of context.

We are in the midst of a truly exciting period for research on the pathways to resilient functioning in individuals who have experienced great adversity and trauma. The advances

in genomics, epigenetics, brain imaging, and hormonal and immunological assay techniques will make important contributions to propelling increased knowledge about the developmental processes leading to resilience (11,12). Such enhanced understanding has great potential for the development and implementation of novel, perhaps even individualized, resilience-promoting interventions for high-risk children and adults who are not functioning well due to experiences of adversity and trauma. In order to comprehend fully how individuals achieve resilient functioning in the face of adversity, it is incumbent upon us to investigate it with a commensurate level of complexity.

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Pathophysiology of depression: do we have any solid evidence of interest to clinicians?

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Due to the clinical and etiological heterogeneity of major depressive disorder, it has been difficult to elucidate its pathophysiology. Current neurobiological theories with the most valid empirical foundation and the highest clinical relevance are reviewed with respect to their strengths and weaknesses. The selected theories are based on studies investigating psychosocial stress and stress hormones, neurotransmitters such as serotonin, norepinephrine, dopamine, glutamate and gamma-aminobutyric acid (GABA), neurocircuitry, neurotrophic factors, and circadian rhythms. Because all theories of depression apply to only some types of depressed patients but not others, and because depressive pathophysiology may vary considerably across the course of illness, the current extant knowledge argues against a unified hypothesis of depression. As a consequence, antidepressant treatments, including psychological and biological approaches, should be tailored for individual patients and disease states. Individual depression hypotheses based on neurobiological knowledge are discussed in terms of their interest to both clinicians in daily practice and clinical researchers developing novel therapies.

Key words: Depression, pathophysiology, genetics, stress, serotonin, norepinephrine, dopamine, neuroimaging, glutamate, GABA

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Major depressive disorder (MDD) is a common and costly disorder which is usually associated with severe and persistent symptoms leading to important social role impairment and increased mortality (1,2). It is one of the most important causes of disability worldwide (3). The high rate of inadequate treatment of the disorder remains a serious concern (1).

This review is aimed at summarizing the solid evidence on the etiology and pathophysiology of MDD that is likely relevant for clinical psychiatry. Neurobiological findings are regarded as solid when they are consistent and convergent, i.e., they have been confirmed by several studies using the same method and fit into results from studies using different methodological approaches.

GENES AND PSYCHOSOCIAL STRESS

Family, twin, and adoption studies provide very solid and consistent evidence that MDD is a familial disorder and that this familiarity is mostly or entirely due to genetic factors (4). This important finding suggests that parental social behavior and other familial environmental risk factors are not as important in the pathogenesis of MDD as previously assumed and should not be

the major focus of the treatment of the disorder.

The above-mentioned studies consistently show that the influence of genetic factors is around 30-40% (4). Non-genetic factors, explaining the remaining 60-70% of the variance in susceptibility to MDD, are individual-specific environmental effects (including measurement error effects and gene-environment interactions). These effects are mostly adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce (5,6).

These results suggest that there is a huge potential in the prevention of MDD by means of psychosocial interventions (e.g., in schools, at workplace). In addition, these results mirror the clinical practice of empirically validated psychotherapies to treat depression (7-9), including interpersonal, psychodynamic and cognitive behavioral psychotherapies and cognitive behavioural analysis system of psychotherapy, which all focus directly or indirectly on interpersonal difficulties and skills. This does not exclude the fact that unidentified non-genetic, non-psychosocial risk factors may also play important roles in some patients (e.g., climatic change, medical conditions).

Stress sensitivity in depression is partly gender-specific. While men and women are, in general, equally sensitive to the depressogenic effects of stressful life events, their responses vary depending upon the type of stressor. Specifically, men are more likely to have depressive episodes following divorce, separation, and work difficulties, whereas women are more sensitive to events in their proximal social network, such as difficulty getting along with an individual, serious illness, or death (10). These findings point to the importance of gender-sensitive psychosocial approaches in the prevention and treatment of MDD.

In contrast to the very solid evidence from epidemiological studies on broad risk factor domains, there is no solid evidence for specific genes and specific gene-by-environment interactions in the pathogenesis of MDD. Genome-wide association studies have indicated that many genes with small effects are involved in complex diseases, increasing the difficulty in identifying such genes (11). While there has been progress in the search for risk genes for several complex diseases despite this methodological problem (12), psychiatric conditions have turned out to be very resistant to robust gene identification. For example, based on a community-based prospective study, it has been proposed that a

specific genetic variation in the promoter region of the serotonin transporter (a target of antidepressant drugs) interacts with stressful life events in the pathogenesis of depression (13). Although there is high clinical and neurobiological plausibility of this interaction, a recent meta-analysis yielded no evidence that the serotonin transporter gene alone or in interaction with psychological stress was associated with the risk of depression (14).

The limited success of genetic studies of depression has been related to use of current classification schemas including ICD-10 and DSM-IV. These diagnostic manuals are based on clusters of symptoms and characteristics of clinical course that do not necessarily describe homogenous disorders but instead reflect common final pathways of different pathophysiological processes (15,16). The clinician should be aware that family history will continue to be the most solid source of information to estimate the genetic risk of MDD.

STRESS HORMONES AND CYTOKINES

Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions. This hormone induces the secretion of pituitary corticotropin, which stimulates the adrenal gland to release cortisol into the plasma. The physiologic response to stress is partly gender-specific: women show generally greater stress responsiveness than men, which is consistent with the greater incidence of major depression in women (17). Moreover, men show greater cortisol responses to achievement challenges, whereas women show greater cortisol responses to social rejection challenges (18).

Although MDD is considered as a stress disorder, most subjects treated for MDD have no evidence of dysfunctions of the hypothalamic-pituitary-adrenal axis (HPA) (19). However, some subjects with MDD do show abnormalities of that axis and of the extrahypothalamic CRH system (20). Altered stress

hormone secretion appeared to be most prominent in depressed subjects with a history of childhood trauma (21). Elevated cortisol may act as a mediator between major depression and its physical long-term consequences such as coronary heart disease, type II diabetes, and osteoporosis (22).

The importance of HPA axis dysfunction for the efficacy of antidepressants is a matter of debate (23). This axis is regulated through a dual system of mineralocorticoid (MR) and glucocorticoid (GR) receptors. Decreased limbic GR receptor function (24,25) and increased functional activity of the MR system (26) suggest an imbalance in the MR/GR ratio in stress-related conditions such as MDD. Epigenetic regulation of the glucocorticoid receptors has been associated with childhood abuse (27). Such environmental programming of gene expression may represent one possible mechanism that links early life stress to abnormal HPA axis function and increased risk of MDD in adults.

While the CRH stimulation test (dex/CRH test) (28) is a sensitive measure of the HPA axis dysfunction in depression, the specificity of this test for MDD is low. However, non-suppression in the dex/CRH test has consistently predicted increased risk for depressive relapse during clinical remission (23). Additionally, the measurement of waking salivary cortisol concentration has been shown to be a simple and sensitive test for HPA axis hyperactivity in depression (29). Hypercortisolemia is almost exclusively found in subjects with severe and psychotic depression, in whom glucocorticoid antagonists may have some therapeutic effect (30).

There is convergent evidence for CRH to play a major role in the pathogenesis of certain types of depression. Levels of CRH in the cerebrospinal fluid are elevated in some depressed subjects (31). Post-mortem studies reported an increased number of CRH secreting neurons in limbic brain regions in depression (32), likely reflecting a compensatory response to increased CRH concentrations (33). In addition, CRH produces a number of physiological and behavioral alterations that resemble the

symptoms of major depression, including decreased appetite, disrupted sleep, decreased libido, and psychomotor alterations (34). There is also preliminary evidence that CRH1 receptor antagonists reduce symptoms of depression and anxiety (35).

“Sickness behavior” as a result of an activation of the inflammatory response system shares many symptoms with depression, including fatigue, anhedonia, psychomotor retardation, and cognitive impairment. Sickness is mediated by pro-inflammatory cytokines such as interleukin-1 α , tumor necrosis factor- α , and interleukin-6, which activate the HPA axis and impair the central serotonin system (36). The prevalence of depression as an unwanted effect of recombinant interferons is around 30% (37). In animals, blocking pro-inflammatory cytokine-mediated signaling produces antidepressant-like effects (38). Clinical data suggest that cytokines may play a role in the pathophysiology of a subgroup of depressed subjects, particularly those with comorbid physical conditions (36). The antidepressant enhancing effect of acetylsalicylic acid (39) points to the possible clinical relevance of psychoneuroimmunology in clinical depression research.

Taken together, the laboratory tests with the highest potential to be clinically useful in the care of depressed individuals are based on abnormalities of the neuroendocrine and neuroimmune systems. Despite the large amount of basic science data suggesting that the HPA axis is importantly involved in the pathophysiology of depression, the effect of pharmacological modulation of this neuroendocrine system as antidepressant therapy has been disappointing. The link between childhood trauma and a permanently altered physiologic stress system points to the use of specific psychotherapies in the treatment of depressed patients with a history of early life trauma (40).

THE MEDIATING ROLE OF MONOAMINES

Most of the serotonergic, noradren-

ergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including mood, attention, reward processing, sleep, appetite, and cognition. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant (19). Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. These observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis.

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system.

Serotonin is the most extensively studied neurotransmitter in depression. The most direct evidence for an abnormally reduced function of central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis. Such a reduction leads to the development of depressive symptoms in subjects at increased risk of depression (subjects with MDD in full remission, healthy subjects with a family history of depression) (41,42), possibly mediated by increased brain metabolism in the ventromedial prefrontal cortex and subcortical brain regions (42). Experimentally reduced central serotonin has been associated with mood congruent memory bias, altered reward-related behaviors, and disruption of inhibitory affective processing (16), all of which add to the clinical plausibility of the serotonin deficiency hypothesis. There is also evidence for abnormalities of serotonin receptors in depression, with the most solid evidence pointing to the serotonin-1A receptor, which regulates serotonin function. Decreased availability of this receptor has been found in multiple brain areas of patients with MDD (43),

although this abnormality is not highly specific for MDD and has been found in patients with panic disorder (44) and temporal lobe epilepsy (45), possibly contributing to the considerable comorbidity among these conditions. However, there is no explanation for the mechanism of serotonin loss in depressed patients, and studies of serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem research on the serotonergic system in depression, have yielded inconsistent results. There is preliminary evidence that an increased availability of the brain monoamine oxidase, which metabolizes serotonin, may cause serotonin deficiency (46). In addition, loss-of-function mutations in the gene coding for the brain-specific enzyme tryptophan hydroxylase-2 may explain the loss of serotonin production as a rare risk factor for depression (47).

Dysfunction of the central noradrenergic system has been hypothesized to play a role in the pathophysiology of MDD, based upon evidence of decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase, and decreased density of norepinephrine transporter in the locus coeruleus in depressed patients (48). In addition, decreased neuronal counts in the locus coeruleus, increased alpha-2 adrenergic receptor density, and decreased alpha-1 adrenergic receptor density have been found in the brains of depressed suicide victims post-mortem (49). Since there is no method to selectively deplete central norepinephrine and no imaging tool to study the central norepinephrine system, solid evidence for abnormalities of this system in depression is lacking.

While the classical theories of the neurobiology of depression mainly focused on serotonin and norepinephrine, there is increasing interest in the role of dopamine (50). Dopamine reuptake inhibitors (e.g., nomifensine) and dopamine receptor agonists (e.g., pramipexole) had antidepressant effects in placebo-controlled studies of MDD (51). In the cerebrospinal fluid and jugular vein plasma, levels of dopamine metabolites were consistently reduced in depression, suggesting decreased dopamine turnover (52). Striatal dopamine transporter bind-

ing and dopamine uptake were reduced in MDD, consistent with a reduction in dopamine neurotransmission (53). Degeneration of dopamine projections to the striatum in Parkinson's disease was associated with a major depressive syndrome in about one half of cases, which usually preceded the appearance of motor signs (54). Experimentally reduced dopaminergic transmission into the accumbens has been associated with anhedonic symptoms and performance deficits on a reward processing task in subjects at increased risk of depression (55,56). These findings are consistent with the clinical observation that depressed patients have a blunted reaction to positive reinforcers and an abnormal response to negative feedback (57).

Almost all established antidepressants target the monoamine systems (58). However, full and partial resistance to these drugs and their delayed onset of action suggest that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Despite this limitation, the monoamine-deficiency hypothesis has proved to be the most clinically relevant neurobiological theory of depression. New findings on the role of dopamine in depression emphasize the scientific potential of this theory, and promising reports of antidepressant effects of drugs that modulate the dopaminergic system (e.g., pramipexole, modafinil) in difficult-to-treat depression underline its clinical relevance (51,59).

THE NEUROIMAGING OF DEPRESSION

Although many historical attempts to localize mental functions have failed, they have considerably contributed to a modern neuroscientific understanding of mental disorders (60). The development of neuroimaging techniques has opened up the potential to investigate structural and functional abnormalities in living depressed patients. Unfortunately, the diversity of imaging techniques used, the relatively small and heterogeneous study samples studied, and the limited overlap of results across imaging paradigms

(61) make it difficult to reliably identify neuronal regions or networks with consistently abnormal structure or function in MDD.

Functional imaging studies have provided the most limited overlap of findings. This may be due to methodological limitations and/or the complexity of neurocircuitry involved in MDD. A recent meta-analytic study found the best evidence for abnormal brain activity in MDD in lateral frontal and temporal cortices, insula, and cerebellum. In these brain regions activity was decreased at rest, they showed a relative lack of activation during induction of negative emotions, and an increase in activity following treatment with serotonin reuptake inhibitors. Opposite changes may exist in ventromedial frontal areas, striatum and possibly other subcortical brain regions (61).

More solid evidence has been provided by structural imaging and post-mortem studies. A recent meta-analytic study on brain volume abnormalities in MDD revealed relatively large volume reductions in the ventromedial prefrontal cortex, particularly in the left anterior cingulate and in the orbitofrontal cortex. Moderate volume reductions were found in the lateral prefrontal cortex, hippocampus and striatum (62). Post-mortem studies consistently identified a reduction in glia cell density in dorsal, orbital and subgenual prefrontal cortices, as well as in the amygdala (63,64).

Overall, functional, structural and post-mortem studies suggest that structural and functional abnormalities in the left subgenual cingulate cortex are the most solid neuroanatomical finding in MDD. Volume reduction in this region was found early in illness and in young adults at high familial risk for MDD (65), suggesting a primary neurobiological abnormality associated with the etiology of the illness. Humans with lesions that include the subgenual prefrontal cortex showed abnormal autonomic responses to social stimuli (66), and rats with left-sided lesions in this region had increased sympathetic arousal and corticosterone responses to restraint stress (67). Most importantly, chronic deep brain stimulation to reduce the potentially elevated activity in the subgenual cingulated cor-

tex produced clinical benefits in patients with treatment-resistant depression (68).

In summary, despite the considerable heterogeneity of findings from neuroimaging studies, there is convergent evidence for the presence of abnormalities in the subgenual prefrontal cortex in some patients with MDD. Neuroanatomical research in depression is of great clinical interest, since novel antidepressant treatments such as deep brain stimulation can target specific brain regions. In addition, there are promising leads for neuroimaging findings to predict the likelihood of responses to specific treatments (69).

THE NEUROTROPHIC HYPOTHESIS OF DEPRESSION

Risk factors for depressive episodes change during the course of the illness. The first depressive episode is usually “reactive”, i.e., triggered by important psychosocial stressors, while subsequent episodes become increasingly “endogenous”, i.e., triggered by minor stressors or occurring spontaneously (70). There is consistent evidence that the volume loss of the hippocampus and other brain regions is related to the duration of depression (71), suggesting that untreated depression leads to hippocampal volume loss, possibly resulting in increased stress sensitivity (72) and increased risk of recurrence (73).

Glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have been proposed as possible mechanisms explaining brain volume loss in depression. There is no solid evidence on any of these mechanisms, since there are no imaging tools to directly examine neurotoxic and neurotrophic processes in vivo. Brain derived neurotrophic factor (BDNF) has attracted considerable interest. Specifically, preclinical studies have shown correlations between stress-induced depressive-like behaviors and decreases in hippocampal BDNF levels, as well as enhanced expression of BDNF following antidepressant treatment (74). The clinician should be aware of the potentially brain-damaging effect of de-

pression and treat depressed patients as early and effectively as possible.

ALTERED GLUTAMATERGIC AND GABAERGIC NEUROTRANSMISSION

A series of magnetic resonance spectroscopy studies consistently showed reductions in total gamma-aminobutyric acid (GABA) concentrations in the prefrontal and occipital cortex in acute depression (75). This may reflect acute stress effects, since psychological stress seems to induce presynaptic down-regulation of prefrontal GABAergic neurotransmission (76). Alternatively, low total GABA concentration may reflect reduction in the density and size of GABAergic interneurons (77). In addition, chronic stress may reduce GABA-A receptor function, possibly through changes in neuroactive steroid synthesis (78). Contradictory evidence of the GABA hypothesis of depression includes the lack of effects of GABAergic drugs on core depressive symptoms (79) and normal prefrontal GABA concentration in subjects with remitted MDD (80).

Several lines of evidence suggest a dysfunction of the glutamate neurotransmitter system in MDD: a single dose of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine produced rapid and large antidepressant effects in patients with treatment-resistant MDD (81); inhibitors of glutamate release (e.g., lamotrigine, riluzole) demonstrated antidepressant properties (82); abnormal glutamate levels were found in depressed subjects as determined by magnetic resonance spectroscopy (75); and there is evidence for abnormal NMDA signaling in post-mortem tissue preparations (83). Since glutamate is the major excitatory neurotransmitter involved in almost every brain activity, the characterization of the specific role of glutamate in depression deserves further investigation (e.g., there are promising leads that the metabotropic glutamate receptor 5 is specifically involved in MDD (84)).

CIRCADIAN RHYTHMS

Sleep disturbances and daytime fa-

Table 1 Clinically relevant neurobiological hypotheses of major depressive disorder (MDD)

Hypothesis	Main strength	Main weakness
Genetic vulnerability	Solid evidence from twin studies that 30-40% of MDD risk is genetic	No specific MDD risk gene or gene-environment interaction has been reliably identified
Altered HPA axis activity	Plausible explanation for early and recent stress as MDD risk factor	No consistent antidepressant effects of drugs targeting the HPA axis
Deficiency of monoamines	Almost every drug that inhibits monoamine reuptake has antidepressant properties	Monoamine deficiency is likely a secondary downstream effect of other, more primary abnormalities
Dysfunction of specific brain regions	Stimulation of specific brain regions can produce antidepressant effects	Neuroimaging literature in MDD provides limited overlap of results
Neurotoxic and neurotrophic processes	Plausible explanation of “kindling” and brain volume loss during the course of depressive illness	No evidence in humans for specific neurobiological mechanisms
Reduced GABAergic activity	Converging evidence from magnetic resonance spectroscopy and post-mortem studies	No consistent antidepressant effect of drugs targeting the GABA system
Dysregulation of glutamate system	Potentially rapid and robust effects of drugs targeting the glutamate system	Questionable specificity, since glutamate is involved in almost every brain activity
Impaired circadian rhythms	Manipulation of circadian rhythms (e.g., sleep deprivation) can have antidepressant efficacy	No molecular understanding of the link between circadian rhythm disturbances and MDD

HPA – hypothalamic-pituitary-adrenal; GABA – gamma-aminobutyric acid

tigue are diagnostic criteria for MDD, suggesting impaired sleep-wake regulation in depressed patients. In addition, some depressive symptoms may show diurnal variations (mood, psychomotor activity, accessibility of memories of positive and negative experiences), and a subgroup of patients with MDD may have a circadian rhythm disorder (85). In healthy young subjects, moderate changes in the timing of the sleep-wake cycle had specific effects on subsequent mood (86). In depressed patients, manipulations of circadian rhythms (light therapy, sleep deprivation, phase advance treatment) can have antidepressant efficacy.

Based on these findings, circadian abnormalities have been hypothesized to be etiologically associated with MDD (16). The association between phase advance of the sleep-wake cycle and phase advances in nocturnal cortisol secretion; shortened REM latency in some subjects with MDD; and the effect of antidepressants on circadian rhythms of behavior, physiology, and endocrinology contribute to the biological foundation of this hypothesis (85,87,88). Despite of the many promising findings, the molecular and genetic underpinnings of this hypothesis are largely unknown. It remains to be determined whether antidepressant

effects of new therapeutics such as agomelatine directly relate to normalization of circadian rhythms (87).

CONCLUSIONS

The main strengths and weaknesses of the various neurobiological hypotheses of depression are summarized in Table 1. The many theories of depression and the relatively low response rate of all available antidepressant treatments clearly argue against a “unified hypothesis of depression” and suggest that depression is a clinically and etiologically heterogeneous disorder.

This encourages research on predictors of the response to therapeutic interventions using biomarkers such as neuroimaging and neuroendocrine tests in combination with genotyping for inter-individual variability with respect to stress sensitivity and antidepressant drug action.

The identification of reliable predictors of therapeutic outcomes will allow for the development of personalized medicine that has the potential to individually tailor interventions and to open up new pathways in the evaluation of novel therapeutic approaches.

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Translating progress in depression research to the clinic: one step at a time on a very long road

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In his article, G. Hasler reviews the strengths and limitations of major theories regarding the neurobiology of depression. A fundamental premise on which the paper is based, which certainly appears warranted by the extant data, is that a unified model is unlikely to explain the variable results across studies of depression or the variable responses to treatments characterized by disparate receptor pharmacologies among patients with mood disorders. Instead, Hasler argues, each prevailing theory of depression likely applies only to mood disordered subtypes. Consequently, antidepressant treatments, including psychological and biological approaches, will continue to require tailoring to individual patients.

Hasler provides examples of how several major models of depression's pathophysiology have guided researchers to develop novel therapeutics for individuals suffering from major depressive disorder. Thus, research involving hypothalamic-pituitary-adrenal axis function, monoaminergic neurotransmitter function, and glutamatergic transmission recently led to reports that corticotropin releasing hormone antagonists, dopamine receptor agonists, and NMDA receptor antagonists/glutamate release inhibitors, respectively, exert antidepressant effects (1,2). In addition, neuroimaging findings implicating the neural circuits involving projections between the subgenual anterior cingulate cortex, amygdala, ventral striatum and medial thalamus have guided the development of deep brain stimulation therapies for treatment of refractory depression (3-6).

As Hasler indicates, the results of genetic association studies suggest that most cases of major depressive disorder are associated with some combination of numerous variants that individually

exert small effects, which interact together with environmental influences to confer vulnerability to affective disease. Thus, each pedigree in which depression is overrepresented may be unique with respect to the combination of single nucleotide polymorphisms and/or copy number variants that interact to increase vulnerability to depression. This observation highlights the importance of research aimed at identifying the neural circuits or systems where dysfunction arising via diverse etiologies can give rise to affective disease.

Hasler concludes from these results that "the clinician should be aware that family history will continue to be the most solid source of information to estimate the genetic risk of major depressive disorder". Nevertheless, the paper later reviews evidence that loss-of-function mutations in genes causing major functional effects may account for some cases of major depressive disorder, such as variation in the gene coding for the brain-specific enzyme tryptophan hydroxylase-2 that impairs serotonin synthesis (7). Such findings raise the possibility that genetic variants of large effect on risk for the disorder will be discovered that hold implications for pharmacotherapy which collectively will justify genetic testing in the management of depression.

Another theme within the paper which conveys optimism that psychiatric morbidity can be reduced is Hasler's conclusion that the large proportion of major depressive disorder cases for whom pathogenesis involves gene-environment interactions implies that "huge potential [exists] in the prevention of major depressive disorder by means of psychosocial interventions". Within this context, Hasler reviews evidence that psychosocial approaches ultimately will prove most effective in preventing and treating major depressive disorder if they are gender-sensitive. This theme was highlighted by evidence that neuroendocrine responses to stress are sex-specific

and that life events that increase vulnerability to depression differ between men and women.

An integration of the data reviewed in Hasler's manuscript illustrates how several seemingly unrelated pathological constructs may link together through interactions across brain systems to underlie the neurobiological bases of depression. Thus, accumulating evidence that increased pro-inflammatory cytokine expression plays a role in the pathophysiology of mood disorders also suggests mechanistic links to the abnormalities in stress-responsive neuroendocrine and monoaminergic neurotransmitter systems found in these disorders (8). This pathological construct also may confer susceptibility to the neuroplasticity effects evidenced by reductions in gray matter volume in neuroimaging studies and in glial cells and neuropil in neuropathological studies of mood disorders (4,9,10). The interactions across these systems are likely to illuminate the mechanisms underlying the medical comorbidities associated with depression, and elucidate targets for novel therapeutic interventions.

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Biological research into depression: a clinician's commentary

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This commentary presents a clinician's view of biological research into depression. It seeks to demonstrate the shortcomings of correlating highly sophisticated biological research with simple and questionable DSM diagnoses of depression.

In his wide-ranging review of the pathophysiology of depression, G. Hasler repeatedly stresses that depression is heterogeneous. It is in fact striking how great is the discrepancy between the simplistic DSM-IV clinical diagnosis of major depressive disorder (applying a top-down approach), on the one hand, and the battery of highly sophisticated, expensive biological research techniques (bottom-up approach) which are used in order to study the disorder's pathophysiology, on the other. In view of this methodological incongruence, it is hardly surprising that biological research contributes very little to the early recognition, clinical application and treatment of depression.

A clinical bottom-up approach would be more promising. It would consist of: a) a careful, exhaustive psychopathological description of all depressive, including somatic, symptoms; b) a syndromal diagnosis (e.g., retarded, agitated, hypochondriacal, somatic, atypical, neuroathenic, mood-congruent and mood-incongruent psychotic depression); and c) a more sophisticated subclassification of major depressive disorder, duly identifying the large subgroup with hidden subthreshold bipolarity, which is an im-

portant element of the diagnostic mood spectrum extending from depression, via several subgroups of bipolar disorder, to pure mania (1).

As a first, and feasible, step in the right direction, all biological studies on depression should be checked for a diagnosis of subthreshold bipolarity of major depressive disorder, and the biological data re-analysed. There is convergent evidence from three epidemiological investigations (2-4) that 40% to 50% of subjects diagnosed as suffering from DSM-IV major depressive disorder are subthreshold bipolars. These epidemiological findings are confirmed by the international BRIDGE study on 5,635 patients with major depressive episodes (5). This study also demonstrates that the DSM exclusion criterion of an antidepressant-induced switch to hypomania is misleading: in fact, patients in whom switches are observed differ greatly from other major depressives in terms of a positive family history of mania and of course characteristics distinguishing bipolar from unipolar depression. Moreover, recent reviews found no sound evidence that patients who switch to hypomania under treatment with placebo differ from those who switch under antidepressants (6,7).

Hasler also summarizes the evidence for important gender differences in the biological findings on depressive patients. The prevalence of major depressive disorder among women is about twice that among men, whereas in bipolar disorder there is only a slight female preponderance. The Zurich epidemiological data suggest that certain components or sub-

types of major depression, namely somatic items of DSM-IV atypical depression (8) and somatic depression (9), may explain those differences. Clearly, biological research should take such findings into account. In addition, there are marked gender differences in childhood adversity which can create biological and psychological vulnerability to stressors in adolescence and adulthood (10).

Hasler states that 60% to 70% of the variance in susceptibility to depression is non-genetic. This leaves promising space for epigenetic and environmental research, which should at the same time also consider gender differences. Findings from the prospective Zurich study confirmed childhood adversity as being associated in both women and men with an earlier onset of depression and bipolar disorder, but also with a more frequent chronicity of the disorders. The risk may be partially mediated by anxious personality traits, poor coping and low self-esteem. Sexual trauma in childhood/adolescence (mainly in females) and conduct problems (mainly in males) were not related to chronicity (10).

As Hasler points out, depression is currently considered to be one of the most important causes of disability worldwide. But, would that conclusion still hold true if subthreshold bipolar depressives were correctly diagnosed and identified as bipolars? The review of Pini et al (11) suggests that bipolar disorder carries an equally high if not higher burden compared to major depressive disorder. The above-mentioned epidemiological studies (3-5) have shown that, when bipolars are properly identified, there is a major shift of comorbidity from the depressive to the bipolar group; for instance, alcohol use disorders and some anxiety disorders become much more strongly associated with bipolarity than

with pure depression. The resulting reduced prevalence rates and comorbidity will probably show pure depression to be less of a burden than bipolar disorders, and the estimates of the World Health Organization (12) may need to be considerably revised.

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Biological psychiatry: still marching forward in a dead end

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Reviewing the data on the pathophysiology of depression, G. Hasler reaches the conclusion that “the current extant knowledge argues against a unified hypothesis of depression”. Indeed, it does; the reason being, I posit, that the construct is ill-defined. This holds for all types of depression presently recognized. Take, for instance, major depression. In terms of symptomatology, course, prognosis, biological findings, therapeutic response, the construct presents profound heterogeneity. The chance that such utterly heterogeneous psychopathological constructs will be produced by well-defined brain disturbances seems to me negligibly small.

What is true for depression is true for almost all DSM-defined disorders. Yet, biological psychiatry, from its rebirth in the fifties of the last century on, has been based on Kraepelinaean suppositions: the idea that mental pathology is subdividable in discrete disease entities, each with its own pathophysiology. This approach has not been productive. The pathophysiology of mental pathology is

still largely unknown. I feel, and have felt for most of my professional life, that the diagnostic process in psychiatry should change direction, in particular if the goal is to explore the biological underpinnings of mental pathology. The strategy proposed to direct that effort I called functionalization. This process implies that diagnosing in psychiatry should proceed stepwise (1-3).

First, the diagnostic grouping to which the disorder belongs should be determined; that is, a categorical diagnosis should be made. For instance, the mental state in question is considered to belong to the basin of depressive disorders. This first diagnostic step provides no more than a global diagnostic indication.

Next, the syndrome is defined. Also this diagnostic information is far from precise. Syndromes often appear in incomplete form and many patients suffer simultaneously from more than one complete or incomplete syndrome.

Hence, a third diagnostic step seems crucial to me, which I have called functionalization of diagnosis. Functionalization means defining, first of all, the psychopathological symptoms constituting the syndrome, and then – most importantly – examining and, if possible,

measuring the psychic dysfunctions underlying the psychopathological symptoms. Psychopathological symptoms and psychic dysfunctions are not synonyms. The psychopathological symptom is the consequence of psychic dysfunctions. It is the way the psychic dysfunction is experienced by the patient and observed by the investigator.

The last step I consider to be quintessential. If no methods are available to measure the assumed dysfunctions, they should be developed.

A few examples. In the case of dementia symptoms, the underlying cognitive disturbances should be tracked and measured. In the case of hallucinations, the same applies to the underlying perceptual disturbances. In the case of anhedonia, the defect in linking a particular perception with the corresponding emotion should be searched for.

Psychic dysfunctions underlying psychopathological symptoms should be, I propose, the focus of biological psychiatric research. It seems much more likely that brain dysfunctions correspond with disturbances in psychological regulatory systems than with largely man-designed categorical entities, or with symptom complexes rather arbitrarily designated as a syndrome.

The search for biological determinants of psychic dysfunctions has indeed been proven to be much more fruitful than the search for the biological cause of a par-

ticular nosological entity, such as depression or schizophrenia.

Our own research may serve as an example (3-5). We established serotonin disturbances in major depression. At least in some patients, not in others. In terms of categorical or syndromal classification, they were not distinguishable. They were, however, on a more basic level. We demonstrated that the serotonin disturbances were linked to particular components of the depressive syndrome, i.e. to disturbances in anxiety and aggression regulation. This relationship was not limited to depression but existed also in non-depressive syndromes. The serotonin disturbances appeared to be functionally specific, not nosologically or syndromally specific.

Functionalization will make psychiatric diagnosing more precise, more scientific, and more attuned to goal-directed biological studies and focused therapeutic interventions. More precise and more scientific, because psychic dysfunctions are much better measurable than disease categories and syndromes, often even quantitatively.

Second, this approach provides the diagnostician with a detailed chart of those psychic domains that function abnormally and those functioning within normal limits. Ultimately this approach will lead to what I have called a psychiatric physiology, a detailed chart of brain dysfunctions underlying abnormally functioning psychological regulatory systems.

Treatment, too, could benefit from this approach. Drug treatment as well as psychotherapy are currently pretty much unfocused. We prescribe drugs because someone is psychotic, depressed, anxious or otherwise out of balance. Any further specification is generally lacking or deemed to be unnecessary. This is not the way to further psychopharmacological research, nor the way to increase the chance of finding new, innovative, and psychopathologically more specific psychotropic drugs.

The same reasoning holds for psychological treatment. We may recommend psychotherapy. For what exactly is seldom clear. What will be its focus? What do we hope to achieve in terms of amelioration of symptoms? This is rarely

defined in any detail. Functionalization of diagnosis would make systematic detailing of therapeutic goals feasible.

The rigid nosological approach has had its time, particularly in biological psychiatry. It has to retreat in favour of a dynamic-functional disease concept. The largely man-made nosological entity should not be its focus, neither should the syndrome, so often capricious in its symptomatological composition, nor the psychopathological dimension, almost by definition ill-defined and hard to demarcate, but rather the psychic dysfunction underlying the psychopathological symptoms. This approach will lead, I assume, to accelerated scientification of psychiatric diagnoses and to a greater yield of biologic psychiatric research.

Major running on the spot

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G. Hasler's overview illustrates the strengths and limitations of recent research into the depressive disorders. Strengths include highly intelligent and assiduously committed researchers. Limitations emerge from the paradigms underpinning our current (DSM and ICD) mood disorder classificatory models. The resulting discordance evokes the old Bavarian proverb: "What's the use of running if you're on the wrong road".

I will argue that Hasler's composite review of pathophysiological studies is compromised by a diagnostic paradigm failure. As a consequence, after tasting a large number of appetizers, the reader will be left hungry in the absence of a digestible main course.

In reality, major depressive disorder is not an entity and thus not an "it" as described by Hasler, and as positioned and reified by most researchers who wish to have their work published. It is, in essence, a "domain" diagnosis that effectively homogenizes multiple heterogeneous expressions of "depression". It has no more precision, defined boundaries

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or entity status than, say, "major breathlessness", an analogy worth pursuing. A diagnosis of "major breathlessness" subsumes a number of acute (e.g., asthma, pneumonia, pulmonary embolus) and chronic (e.g., emphysema) conditions, and might risk including transient normative states (e.g., an unfit mountain climber). The DSM criteria for major depression are relatively few and each criterion is operationalized at a low order of inference, generating quite high prevalence estimates and blurring boundaries with "normal depression" (1). A domain diagnosis of "major depression" can be assumed to encapsulate more categorical conditions (e.g., psychotic and melancholic depression) as well as many non-melancholic disorders (e.g., acute and chronic reactive depressive states, depressions secondary to predisposing personality styles). Such constituent domain disorders may have quite different principal causes (e.g., primary biological underpinnings for melancholia; primary social and psychological causes for reactive and personality-based depressions respectively). Such heterogeneity across the domain diagnosis will obscure identification of disorder-specific causal factors and compromise attempts to iden-

tify any treatment specificity.

Any attempt to study causes of “major depression” should also respect the reality (as for studies investigating “major breathlessness”) that findings will be highly dependent on the prevalence of constituent disorders within the “domain diagnosis”. Thus, if studies of those with “major breathlessness” were dominated by, say, patients with asthma, then the capacity to identify asthma’s causes within a sample dominated by those with respiratory infection would be compromised. As differing depressive disorders will be variably represented across differing samples with quite varying distributions of constituent depressive conditions (e.g., inpatients, psychiatric outpatients, primary practice, community groups), sample selection alone will also influence findings.

In essence, if a diagnosis is essentially “non-specific”, identification of its causes and treatments will be compromised by that non-specificity, and generate non-specific findings. It would be possible to proceed through Hasler’s paper demonstrating non-specific findings in relation to each evidence point but, as this would narrow the focus, one illustration is offered.

In the third paragraph – imputing genetic influences – Hasler states that “major depressive disorder is a familial disorder and that this familiarity is mostly or entirely due to genetic factors”, referencing a meta-analysis by Sullivan et al (2). Perhaps as a corollary, Hasler states that such findings indicate that parental behaviors and other environmental risk factors are not as important “as previously assumed” and should not be the focus of treatment. However, when the meta-analysis by Sullivan et al is examined, their conclusions were that “environmental influences specific to an individual are also etiologically significant”. These two interpretations are somewhat contradictory. Shortly after, Hasler switches emphasis to note a dominance of non-genetic factors, which “suggest that there is a huge potential” for psychosocial interventions to prevent major depression. In two paragraphs, Hasler variably argues for the dominance of genetic factors and then for non-genetic factors. Later, across three

consecutive paragraphs, he suggests that environmental factors should not be the main focus of treatment before suggesting that psychosocial interventions focusing on interpersonal difficulties and skills offer “huge potential”.

The subtitle of Hasler’s paper indicates that it is designed to assist clinicians. Again, this objective can be challenged with one illustration. At the end of the “Genes and psychosocial stress” section, Hasler states that “The clinician should be aware that family history will continue to be the most solid source of information to estimate the genetic risk of major depressive disorder”. But what does “family history” mean in this context? Does it mean “major depression” or some other psychiatric condition in a family member? Or does it mean a family member being hospitalized for a psychiatric condition, attempting or committing suicide, or receiving treatment by a psychiatrist (all difficult to establish and all likely to have quite varying signal propensities)? Or does it mean less substantive condi-

tions (e.g., being “nervy and a worrier”) in a family member. The non-specificity of this “solid source” recommendation challenges the paper’s clinical utility.

Having posed the question (i.e., is there a solid neurobiological base to “depression”?), Hasler effectively votes against the proposition to conclude that “depression is a clinically and etiologically heterogeneous disorder”. Indeed.

Should we therefore continue to pursue research into this non-specific domain diagnosis and risk further non-specific findings? Not, in my view, if we wish to stop running on the spot.

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A yes or no answer

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Medical students are chosen, at least largely, for academic and scholarly potential, and most physicians enjoy reading and keeping up in the literature of their field. However, since medicine is a practical art, physicians read with the goal of updating their knowledge to maximize their treatment of their patients.

The literature on biological pathophysiology of depression has expanded exponentially over the last 30 years, and physicians who completed their training in the 1970s, 1980s and 1990s have been faced with a huge amount of literature promising insights into depression, one of their most common areas of professional activity (1). Sophisticated molecular genetics, revolutionary imaging technology, erudite neuroendocrine analyses and numerous other approaches have

strained the ability of many clinicians to feel that they are up-to-date in their field. In the last few years, a creeping feeling of doubt has entered the hearts and minds of numerous clinicians around the world as to whether the mountain of new data is really of any value to the clinical practitioner of psychiatry. The title of G. Hasler’s paper, therefore, is guaranteed to attract a huge audience, as is appropriate for *World Psychiatry*.

However, in my opinion, this paper does not bite the bullet and avoids giving an answer to its own question. The abstract states that antidepressant treatments should be tailored for individual patients and disease states, but nowhere in the paper does the author say how to do this. The conclusion relates to a table where the various neurobiological hypotheses are presented and an argument made against a unified hypothesis of depression. Fair enough. The paper goes on to state that “this encourages research

on predictors of response” and that “the identification of reliable predictors will allow for the development of personalized medicine”. Promises, promises, promises. I had hoped this article was going to tell me whether we have any solid evidence of interest to clinicians *now*. Personally, I think the answer is no and that we must bravely face this fact.

I share Hasler’s belief that depression is heterogeneous and his hope that future research will allow for better treatments. However, clinicians will be more honest with themselves, their patients and our society if we answer this paper’s question with a clear “no”. There is no genetic test, blood test, spinal fluid test or imaging test today that can aid in the diagnosis of depression. There are many findings reported in groups of depressed patients of changes in spinal fluid or blood metabolites or proteins or in brain functional imaging. However, few if any

are consistently replicable. Many could be secondary to the powerful lifestyle changes induced by depression, such as weight loss, inactivity, and poor sleep (2). Even more important for a clinician to understand is that a mean difference reported as a finding in a research paper, even when highly statistically significant, often conceals a large overlap between patient and control populations that makes diagnostic use of the finding impossible.

I have sometimes been told by those who agree with the previous statement that my views should be hidden from the public, so as not to endanger the prestige of psychiatry or our rightful share of research funding. Such an opinion, of course, has more to do with ethics and values than with science. However, the psychoanalytic tradition that the truth makes one free has always seemed to me even more relevant in biological psy-

chiatry. Our trainees, patients and public are increasingly confused by contradictory claims to have found the biological basis of depression in genetics, imaging, neuroendocrinology, or neurotrophic factors.

We must create a new style of discourse where research results, exciting as they are, are translated into a proper understanding of the long slow road we are likely to travel in order to understand depression pathophysiology (3).

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Clinical pleomorphism of major depression as a challenge to the study of its pathophysiology

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There are many studies showing that, as a group, major depressive disorder is associated with abnormalities in neurotransmitter systems such as serotonin, norepinephrine, dopamine, GABA and glutamate, as well as in neurotrophic factors which are in turn affected by hyper-responsive stress response systems such as the hypothalamic-pituitary-adrenal axis and altered cytokine function. Finally, there are alterations in circadian rhythms and sleep architecture which may be the consequence of these abnormalities or contribute to the risk or alter the course of major depression.

It has long been puzzling how to reconcile research approaches looking at a single biologic explanatory model with the heterogeneity of the clinical picture of major depression. It would seem that this pleomorphic picture must be reflect-

ed by an equal variety in the pathophysiology. An examination of the DSM-IV criteria for a major depressive episode indicates there are over 1000 combinations of features that allow one to make that diagnosis. Furthermore, researchers point to the interindividual variability in score profile across the items of scales like the Hamilton Depression Rating Scale (HDRS). But this view only tells part of the story. We reported that there was no quantitative relationship within patients between episodes of major depression (1). This was true whether one examined the overall severity of successive episodes (as in the HDRS total score), or factors derived from a factor analysis looking at relatively independent domains of psychopathology, or even when one examined individual item scores. The key point here is that clinical presentation seems to vary about as much within patients in successive episodes, as between patients.

The implications of this phenomenon

were recognized by Eugen Bleuler in his landmark book on schizophrenia (2). He linked catatonia, paranoid schizophrenia, hebephrenia and what he called a defect state because he observed all of these in different combinations appearing in the same patient over time. In other words, even though these clinical pictures looked very different, they seemed to be part of a single illness since they were manifested by the same patient. If we consider that illnesses such as major depressive disorder or schizophrenia result from genetic causes and reported childhood adversity, including famine and physical or sexual abuse, and these environmental effects occur early in life, then the biological predisposition to illness should be largely set in an individual by early adolescence. If we presume that this biological substrate is fairly stable, then it is difficult to explain why there is such a variation in clinical picture within individuals. One possibility is that each episode alters the brain biology due to

some sort of scaring or sensitization. Epigenetic effects may be a mechanism for enduring changes. But then one would predict a similar set of steps in terms of the evolution of the illness over time (as seen in schizophrenia with the evolution towards more negative symptoms and fewer positive symptoms). In major depression, the changes in clinical picture do not seem to follow a simple pattern, except perhaps for a longer duration of episodes.

Brain imaging studies offer some clue in this respect and raise further questions. We have reported that the severity of different clinical domains of major depression, as defined by factors derived from either the HDRS or the Beck Depression Inventory (BDI), correlate with relative resting regional brain glucose uptake as measured by [¹⁸F]-FDG positron emission tomography (PET) (3). The degree to which these factor scores are correlated with each other is highly related to the degree to which the brain regions overlap for different factors. Each factor is related to a partly independent

brain region (3). Clinical heterogeneity is reflected in a corresponding variety in relative resting regional brain activity in major depression. Not surprisingly, successful treatment with antidepressants or psychotherapy can alter this pattern towards that seen in healthy volunteers, and induced sadness in healthy volunteers can reproduce some of the changes seen in major depression (4).

This provides a biological basis for variation in clinical picture, but not a causal explanation or mechanism. There are more stable biologic abnormalities that are present during episodes of major depression and between episodes. The best example is the abnormality in the serotonin system, which has been shown in terms of return of depression during remission after acute tryptophan depletion from the brain, the blunted prolactin response to the indirect serotonin releasing drug fenfluramine during an episode and between episodes, and the higher 5-HT_{1A} receptor binding on PET imaging in depressed and remitted drug-free patients.

To further study the clinical and biological heterogeneity between patients, one would recommend a focus on regional brain variation as revealed by the PET FDG studies and then seeking a cause for that variation in terms of serotonin, neorepinephrine and dopamine inputs and GABA and glutamatergic target neuron function.

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Reducing the treatment gap for mental disorders: a WPA survey

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The treatment gap for people with mental disorders exceeds 50% in all countries of the world, approaching astonishingly high rates of 90% in the least resourced countries. We report the findings of the first systematic survey of leaders of psychiatry in nearly 60 countries on the strategies for reducing the treatment gap. We sought to elicit the views of these representatives on the roles of different human resources and health care settings in delivering care and on the importance of a range of strategies to increase the coverage of evidence-based treatments for priority mental disorders for each demographic stage (childhood, adolescence, adulthood and old age). Our findings clearly indicate three strategies for reducing the treatment gap: increasing the numbers of psychiatrists and other mental health professionals; increasing the involvement of a range of appropriately trained non-specialist providers; and the active involvement of people affected by mental disorders. This is true for both high income and low/middle income countries, though relatively of more importance in the latter. We view this survey as a critically important first step in ascertaining the position of psychiatrists, one of the most influential stakeholder communities in global mental health, in addressing the global challenge of scaling up mental health services to reduce the treatment gap.

Key words: Mental disorders, treatment gap, mental health services, primary care, human resources, coverage of care, evidence-based treatments
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The treatment gap for people with mental disorders exceeds 50% in all countries of the world, approaching astonishingly high rates of 90% in the least resourced countries, even for serious mental disorders associated with significant role impairments (1-3). A number of recent initiatives have called for action to scale up services for people with mental disorders based on evidence of effective interventions and respect for human rights (4,5). Evidence on effective treatments has been synthesized in the forthcoming Mental Health Gap Action Programme (mhGAP) guidelines of the World Health Organization (WHO) for eight mental, neurological and substance use disorders (6). Evidence on delivery mechanisms for such treatments has been summarized in a recent series of articles in *PLoS Medicine* (7). A major question is how these treatments and delivery mechanisms can be scaled up in the context of limited resources in all countries.

One of the goals of the WPA Action Plan 2008-2011 is to partner with Member Societies in their effort to increase the coverage of care for mental disorders across the life course (8,9). The survey reported in this paper aimed to explore the opinions of WPA Zonal Representatives and Member Societies regarding strategies to increase coverage of services, focusing on areas where mental health specialists are scarce. More specifically, we sought to elicit views on the role of different human resources and health care settings and of specific strategies to increase the coverage of evidence-based treatments for priority mental disorders in each demographic stage (childhood, adolescence, adulthood and old age). Since human and financial resource constraints differ between high income (HIC) and low and middle income

(LMIC) countries, we aimed to define and compare strategies for these two contexts.

METHODS

The study consisted of two consecutive surveys with two groups of respondents. The first survey was a scoping exercise to identify priority mental disorders and their specific treatments for each of the four demographic stages. All 18 WPA Zonal Representatives were invited to participate in this round. The second survey was carried out with WPA Member Societies and focused on improving the coverage of treatments and the overall outcomes of the priority disorders identified in the first round. In order to maximize country level responses, all Member Societies in a country were asked to participate. In the event that more than one Member Society from the same country responded, the response from the most nationally representative Society was included in the analyses.

Round 1 respondents were asked to identify priority conditions based on their assessment of the burden (prevalence and impact) in their region. Next, they were asked to list the acceptable and affordable evidence-based treatments for these disorders given current resources. Respondents were then asked about the roles of various health care providers and treatment settings (such as primary care) in the delivery of mental health care. Lastly, three open-ended questions were asked to elicit strategies for improving access to mental health care, help-seeking behaviour, and adherence with long term care. Eight disorders were identified as priorities in

this round (hyperkinetic disorder and anxiety disorder for children; depression and substance abuse for adolescents; schizophrenia and depression for adults; depression and dementia for older people). As we considered the overlap between depressive disorder in adults and older people to be large, we merged these two disorder groups for Round 2.

The response categories used for Round 2 were derived from Round 1. Respondents were asked to focus on the most acceptable and cost-effective way to increase coverage of care particularly for the underserved in their country. For each priority condition, respondents rated human resources and settings of care according to their importance for improving the coverage of the priority treatments with respect to diagnosis, medication management and psychosocial interventions. Human resources were: psychiatrists; other mental health specialists; other medical workers (e.g., primary care doctors); non-medical health workers; and service users or families. For dementia in older people, we also inquired about the role of other specialists (geriatricians and neurologists). Settings of care were: psychiatric inpatient and outpatient units; community mental health units; primary care and/or general medical units; HIV/AIDS units for younger age groups; schools (for children and adolescents); and home-based care. Next, respondents were asked to rate the importance of six strategies (increasing psychiatric/specialist human resources; increasing other health human resources; public education campaigns; increasing availability of treatments; increasing diversity of settings of care; and increasing service user/family involvement) for improving four key outcomes for each disorder: access to care; help-seeking; adherence; and effectiveness. One final open-ended question asked respondents to provide examples of any other strategies to increase coverage for each disorder.

Respondents were invited to complete an online questionnaire in a personal email from the WPA President, who subsequently followed up the non-responders. Questionnaires for both rounds were divided into four sections: children, adolescents, adults, and older people. Respondents were asked to answer the same set of questions for each demographic stage in order to build up a picture of the continuum of care for mental disorders across the life course.

For Round 1, we conducted a thematic descriptive analysis, defining the priority disorders and treatments identified for each demographic stage. A qualitative analysis of the open-ended questions was used to identify important strategies for improving outcomes for people with mental disorders. The results from Round 1, including additional data on the types of health workers and settings of care most relevant for specific demographic stages, were used to inform the content of the questionnaire for Round 2.

For Round 2, a thematic descriptive analysis of data was done for each demographic stage, focusing on service delivery of interventions and improving outcomes for the priority disorders identified in Round 1. The ratings in Round 2 were based on a four-point scale ranging from "not at all" to "extremely" important. In presenting the results, we used an al-

gorithm to rank categories rated "extremely important" by at least 75% of respondents or "extremely or moderately important" by at least 90% of respondents as "most important"; categories rated "extremely important" by 50-74% respondents or "extremely or moderately important" by 75-89% of respondents as "very important"; and categories rated "extremely or moderately important" by 60-74% of respondents as "important". Qualitative responses to the final open-ended questions for each disorder were analysed thematically. Responses which duplicated the closed rating categories, for example on improving availability of specific treatments, were excluded. Analyses were stratified by resource level.

Countries were classified using the World Bank Atlas method according to 2004 gross national income (GNI) per capita as either high (GNI of \$10,066 or more) or middle/low income (GNI of \$10,065 or less). We conducted sensitivity analyses using level of mental health professionals derived from the WHO Atlas (10) (number of psychiatrists, psychiatric nurses and psychologists per 100,000 inhabitants) to assess the validity of this classification of countries for the purposes of our study. A good correspondence was found between the World Bank classification and the WHO Atlas figures, apart from a few exceptions such as Spain (a high income country with only 9.7 mental health professionals per 100,000 inhabitants) and Argentina (a middle income country with 122.6 mental health professionals per 100,000 inhabitants).

RESULTS

All 18 WPA Zonal Representatives and Member Societies representing 60 countries agreed to participate in the survey. In Round 1, all 18 WPA Zonal Representatives returned questionnaires (100% response rate). In Round 2, Member Societies representing 57 countries returned questionnaires (95% response rate). Eighteen countries were classified as HIC, and 39 as LMIC.

Priority disorders and treatments

Table 1 shows the mental disorders currently considered the main focus of attention for health services and those regarded by the respondents as needing greater attention, while Table 2 presents the treatments which are currently considered by respondents to be the most common for priority disorders and those which, in their view, should be used more often.

For children, conduct disorders and hyperkinetic disorder were identified as priority disorders in both HIC and LMIC contexts, with anxiety disorders a further priority in HICs and mental retardation the main priority in LMICs. In both contexts, hyperkinetic disorder was thought to need greater attention, together with childhood autism and other pervasive developmental disorders in HICs and anxiety disorders in LMICs. Stimulant medication and psychosocial interventions with caregivers were the most common treatments for

Table 1 Mental disorders currently representing a major focus for health services and those regarded as needing greater attention (in order of importance)

Children		Adolescents		Adults		Older people	
Current priority mental disorders							
HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC
- Conduct disorder	- Mental retardation	- Depression	- Schizophrenia	- Schizophrenia	- Schizophrenia	- Dementia	- Dementia
- Hyperkinetic disorder	- Hyperkinetic disorder	- Anxiety disorders	- Substance abuse	- Depression	- Depression	- Depression	- Depression
- Anxiety disorders	- Conduct disorder	- Schizophrenia	- Depression	- Bipolar disorder	- Anxiety disorders		
Disorders needing greater attention							
HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC
- Pervasive developmental disorders	- Hyperkinetic disorder	- Substance abuse	- Depression	- Personality disorders	- Depression	- Depression	- Depression
- Hyperkinetic disorder	- Anxiety disorders		- Substance abuse	- Substance abuse	- Anxiety disorders	- Dementia	- Dementia
	- Depression		- Anxiety disorders		- Bipolar disorder		

HIC – high-income countries; LMIC – low- and middle-income countries

Table 2 Interventions for the seven priority mental disorders (in order of importance)

Children		Adolescents		Adults	Adults and older people	Older people
Hyperkinetic disorder	Anxiety disorders	Depression	Substance abuse	Schizophrenia	Depression	Dementia
<i>Commonly used interventions</i>						
<i>HIC:</i> stimulant medication; psychoeducation with caregivers; atomoxetine; educational intervention	<i>HIC:</i> SSRIs; CBT; psychoeducation with caregivers <i>LMIC:</i> SSRIs; psychoeducation with caregivers; CBT	<i>HIC:</i> SSRIs; CBT <i>LMIC:</i> SSRIs; CBT	<i>HIC:</i> group psychotherapies; substitution medications; motivational interviewing <i>LMIC:</i> anxiolytics; motivational interviewing; group psychotherapies	<i>HIC:</i> atypical antipsychotics; social skills training; occupational skills training; family intervention strategies <i>LMIC:</i> typical antipsychotics; atypical antipsychotics; family intervention strategies	<i>HIC:</i> SSRIs; SNRIs; CBT <i>LMIC:</i> SSRIs; tricyclic antidepressants; SNRIs	<i>HIC:</i> anticholinesterase drugs; NMDA receptor agonist; risperidone <i>LMIC:</i> haloperidol; risperidone; anticholinesterase drugs
<i>LMIC:</i> stimulant medication; psychoeducation with caregivers						
<i>Interventions to be used more frequently</i>						
<i>HIC:</i> psychoeducation with caregivers; CBT; social skills training <i>LMIC:</i> psychoeducation with caregivers; stimulant medication; social skills training; educational interventions	<i>HIC:</i> CBT; group psychotherapies; psychoeducation with caregivers <i>LMIC:</i> CBT; psychoeducation with caregivers; group psychotherapies	<i>HIC:</i> CBT; interpersonal therapy; family psychotherapies <i>LMIC:</i> family psychotherapies; CBT; interpersonal therapy	<i>HIC:</i> CBT; interpersonal therapy; family psychotherapies <i>LMIC:</i> CBT; family psychotherapies; group psychotherapies	<i>HIC:</i> CBT; family intervention strategies; occupational skills training; neuro-cognitive therapy <i>LMIC:</i> social skills training; occupational skills training; family intervention strategies	<i>HIC:</i> CBT; interpersonal therapy; ECT <i>LMIC:</i> CBT; interpersonal therapy; SNRIs	<i>HIC:</i> psychoeducation with caregivers; caregiver respite (daycare); caregiver respite (homecare) <i>LMIC:</i> psychoeducation with caregivers; caregiver respite (daycare); caregiver respite (homecare)

HIC – high-income countries; LMIC – low- and middle-income countries; SSRIs – selective serotonin reuptake inhibitors; CBT – cognitive behaviour therapy; SNRIs – serotonin and norepinephrine reuptake inhibitors; ECT – electroconvulsive therapy

hyperkinetic disorder in both contexts. Psychosocial interventions and social skills training for the child were identified as treatments that should be used more often for hyperkinetic disorder in both contexts. For anxiety disorders, there was agreement between HIC and LMIC in terms of what treatments were most common (selective serotonin reuptake inhibitors, SSRIs; cognitive behaviour therapy, CBT; and psychoeducational interventions with caregivers) and what treatments should be used more often (CBT, group psychotherapies, and psychoeducational interventions with caregivers).

For adolescents, depression and schizophrenia/other psychoses were ranked as the priority disorders in both contexts, with anxiety and substance use disorders regarded as additional priorities in HIC and LMIC respectively. Substance use disorders and depression/anxiety disorders were identified as requiring much greater attention in both contexts. Medications were the most common forms of treatment for both disorders: SSRIs dominated for depression, while substitution treatment and benzodiazepines were the most common treatments for substance use disorders in HIC and LMIC respectively. Although psychological treatments were reported to be frequently used in both contexts, they were also rated as treatments which need to be used more often.

For adults, nearly all respondents reported schizophrenia/other psychoses and depression as the priority disorders in both contexts, followed by bipolar disorder in HIC and anxiety disorders in LMIC. Greater attention was thought to be needed on depression, anxiety disorders and bipolar disorder in LMIC, and personality disorders and substance use disorders in HIC. Atypical antipsychotics dominated the treatment of schizophrenia in HIC, whereas typical antipsychotics remain by far the most frequently used treatment in LMIC. All other evidence-based treatments are much less frequently implemented, with only family intervention strategies being in relatively common use. There was a consistent feedback from respondents that psychosocial interventions should be more frequently used for people with schizophrenia, with psychiatrists from HIC emphasizing CBT, and those from LMIC focusing on social and occupational skills training. SSRIs were reported by all respondents to be the most common treatment for depression in both contexts, with tricyclic antidepressants still commonly prescribed in LMIC. Respondents from both HIC and LMIC almost unanimously felt that psychological therapies, in particular CBT, deserve to be more frequently implemented in people with depression.

For older people, almost all respondents considered dementia and depression to be the priority disorders, and also the two conditions that merited more attention. Medications were by far the most currently used interventions in both contexts, though the drug type differed between contexts (antidementia drugs and atypical antipsychotics in HIC, and haloperidol in LMIC). Psychosocial interventions for carers and respite care were considered to be commonly used by around a half of HIC respondents, but by only a small minority of LMIC respondents. In the opinion of respondents from both contexts, non-pharmacological interventions are significantly

underused, particularly psychosocial interventions for carers and non-institutional respite care. Around a half of LMIC respondents also felt that antidementia drugs were underused in their countries, and around a third that the atypical antipsychotic risperidone was underused in the treatment of severe behavioural and psychological symptoms of dementia.

Increasing the coverage of care

Tables 3 and 4 summarize, respectively, the responses concerning the perceived importance of different human resources and of different health care settings in increasing the coverage of treatments for the seven priority mental disorders across the life course. Table 5 summarizes the responses concerning strategies to improve outcomes for each of these disorders.

Psychiatrists were ranked as being an extremely or very important resource for all clinical roles for all mental disorders across the age groups in both contexts. Other mental health specialists were regarded as an extremely or very important resource for psychosocial interventions for all mental disorders and for diagnosis (particularly of child and adolescent disorders) in both contexts; they were not, however, considered to have an important role to play in medication prescription or review. Other medical workers (such as primary care doctors) were regarded as being important or very important for diagnosis and medication in child and adolescent mental disorders and adult depression in both contexts, and in schizophrenia and dementia in LMIC. Other medical specialists, such as geriatricians and neurologists, were considered to be extremely important for diagnosis and very important for medication in dementia in both HIC and LMIC. Non-medical health workers were considered to be important for psychosocial interventions in all mental disorders in both contexts. Service users and family members were reported to be important or very important for psychosocial interventions in all mental disorders in both contexts and for diagnosis and medication provision in substance abuse and depression in LMIC.

Psychiatric inpatient or outpatient units and community mental health units were reported to be extremely or very important for all roles in all mental disorders in both contexts, in particular for diagnosis and medication initiation/review. General medical units were considered to be important or very important for all roles in substance use disorders in both contexts, and in depression in LMIC, and for diagnosis and medication of childhood disorders in LMIC. Primary care units were rated as important or very important, in particular for diagnosis and medication management of all mental disorders, with the exception of hyperkinetic disorder and schizophrenia in HIC. In both contexts, schools and other community settings were rated as important to extremely important for diagnosis and psychosocial interventions in child and adolescent mental disorders, as were other community settings for psychosocial interventions in dementia. Home-based care was reported to be important or very important

Table 3 Importance of human resources for increasing coverage of care for priority disorders according to respondents

Human resource	Roles	Children				Adolescents				Adults		Adults and older people		Older people	
		Hyperkinetic disorder		Anxiety disorders		Depression		Substance abuse		Schizophrenia		Depression		Dementia	
		HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC
Psychiatrist	Diagnosis	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
	Medication	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
	Psychosocial	√√	√√	√√√	√√	√√√	√√	√√√	√√	√√√	√√√	√√√	√√	√√	√√
Other mental health specialist	Diagnosis	√√√	√√√	√√√	√√√	√√√	√√	√√	√√√	√	√√	-	√√	-	√√
	Medication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Psychosocial	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√	√√√	√√√	√√√	√√√	√√
Primary care doctor	Diagnosis	√	√√	√√	√√	√√	√√	√√	√√√	-	√√	√√√	√√√	√√√	√√√
	Medication	√	√	√	√√	√√	√√	√√	√√	-	√	√√	√√	√√	√√
	Psychosocial	-	-	√	√	√	√	√	√√	-	√	√	√	-	√
Non-medical health worker	Diagnosis	-	-	-	-	-	-	-	√	-	-	-	-	-	-
	Medication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Psychosocial	-	√	√	√√	√√	√√	√√	√√	√√	√√	√	√√√	√√	√√
Service users/family members	Diagnosis	-	-	-	√	-	√	√√	√√	-	√	-	√√	√	√
	Medication	-	-	-	-	-	√	-	√	-	√	-	√	-	-
	Psychosocial	√	√√	√√	√√	√√	√√	√√	√√	√√√	√√	√√	√√	√√	√√

HIC – high-income countries; LMIC – low- and middle-income countries; √√√ – extremely important; √√ – very important; √ – important

Table 4 Importance of health care settings in increasing coverage of care for priority disorders according to respondents

Setting	Roles	Children				Adolescents				Adults		Adults and older people		Older people	
		Hyperkinetic disorder		Anxiety disorders		Depression		Substance abuse		Schizophrenia		Depression		Dementia	
		HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC
Psychiatric units	Diagnosis	√√√	√√	√√√	√√	√√√	√√√	√√√	√√	√√√	√√√	√√√	√√√	√√√	√√√
	Medication	√√√	√√	√√√	√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
	Psychosocial	√√	√√	√√√	√√	√√√	√√	√	√√	√√√	√√	√√√	√√	√√	√√
Community mental health units	Diagnosis	√√	√√√	√√√	√√	√√√	√√	√√√	√√√	√√	√√√	√√√	√√	√√	√√
	Medication	√√	√√	√√	√√	√√	√√	√√	√√	√√	√√	√√√	√√	√√	√√
	Psychosocial	√√	√√√	√√√	√√√	√√√	√√	√√√	√√√	√√√	√√√	√√√	√√√	√√	√√√
General medical units	Diagnosis	√	√√	√	√√	√	√√	√√	√√√	-	√	√	√	√√√	√√√
	Medication	-	√√	-	√√	-	√√	√√	√√	-	√	√	√	√√√	√√√
	Psychosocial	-	√	√	√	√	√√	√√	√√	-	√	√	√√	√√	√√
Primary care units	Diagnosis	-	√√	√	√√	√	√	√√	√√	-	√√	√√√	√√√	√√	√√
	Medication	√	√	√√	√	√	√	√√	√√	-	√√	√√√	√√	√√	√√
	Psychosocial	-	√	-	√	√	√	√	√	-	√	√	√	√	√
Schools/other community settings	Diagnosis	√	√√	√	√	-	√	-	√√	-	-	-	-	-	-
	Medication	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Psychosocial	√√	√√√	√√	√√	√	√√√	√√	√√	-	-	-	√	√√	√√
Home based care	Diagnosis	√	√	√	√√	-	√	-	√	-	√	-	√	-	√√
	Medication	-	-	-	√	-	-	-	√	√	√	-	-	-	√
	Psychosocial	-	√√	√	√√	√	√√	-	√√	√√√	√√	√	√√	√√	√√

HIC – high-income countries; LMIC – low- and middle-income countries; √√√ – extremely important; √√ – very important; √ – important

for psychosocial interventions in all mental disorders in both contexts and, in LMIC, for diagnosis of child mental disorders and diagnosis and medication management of dementia. In general, all treatment settings were considered to be important for increasing the coverage of psychosocial treatments, with community mental health units most frequently rated as extremely important for this.

Across all four outcomes (improved access to health ser-

vices, improved help-seeking, improved adherence and improved effectiveness of treatment), four strategies were regarded as extremely or very important for all disorders and both contexts: increasing psychiatric human resources; increasing appropriately trained non-psychiatric human resources; increased availability of treatments; and increased user and carer involvement. Public education campaigns were also rated as extremely or very important for all mental

Table 5 Importance of strategies for improving outcomes according to respondents

	Children				Adolescents				Adults		Adults and older people		Older people	
	Hyperkinetic disorder		Anxiety disorders		Depression		Substance abuse		Schizophrenia		Depression		Dementia	
	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC	HIC	LMIC
<i>Improved access to health services</i>														
Increase psychiatric HR	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
Increase trained non-psychiatric HR	√√√	√√√	√√	√√√	√√	√√	√√√	√√√	√√	√√√	√√√	√√√	√√√	√√√
Public education campaigns	√√√	√√√	√√	√√√	√√	√√√	√√√	√√√	√√	√√√	√√√	√√√	√√	√√
Increase availability of range of treatments	√√	√√	√√	√√	√√	√√	√√	√√√	√√	√√	√√	√√	√√√	√√
Increase delivery in non-psychiatric settings	√	√√	√	√√	√√	√√	√√	√√	-	√√	√√	√√	√√	√√√
Increase family/user involvement	√√√	√√	√√	√√√	√√√	√√	√√√	√√√	√√√	√√	√√√	√√	√√√	√√√
<i>Improved help-seeking with health services</i>														
Increase psychiatric HR	√√	√√	√√√	√√√	√√√	√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
Increase trained non-psychiatric HR	√√	√√√	√√	√√√	√√	√√√	√√√	√√√	√√	√√√	√√√	√√	√√√	√√
Public education campaigns	√√	√√√	√√	√√√	√√	√√√	√√	√√√	√√	√√	√√√	√√	√√	√√√
Increase availability of range of treatments	√√	√√	√√	√√	√√	√√	√√	√√	√√	√√√	√√	√√	√√√	√√
Increase delivery in non-psychiatric settings	√	√√	√	√√	√√	√√	√√	√√	√	√√	√√	√√	√√	√√√
Increase family/user involvement	√√√	√√	√√	√√√	√√	√√	√√√	√√√	√√√	√√√	√√√	√√	√√√	√√√
<i>Improved adherence with treatment</i>														
Increase psychiatric HR	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√	√√√
Increase trained non-psychiatric HR	√√√	√√	√√√	√√	√√	√√	√√√	√√√	√√√	√√	√√√	√√	√√	√√
Public education campaigns	√√	√√	√√	√√	√√	√√	√√	√√	√√	√√	√	√√	√√	√√
Increase availability of range of treatments	√√√	√√√	√√	√√√	√√	√√√	√√	√√√	√√	√√	√√√	√√	√√√	√√
Increase delivery in non-psychiatric settings	-	√√	√	√	√√	√	-	√√	√	√	√	√	√√	√√
Increase family/user involvement	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
<i>Improved effectiveness of treatment</i>														
Increase psychiatric HR	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√	√√√
Increase trained non-psychiatric HR	√√√	√√	√√	√√	√√	√√	√√√	√√	√√	√√	√√√	√√	√√√	√√
Public education campaigns	√	√√	-	√	√	√	√	√	-	√	√	√	√	√
Increase availability of range of treatments	√√√	√√√	√√	√√	√√	√√√	√√	√√√	√√	√√	√√	√√	√√√	√√
Increase delivery in non-psychiatric settings	√	√	√	√	√	√√	√	√	√	√	√	√	√√	√√
Increase family/user involvement	√√	√√	√√	√√	√√	√√	√√√	√√	√√	√√	√√√	√√	√√√	√√

HIC – high-income countries; LMIC – low- and middle-income countries; HR – human resources
 √√√ – extremely important; √√ – very important; √ – important

disorders in both contexts for improving access, help-seeking and adherence. Increased delivery in non-psychiatric settings was reported as extremely or very important for improving all outcomes for dementia; for improving access for all conditions other than childhood disorders and schizophrenia in HIC; and for improving help-seeking for all conditions other than childhood disorders in HIC.

A total of 135 responses were obtained for the open-ended final question on other strategies for improving outcomes. Many of the strategies proposed were related to those already covered in the main questionnaire (for example, increasing the availability of specific treatments) and are not reported again. Additional strategies focused on building awareness among professional and user communities about mental disorders; provision of services other than those included in the main questionnaire (such as half-way homes for people with schizophrenia and special education for children with mental disorders); expanding the scope of providers (e.g., through traditional or religious healers); strategies to combat stigma associated with mental disorders across the life course; early detection and intervention strategies; and policy initiatives such as for alcohol abuse and older people.

DISCUSSION

We report the findings of the first systematic survey of leaders of psychiatry in nearly 60 countries on the strategies for reducing the treatment gap for seven mental disorders across the life course. This survey was carried out in the context of the severe shortage and inequity in the distribution of mental health resources in almost all countries, and the recent global initiatives leading to the recommendation of specific treatments for mental disorders.

Four broad themes emerge from our findings across both HIC and LMIC contexts. First, the need to increase specialist mental health human resources, both psychiatrists and allied clinical mental health professionals. Second, a need to increase access through primary care by increasing the involvement of non-specialist health workers, including medical and nursing professionals and non-medical health workers. These themes are consonant with the evidence base that, while task-shifting to non-specialist health workers is a cost-effective way of improving outcomes in people with mental disorders, especially in LMIC, continuing supervision and support from mental health professionals is required (11).

Thus, reducing the treatment gap will require more, and more widely distributed mental health professionals to lead the design, implementation and evaluation of community-based mental health care programs. The third theme was the demand for greater access to psychosocial interventions for all mental disorders. Evidence-based care programs need to emphasize psychological treatments such as CBT and interpersonal therapy and social interventions such as carer respite alongside pharmacological treatments. The fourth theme was the need for an increased involvement of service users and family members in mental health care, particularly in LMIC. Service users and family members need to be empowered as active participants in service planning and delivery, as opposed to mere passive recipients of care. While there were more similarities between HIC and LMIC respondents than might have been expected, there were also notable differences, reflecting the discrepancies in available resources. Thus, typical antipsychotics were more widely used than atypicals in LMIC, as expected given the limited availability of newer and more expensive therapies. Also, in LMIC, other mental health specialists and non-specialists were accorded a relatively greater role in increasing the coverage of diagnosis and treatment for most mental disorders.

Our study has some obvious limitations. The most important one is the small coverage of countries in some areas, such as Africa, where only few national psychiatric societies exist. Secondly, respondents were all psychiatrists, which may explain the high salience attributed to psychiatric treatment settings in increasing the coverage of mental health care. What was noteworthy, however, was the equally emphatic readiness to acknowledge the crucial role of users of mental health services and their families, and the important role of non-specialist providers (primary care doctors, non-medical health workers) in diagnosis, medication management and psychosocial support. To the extent to which these professional leaders represent or influence the opinions of their members, this suggests that task shifting and collaborative care is considered both practicable and desirable. This is an important finding in the context of observations that psychiatrists can, on occasions, represent an obstacle to reform in this direction (12). On the other hand, this is the first systematic survey of the opinions of leading psychiatrists worldwide on strategies for reducing the treatment gap, supported by the largest professional body in global mental health. We acknowledge the need to consult all relevant stakeholders in planning the scaling up of mental health services to meet the need and reduce the treatment gap, and see this survey as a critically important first step in ascertaining the position of psychiatrists, arguably one of the most influential stakeholder communities in global mental health.

Our findings clearly indicate three strategies for reducing the treatment gap: increasing the numbers of psychiatrists and other mental health professionals; increasing the involvement of a range of other non-specialist providers and settings in mental health care; and the active involvement of people affected by mental disorders. This is true for both HIC

and LMIC, though relatively of more importance in LMIC. The strong support for the increased role of those affected by mental disorders in mental health care is in line with the goals of the Movement for Global Mental Health, which advocates a broad-based approach to addressing mental health needs and reducing the treatment gap, with a strong partnership between practitioners and those affected by mental disorders. Through the implementation of its Action Plan 2008-2011 (8-9), the World Psychiatric Association is working to increase the number of psychiatrists and to improve the quality of psychiatric training and continuing education.

In conclusion, scaling up of mental health services can only be achieved effectively if three elements are in place: task shifting to non-specialist providers; an increase in the specialist mental health resources to provide effective and sustained supervision and support; and a decentralization of those specialist mental health resources. The WPA will continue to promote the development of mental health care and its integration into primary care in all countries, promoting the implementation of all the strategies identified in this study.

APPENDIX

The WPA Zonal and Member Society Representatives participating in the survey include: Raymond Tempier (WPA Zone 1 and Canadian Psychiatric Association), Michelle B. Riba (WPA Zone 2 and American Psychiatric Association), Mauricio Sanchez (WPA Zone 3), Fabrizio Delgado Campodonico (WPA Zone 4), Luis Risco (WPA Zone 5), Linda Gask (WPA Zone 6), Henrik Wahlberg (WPA Zone 7), Miquel Roca (WPA Zone 8), Dusica Lecic-Tosevski (WPA Zone 9), Armen Soghoyan (WPA Zone 10 and Armenian Association of Psychiatrists and Narcologists), Driss Mousaoui (WPA Zone 11), Charles Baddoura (WPA Zone 12), Joseph Adeyemi (WPA Zone 13), Solomon Rataemane (WPA Zone 14), S. Ahmed Jalili (WPA Zone 15), E. Mohandas (WPA Zone 16 and Indian Psychiatric Society), Naotaka Shinfuku (WPA Zone 17), Julian Freidin (WPA Zone 18), Juan Carlos Stagnaro (Association of Argentinean Psychiatrists), Ines Josefina Puig (Foundation for Interdisciplinary Investigation of Communication, Argentina), Kenneth Kirkby (Royal Australian and New Zealand College of Psychiatrists), Michael Musalek (Austrian Association of Psychiatry and Psychotherapy), Nadir Ismayilov (Azerbaijan Psychiatric Association), Golam Rabbani (Bangladesh Association of Psychiatrists), Sharon Harvey (Barbados Association of Psychiatrists), Bernard Sabbe (Society of Flemish Neurologists and Psychiatrists, Belgium), Nils Noya-Tapia (Bolivian Society of Psychiatry), Marija Burgic-Radmanovic (Psychiatric Association of Bosnia-Herzegovina), Luiz Alberto Hetem (Brazilian Association of Psychiatry), Fatima Vasconcellos (Psychiatric Association of Rio de Janeiro State, Brazil), Juan Maass (Society of Neurology, Psychiatry and Neurosurgery, Chile), Carlos Miranda (Colombian Psychiatric Associa-

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Depression treatment patterns among women veterans with cardiovascular conditions or diabetes

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The study aimed to examine treatment patterns for depression among women veterans diagnosed with cardiovascular conditions or diabetes. We used longitudinal data from the 2002-2003 merged Veteran Health Administration (VHA) and Medicare files. Chi-square tests and multinomial logistic regression were performed to analyse depression treatment among veteran women with incident depressive episode and one of the following chronic conditions: diabetes or coronary artery disease or hypertension. Overall, 77% received treatment for depression, 54% with only antidepressants, 4% with only psychotherapy, and 19% with both. Multinomial logistic regression revealed that African American women were more likely to be in the no treatment group and were more likely than white women to receive psychotherapy rather than antidepressants. Older women and women with coronary artery disease only were less likely to receive treatment.

Key words: Depression, women, coronary artery disease, hypertension, diabetes, antidepressants, psychotherapy

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The worldwide higher prevalence of depression in women compared to men has been well established (1). However, research on treatment for depression among women, specifically when depression co-exists with medical illnesses, has not received much attention. One can piece together some indirect evidence on treatment patterns for depression among women through studies that analyse gender differences in depression or studies that assess quality of depression care. One study from the 1990s reported that women in primary care were more likely to receive a prescription for antidepressant medication than men (2). In adults over 60 years of age, women were more likely than men to receive depression care (3). In randomized controlled trials that assess quality improvement for depression care, women were more likely to receive depression care than men over time (4). Based on psychiatrists' responses to video vignettes depicting an elderly patient with late-life depression, it was concluded that patient's gender did not influence depression management (5).

However, none of those studies examined treatment for depression when chronic illnesses co-exist with the depressive syndrome. An analysis of depression treatment rates and patterns in cardiovascular diseases and diabetes is needed. One in five women have some form of cardiovascular disease (6) and there are more women with diabetes than men (7). In a sample of women with diabetes, major depression was an independent risk factor that accelerated the development of coronary heart disease (8). In addition, the first clinical trial testing the relationship between depression treatment and mortality in coronary heart disease patients reported a significant treatment-sex interaction, suggesting that women may have had worse outcomes compared to men (9).

The primary objective of this study was to report rates of treatment for depression (antidepressants and/or psychotherapy) among women with diabetes or coronary artery disease or hypertension and analyse variations in these rates by

demographic, socioeconomic and health status characteristics. The population of women veterans is of special interest because research on women veterans with chronic physical conditions is scant (10) and, specifically, treatment issues in women veterans with co-occurring physical and mental illnesses have remained an understudied area of research within the Veteran Health Administration (VHA) (11).

We studied women veterans who used the VHA clinics and were diagnosed with either diabetes or coronary artery disease or hypertension in fiscal year 2002 and evaluated depression treatment for incident depression episodes in fiscal year 2003.

METHODS

Data for our study come from the merged VHA and Medicare data in fiscal years 2002-2003. Fiscal year 2002 represented the year from October 1, 2001 to September 30, 2002; fiscal year 2003 represented the year from October 1, 2002 to September 30, 2003. We excluded women veterans who died by the end of fiscal year 2003. Among dual VHA/Medicare enrollees, we included only those women veterans who had fee-for-service enrollment for all of the 12 months in 2002 and 2003.

We identified women veterans with diabetes or coronary artery disease or hypertension during fiscal year 2002 using an algorithm based on disease-specific ICD-9-CM codes, the number of clinical care encounters, site of care (inpatient versus outpatient), and level of diagnosis (primary versus other). For example, to identify women with coronary artery disease, we required that there was at least one inpatient visit or one outpatient visit with primary diagnosis of coronary artery disease or two outpatient visits with diagnosis of primary or secondary coronary artery disease.

Any depression diagnosis was identified using ICD-9-CM codes 296.2 (major depressive disorder, single episode), 296.3 (major depressive disorder, recurrent episode), 311 (depression not elsewhere classified), 309.1 (prolonged depressive reaction), 300.4 (neurotic depression), 309.0 (adjustment disorder with depression), and 298.0 (depressive type psychosis). To define an incident episode of depression in fiscal year 2003, we followed an algorithm used in our prior published work: the criteria consisted of 120-day negative depression and/or antidepressant medication history on or before the first depression diagnosis date in fiscal year 2003 (12). To allow for sufficient follow-up for depression treatment, we included only those who had at least 6 months of follow-up period in fiscal year 2003.

Thus, the final study population for analysis consisted of women veterans who used VHA clinics and were diagnosed with diabetes or coronary artery disease or hypertension, of whom 8,147 had an incident depression diagnosis in fiscal year 2003.

Antidepressant medications were identified using drug names from the VHA Pharmacy Benefit Management (PBM) files. During the period of observation, Medicare did not provide prescription drug benefits. Therefore, antidepressants were derived only from VHA files. Among women veterans with incident depression in fiscal year 2003 and diagnosed with diabetes or coronary artery disease or hypertension in fiscal year 2002, any woman with at least one prescription for antidepressant medications on or after the depression diagnosis date in 2003 was considered to be receiving antidepressant treatment for depression.

We compiled a comprehensive list of psychotherapy codes using current procedural terminology (CPT) codes from both the VHA and Medicare files to assess psychotherapy treatment for depression. The list of codes was reviewed by psychologists and psychiatrists of the research team. Again, among women veterans with incident episodes of depression, any visit with psychotherapy codes within 180 days on or after the start date of the incident episode of depression in fiscal year 2003 was defined as psychotherapy use.

Based on antidepressant prescriptions and psychotherapy visits, we classified women veterans into four mutually exclusive categories: no depression treatment; antidepressant use only; psychotherapy use only; and both antidepressants and psychotherapy. Due to very small number of women veterans ($n=297$; 3.6%) using psychotherapy only, subgroup differences in psychotherapy only yielded many cells with less than two individuals. Therefore, we combined the groups receiving psychotherapy with and without antidepressant, and analysed depression treatment with three categories.

Independent variables consisted of race/ethnicity (white, African American, Latino, other, and missing), age (less than 50 years, 50-64 years, 65-74 years, and 75 or older), Medicare enrollment (12 months fee-for-service Medicare enrollment versus only VHA coverage), region (Northeast/Midwest/South/West), index diagnosis in fiscal year 2002 (diabetes only, coronary artery disease only, hypertension only, diabe-

tes and coronary artery disease, diabetes and hypertension, coronary artery disease and hypertension, or all three conditions), other physical conditions (none, one, two or more), and psychiatric comorbidities (anxiety disorders, bipolar disorder, psychoses other than schizophrenia, post-traumatic stress disorder (PTSD), schizophrenia, substance abuse). All medical and psychiatric comorbidities were based on ICD-9-CM codes in fiscal year 2002.

Group differences in depression treatment were tested with the chi-square statistic. To examine depression treatment patterns among women veterans, we used multinomial logistic regression. Bivariate and multivariate analyses were conducted with the 3-level depression treatment variable ("no treatment", "antidepressants only", and "psychotherapy with or without antidepressants"). The parameter estimates from the multinomial logistic regression were transformed to odds ratios and their corresponding 95% confidence intervals. In the multinomial regression, for the dependent variable, the reference group was "antidepressant use only".

RESULTS

A description of our study population of 8,147 women veterans with incident depression episode in fiscal year 2003 and a diagnosis of diabetes or coronary artery disease or hypertension in fiscal year 2002 is provided in Table 1. A majority of women veterans were white (69% white versus 19% African American and 1.9% Latino); 25% of women veterans were 65 years or older. About half (55%) of the women veterans were enrolled in the Medicare fee-for-service system. An overwhelming majority of women veterans (84%) had hypertension, either alone (55%) or in combination with diabetes or coronary artery disease (29%). Thirty-nine percent of the women veterans qualified for VHA enrollment because of low-income status. The most highly prevalent psychiatric comorbidity was anxiety disorders (20%). Another common condition was substance use disorders: 20% had clinical encounters with substance use diagnosis (alcohol, drugs and/or tobacco) codes.

Among those with incident episodes of depression in fiscal year 2003, 54% were prescribed antidepressants only, 23% had psychotherapy with or without antidepressants and 23% had no depression treatment (Table 2). All bivariate subgroup differences in depression treatment were significant; therefore we highlight only those that were significant in multinomial logistic regression (Table 3). A significantly higher percentage of African Americans women compared to white women (26.5% vs. 17.1%) had no prescriptions for antidepressants or psychotherapy visits within 180 days of follow-up. The adjusted odds ratio for no treatment for African Americans was 1.25 (95% CI=1.05, 1.49) compared to only antidepressants (Table 3). Psychotherapy rather than antidepressant use was more likely among African American women compared to white women (32.0% versus 18.9%), with an adjusted odds ratio of 1.38 (95% CI=1.19, 1.59).

Table 1 Description of study population (N=8,147)

	N	%
<i>Race/ethnicity</i>		
White	5,598	68.7
African American	1,530	18.8
Latino	153	1.9
Other	73	0.9
<i>Age</i>		
< 50 years	3,018	37.0
50-64	2,253	27.7
65-74 years	874	10.7
75, +	2,002	24.6
<i>Priority status</i>		
Disabled	3,706	45.5
Poor	3,157	38.8
Co-pay	1,188	14.6
<i>Index diagnosis</i>		
Diabetes only	685	8.4
Coronary artery disease only	295	3.6
Hypertension only	4,435	54.4
Diabetes plus coronary artery disease	53	0.7
Diabetes plus hypertension	1,199	14.7
Coronary artery disease plus hypertension	927	11.4
All the three conditions	555	6.8
<i>Other physical conditions</i>		
None	252	3.1
One	1,688	20.7
Two or more	6,207	76.2
<i>Other mental disorders</i>		
Anxiety disorders	1,662	20.4
Bipolar disorder	733	9.0
Psychoses other than schizophrenia	527	6.5
Post-traumatic stress disorder	897	11.0
Schizophrenia	524	6.4
Any substance abuse	1,647	20.2

Older women (65 years and older compared to those in the age group 50 years and younger) were more likely to have “no depression treatment”. The adjusted odds ratio for no treatment was 1.40 (95% CI=1.03, 1.90) for veteran women with coronary artery disease only compared to veteran women with hypertension only. Variations in the relationships between type of mental illness and depression treatment were observed. For example, those with anxiety disorders or PTSD were less likely to receive “no depression treatment”, whereas those with psychoses were more likely to receive “no depression treatment”. Those with any substance use disorders were less likely to receive “no depression treatment”.

DISCUSSION

In this study, we set out to examine depression treatment patterns in women veterans with cardiovascular conditions or diabetes and incident depression. Because very few observational studies have analysed depression treatment in women with chronic illnesses, we are unable to compare the rates of depression treatment in our study to other studies. Although not directly comparable, in one study based on 18

women with well-controlled diabetes and depression living in Northeastern Connecticut, only 18% were treated with psychotherapy and antidepressants (13), which is similar to our overall rates of psychotherapy estimated at 23%.

The lower likelihood of antidepressant only treatment among African American women compared to white women is similar to findings of racial disparities in the general population (14,15), in individuals with heart disease (16), and in veterans with diabetes (12). All women in our study had prescription drugs coverage. In the presence of equalized access in terms of insurance coverage, one of the factors that could explain the racial differences may be the greater mental health stigma among African Americans in general (17,18) and specifically in African American women compared to white women (19).

However, African American women were as likely as white women to receive psychotherapy. Among both men and women, African Americans are less likely than whites to accept antidepressant medication for depression treatment (17). A majority of women who received psychotherapy reported that the treatment is acceptable (20) and racial minorities in general prefer counseling for depression over antidepressants (21). Taken together, our findings and those from the literature suggest that promoting psychotherapy in this population could be one way to reduce racial disparities in depression treatment.

Compared to women with hypertension only, women with coronary artery disease were more likely to be in the no depression treatment category. Further research needs to explore whether such lower likelihood of treatment in these women is related to the adverse outcomes observed in the ENRICH trial. Women with coronary artery disease in our study were as likely as women with hypertension only to use psychotherapy. Given the beneficial effects of psychotherapy found in the ENRICH trial (9,22), psychotherapy could be encouraged for depression treatment in this population of women veterans (23). In addition, as recommended by the advisory panel for heart disease and depression care, these women need to be closely monitored for both mental and cardiac health outcomes (24).

Our study findings did not support the general perception that multimorbidity may lead to less treatment for depression (25). In our study, women veterans with combinations of diabetes, coronary artery disease, and hypertension as well as increased number of other physical conditions did not have a lower likelihood of depression treatment. This is consistent with a recently published study that concluded that depression treatment in primary care settings is not influenced by competing demands for care for other comorbid medical conditions (26). It is possible that lack of significant difference in treatment by comorbidity could be due to close monitoring of individuals with serious mental illness such as depression and chronic diseases (27).

Although improvement in depressive symptoms due to depression treatment within integrated settings (i.e. mental health and primary care) like the VHA has been observed in

Table 2 Description of population by depression treatment categories

	No treatment		Antidepressants only		Psychotherapy		p
	N	%	N	%	N	%	
	1,887	23.2	4,388	53.9	1,872	23.0	
<i>Race/ethnicity</i>							<0.001
White	1,486	26.5	3,055	54.6	1,057	18.9	
African American	261	17.1	780	51.0	489	32.0	
Latina	27	17.6	79	51.6	47	30.7	
Other	17	23.3	39	53.4	17	23.3	
<i>Age</i>							<0.001
< 50 years	421	13.9	1,648	54.6	949	31.4	
50-64	354	15.7	1,298	57.6	601	26.7	
65-74 years	290	33.2	449	51.4	135	15.4	
75, +	822	41.1	993	49.6	187	9.3	
<i>Married</i>							<0.001
Married	605	23.4	1,427	55.3	550	21.3	
Widowed	478	35.3	694	51.3	181	13.4	
Divorced/Separated	484	18.4	1,439	54.8	702	26.7	
Never married	309	20.1	803	52.3	422	27.5	
<i>Priority status</i>							<0.001
Disabled	731	19.7	2,023	54.6	952	25.7	
Poor	792	25.1	1,646	52.1	719	22.8	
Co-pay	347	29.2	662	55.7	179	15.1	
Missing	17	17.7	57	59.4	22	22.9	
<i>Index diagnosis</i>							<0.001
Diabetes only	126	18.4	368	53.9	189	27.7	
Coronary artery disease only	74	25.1	147	49.8	74	25.1	
Hypertension only	920	20.7	2,418	54.5	1,097	24.7	
Diabetes plus coronary artery disease	20	37.7	29	54.7	4	7.5	
Diabetes plus hypertension	280	23.4	659	55.0	260	21.7	
Coronary artery disease plus hypertension	294	31.7	480	51.8	153	16.5	
All the three conditions	173	31.2	287	51.7	95	17.1	
<i>Other physical conditions</i>							<0.001
None	33	13.1	134	53.2	85	33.7	
One	289	17.1	914	54.1	485	28.7	
Two or more	1,565	25.2	3,340	53.8	1,302	21.0	
<i>Anxiety disorders</i>							<0.05
Yes	344	20.7	938	56.4	380	22.9	
No	1,543	23.8	3,450	53.2	1,492	23.0	
<i>Bipolar disorder</i>							<0.01
Yes	148	20.2	440	60.0	145	19.8	
No	1,739	23.5	3,948	53.3	1,727	23.3	
<i>Psychoses other than schizophrenia</i>							<0.001
Yes	163	30.9	273	51.8	91	17.3	
No	1,724	22.6	4,115	54.0	1,781	23.4	
<i>Post-traumatic stress disorder</i>							<0.001
Yes	94	10.5	583	65.0	220	24.5	
No	1,793	24.7	3,805	52.5	1,652	22.8	
<i>Schizophrenia</i>							<0.05
Yes	118	22.5	307	58.6	99	18.9	
No	1,769	23.2	4,081	53.5	1,773	23.3	
<i>Any substance abuse</i>							<0.001
Yes	273	16.6	923	56.0	451	27.4	
No	1,614	24.8	3,465	53.3	1,421	21.9	

older adults (28) and in those with chronic illnesses (29), we found differences in depression treatment by age. These differences were similar to those observed in the general population (30) and in the veteran population with diabetes (12).

Multiple barriers to depression care among older individuals are documented (30). However, older individuals generally prefer integrated treatment in the context of heart disease (29). Interventions to improve depression treatment in older

Table 3 Adjusted odds ratios (AOR) from multinomial logistic regression on depression treatment

	No treatment			Psychotherapy use		
	AOR	95% CI	P	AOR	95% CI	p
<i>Race/ethnicity</i>						
White						
African American	1.25	1.05,1.49	<0.05	1.38	1.19,1.59	<0.001
Latina	1.05	0.66,1.67		1.35	0.92,1.98	
Other	1.33	0.73,2.40		1.03	0.58,1.85	
<i>Age</i>						
< 50 years						
50 – 64	0.99	0.84,1.17		0.86	0.75,0.98	<0.05
65 - 74 years	1.62	1.29,2.03	<0.001	0.77	0.60,0.99	<0.05
75, +	2.01	1.63,2.47	<0.001	0.49	0.39,0.61	<0.001
<i>Index diagnosis</i>						
Diabetes only	1.22	0.96,1.56		1.03	0.82,1.28	
Coronary artery disease only	1.40	1.03,1.90	<0.05	1.15	0.84,1.56	
Hypertension only						
Diabetes plus coronary artery disease	1.62	0.88,2.97		0.38	0.13,1.09	
Diabetes plus hypertension	1.03	0.87,1.21		0.98	0.83,1.15	
Coronary artery disease plus hypertension	1.08	0.91,1.29		1.04	0.85,1.28	
All the three conditions	1.06	0.86,1.31		1.12	0.87,1.45	
<i>Other physical conditions</i>						
None						
One	1.41	0.91,2.19		0.89	0.63,1.24	
Two or more	1.42	0.92,2.20		0.88	0.63,1.23	
<i>Anxiety disorders</i>						
Yes	0.81	0.70,0.94	<0.01	1.07	0.93,1.23	
No						
<i>Bipolar disorder</i>						
Yes	0.92	0.74,1.14		0.79	0.64,0.98	<0.05
No						
<i>Psychoses other than schizophrenia</i>						
Yes	1.30	1.04,1.62	<0.05	1.05	0.81,1.37	
No						
<i>Post-traumatic stress disorder</i>						
Yes	0.45	0.36,0.57	<0.001	0.77	0.65,0.9]	<0.01
No						
<i>Schizophrenia</i>						
Yes	1.00	0.78,1.28		0.81	0.63,1.05	
No						
<i>Any substance abuse</i>						
Yes	0.84	0.72,0.99	<0.05	1.12	0.98,1.29	
No						

adults could include education materials highlighting depression as a cardiovascular risk factor.

The study had many advantages, such as the use of a large nationwide database of women veterans, the availability of information from Medicare and VHA to help capture complete utilization data, and the ability to identify diagnosed diabetes, coronary artery disease, hypertension and depression. One of the major limitations of the study is that we only observed prescription for antidepressants and we do not have information on the actual use of the medications. Similarly, we only observed actual psychotherapy visits and we do not know whether women veterans were referred to psychotherapy and did not follow through on the referral. Another limitation of our study is the generalizability of the findings outside of the VHA system. Furthermore, the use of di-

agnostic codes from specific years to identify chronic diseases has its drawbacks: these data cannot be used to derive variables such as date of onset, severity and duration of physical and mental illnesses. Severity of depression could have attenuated the relationship between low depression treatment rates and coronary artery disease only. Similarly, severity of physical illnesses could be a barrier to depression care in the presence of multimorbidity (26).

Despite these limitations, our study contributes to the nascent literature that has begun to explore treatment patterns among women with chronic diseases. Subgroup differences in depression treatment of women veterans with chronic diseases were generally similar to the patterns observed in the general population of men and women. Our study findings suggest the need for further research in improving depression

care among women with heart diseases, integrating depression care in the context of cardiovascular risk reduction, and promoting psychotherapy use to reduce racial disparities in depression treatment.

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Use of ICD-10 diagnoses in Danish psychiatric hospital-based services in 2001-2007

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The Danish version of the ICD-10 chapter on mental and behavioural disorders has 380 different diagnoses when three digits are used. This study examines how many of the available diagnoses were used and to what extent in Danish psychiatric hospital-based services in the period from 2001 to 2007, through an analysis of the total number of diagnoses reported to the Danish Psychiatric Central Research Register (n=1,260,097). The 50th percentile (50.1%) was reached by using 16 diagnoses (4.2% of 380 available). The three most frequently registered diagnoses were paranoid schizophrenia, alcohol dependence and adjustment disorder, used 10.2%, 8.3% and 5.9% of the times, respectively. Seven diagnoses (1.8%) were used between 1 and 4 times during the 7-year period. One hundred nine (28.7% of available diagnoses) were used less than 100 times each. These data suggest that it may be sensible to reconsider the number of diagnoses needed in the revision of the ICD-10 chapter on mental and behavioural disorders.

Key words: Psychiatric diagnoses, ICD-10, Danish hospital-based services

(World Psychiatry 2010;9:183-184)

Psychiatric health care statistics and epidemiological research almost always use a very limited number of classificatory groups for result presentation, rarely more than 8 to 10. Current classification systems, the ICD-10 and DSM-IV-TR, open up for several possibilities for detailed diagnosing aiming at treatment and research. The ICD-10 chapter on mental and behavioural disorders, used in Denmark since January 1994, has 380 different diagnoses when three digits are used (xx.x). The purpose of this study was to investigate how many of the psychiatric diagnoses available were used and to what extent in the Danish psychiatric hospital-based services in the period from 2001 to 2007.

The data used were all diagnoses reported to the Danish Psychiatric Central Research Register (DPCRR) (1) from

January 1, 2001 through December 31, 2007. Diagnoses are reported to the register in connection with discharge from a treatment episode. Diagnoses from inpatient and outpatient treatment episodes as well as visits to psychiatric emergency services were included. Patients in community psychiatric treatment were included in the group of outpatients. Both main and auxiliary diagnoses were considered.

During the seven-year period, 1,260,097 diagnoses from 1,041,589 discharges of 653,754 patients from in- and outpatient treatment episodes were reported to the DPCRR. All 380 possible diagnoses from the Danish version of the ICD-10 were used.

The 50th percentile (50.1%) of the total of 1,260,097 diagnoses was reached by including 16 different diagnoses, with

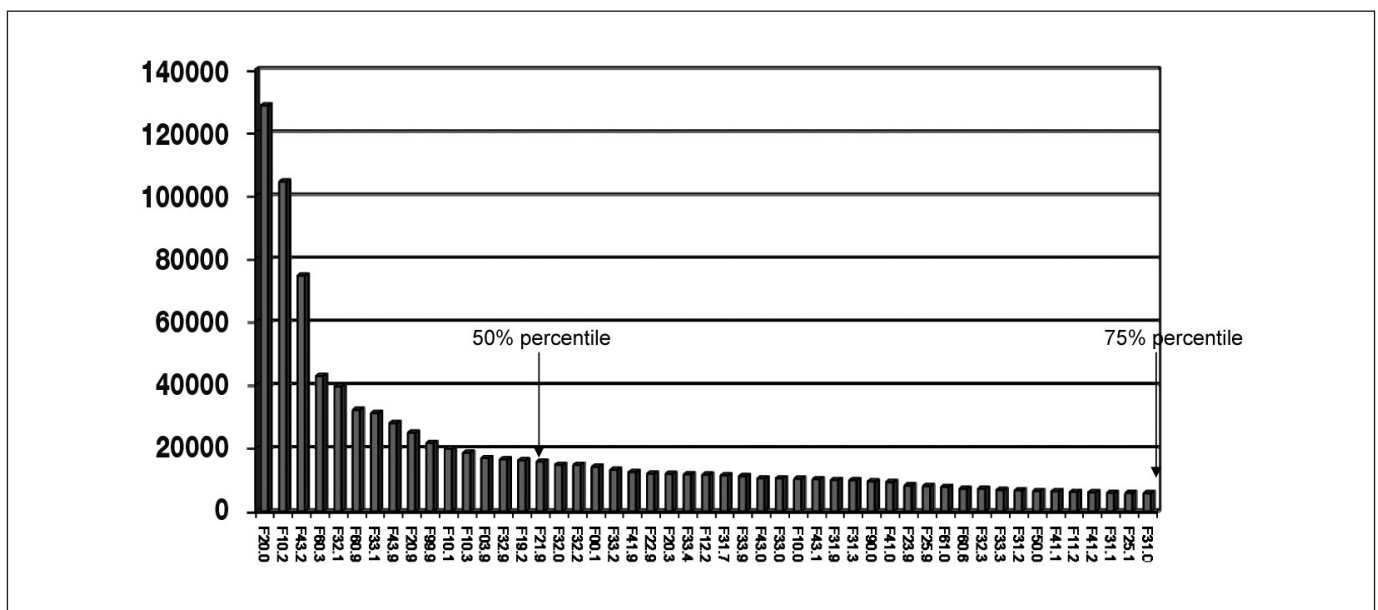


Figure 1 The 49 ICD-10 categories accounting for 75% of the diagnoses given in Danish public psychiatry from 2001 to 2007

F20.0 (paranoid schizophrenia) as the most frequently used, 128,537 (10.2%) times. F10.2 (alcohol dependence syndrome) was used 104,445 (8.3%) times, and F43.2 (adjustment disorder) 74,687 (5.9%) times.

The 75th percentile was reached by including 49 diagnoses (Figure 1). One hundred and forty-six diagnoses (38.4%) were sufficient to reach the 95th percentile. One hundred forty-four diagnoses (37.9%) were registered less than 200 times each; 109 (28.7%) less than 100 times each; 141 (37.1%) were used 0.01% or less of the total of 1,260,097 diagnoses.

Three diagnoses were used only twice: cluttering (F98.6), abuse of volatile solvents (F18.8), and amnestic syndrome due to abuse of volatile solvents (F18.6). Two were used only 3 times: acquired aphasia with epilepsy (F80.3), and other impairment of behaviour due to profound mental retardation (F73.8). Two were used only 4 times: pica of infancy and childhood (F98.3), and other mental and behavioural disorders due to use of hallucinogens (F16.8).

These results indicate that very few of the 380 available diagnoses in the Danish version of the ICD-10 account for a majority of the diagnoses given. This is in line with the report by Müssigbrodt et al (2), who investigated 25,470 main diagnoses given in 19 departments from 10 countries in 4 continents. They found that 10 diagnoses accounted for 40% of all cases and 121 were used in less than 0.1% of the cases.

In the absence of a clear knowledge about the pathogenesis of mental disorders, psychiatry is open to introducing

new diagnostic concepts. This process is welcomed by the pharmaceutical industry (3), and may be supported by the decreasing threshold for discomfort and personal responsibility for one's own life in Western populations (4).

This tendency could be corrected when revising the ICD and DSM systems, preferably by involving also the WPA (5), and by rethinking the evidence needed for coining new "disorders", although taking cultural diversities (6) into account.

As our study was based on a register covering hospital- and community-based psychiatric practice, we cannot exclude a possible usefulness in private practice of some of the diagnoses not frequently used in public settings.

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Lessons learned in developing community mental health care in Africa

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This paper summarizes the findings for the African Region of the WPA Task Force on Steps, Obstacles and Mistakes to Avoid in the Implementation of Community Mental Health Care. We present an overview of mental health policies, plans and programmes in the African region; a summary of relevant research and studies; a critical appraisal of community mental health service components; a discussion of the key challenges, obstacles and lessons learned, and some recommendations for the development of community mental health services in the African region.

Key words: Community mental health care, Africa, primary health care, mental health services, systematic review, lessons learned

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This paper is one of a series which describes the development of community mental health care in regions around the world. In 2008 the WPA General Assembly approved the Action Plan of the Association for the triennium of the Presidency of Professor Mario Maj (1,2), who commissioned a Task Force to produce a WPA Guidance on Steps, Obstacles and Mistakes to Avoid in the Implementation of Community Mental Health Care. The purpose, methods and main findings of this Task Force have recently been published (3). In this article, we describe these issues in relation to Africa.

The Africa region of the World Health Organization (WHO) includes 46 countries, 30 of which are classified as low-income. Mental disorders appear to be at least as prevalent as in high-income countries, with a lifetime prevalence estimated to be 30.3% (4). Mental health vies for its place amongst other compelling public health priorities and yet has demonstrated importance for achieving the Millennium Development Goals (5). However, funding for mental health care in the African region remains disproportionately low when compared to the associated burden of mental disorder (6). Further challenges to the development of mental health services in the Africa region come from the impact of conflicts, natural disasters and the brain drain of mental health professionals from government services (7).

In this paper, we review the implementation of community mental health care across African countries, with particular emphasis given to published evaluations of services and the experience of experts within the region.

MENTAL HEALTH POLICIES, PLANS AND PROGRAMMES IN THE AFRICA REGION

At the time of the publication of the WHO Mental Health Atlas (8), there were only 23 countries with a mental health policy in the Africa region, with a further six countries in the process of developing a policy. Nine countries had a mental health programme in the absence of a policy. Twenty five

countries had mental health legislation, although the majority had not been revised recently. Only 56.5% of African countries reported having community-based mental health care.

Even though many policies support the decentralization of mental health services and development of community-oriented services, actual implementation has been a great challenge across the African continent (9-11). For most low-income African countries, achieving adequate population coverage with any kind of mental health care provision has been problematic, resulting in high treatment gaps for even the most severe mental disorders (6).

SUMMARY OF RELEVANT RESEARCH WITHIN THE AFRICA REGION

A systematic review of published and grey literature was undertaken in order to identify studies evaluating the implementation of community mental health care in Africa. The methodology has been described (3). In this paper, only studies conducted between 1995 and 2009 are considered, as older studies have been reviewed previously (12).

A total of 24 evaluations of community mental health services were identified. Their findings have been synthesized and presented in Tables 1-3. Reviews of evidence and experience arising from implementation of community mental health care were also identified, both from South Africa (34,35).

The vast majority of published mental health service research in sub-Saharan Africa has been carried out in South Africa (n=17; 70.8%), an upper-middle income country. There is a conspicuous lack of published literature evaluating the implementation of community mental health care in low-income sub-Saharan Africa countries. Only a minority of studies (n=5; 20.8%) included a comparative element to their evaluation, either comparing pre- to post-intervention, or referring to another service model, and none employed randomization.

The identified studies have considered different models of

Table 1 Synthesis of studies evaluating quality of mental health care in primary care settings in sub-Saharan Africa

Evaluated component	Findings
Diagnosis	Diagnostic sensitivity 76%, specificity 98% (Guinea-Bissau) (13); diagnosis not recorded in 44% of cases (S. Africa) (14); low awareness of non-psychotic mental illness (S. Africa) (15)
Psychiatric history	Judged adequate in 89% of cases (S. Africa) (16)
Medication	Inappropriate prescription in 8% of cases for emergency medication, in 40% for long-term medication (S. Africa) (16); polypharmacy in 88% of cases (S. Africa) (14); only 10% of nurses confident to make changes (S. Africa) (14); erratic medication supply in Ghana, Kenya, Tanzania, Uganda (18)
Psychosocial therapies	After brief training in rehabilitation, fidelity to model maintained after 18 months (S. Africa) (19); limited availability of therapies in routine practice (15,20)
Continuity of care	15-18% lost to follow-up (S. Africa) (17); 36% not seen in six months (S. Africa) (14)
Staffing	High turnover (S. Africa, Guinea-Bissau, Tanzania) (13,15,18)
Supervision	Lined to specialist service found to be essential (Guinea-Bissau) (13)

Table 2 Synthesis of studies evaluating professionals' and users'/carers' views on mental health care in primary care settings in sub-Saharan Africa

Evaluated component	Findings
<i>Primary health care workers' views</i>	
Training in mental health care	Inadequate (15,21,22)
Attitudes towards new role	Increased stress in 50% of respondents (S. Africa) (21); 84% said specialists should retain responsibility (S. Africa) (21); back-up highly appreciated (S. Africa) (23); residual negative attitudes towards new role (S. Africa) (23)
Implementation	62% felt services were understaffed (S. Africa) (23); no transport/time for outreach (S. Africa) (23); 79% felt services were restricted to prescribing medication (S. Africa) (21); understand need for psychosocial care but in practice constrained (S. Africa) (24); limited social services (S. Africa) (23)
<i>Patients' views</i>	
Satisfaction with care	Majority (>90%) satisfied but >50% of black patients preferred long-stay hospital care (S. Africa) (25); good accessibility, less stigmatizing when integrated into general care (S. Africa) (23); generally high satisfaction with care (Uganda) (23); lack of attention to physical health if separate mental health clinic but longer waits, less continuity, poorer quality if integrated into general care (S. Africa) (23)
Symptoms	Reduction following intervention reported by patients/carers (Guinea-Bissau) (13)
Functioning	Vocational/occupational functioning improved after rehabilitation (S. Africa) (19)
<i>Carers' views</i>	
Attitudes towards providing care	Majority happy but high proportion preferred day/long-stay hospital care (S. Africa) (25)
Satisfaction with provided care	High overall satisfaction (S. Africa) (22); lack of continuity and long waiting times (S. Africa) (22); need for more support (26)

community-based mental health care, ranging from specialist assertive outreach teams to variations on the integration of mental health into primary health care, for example: joint clinics between primary care workers and mental health nurses, mental health nurses working in a primary care setting, and primary care workers providing the bulk of mental health care with varying degrees of specialist mental health support. Little is known about the relative merits of these different approaches, as direct comparisons of effectiveness are rare (23).

Much of the focus of studies has been on the quality of mental health care provided within primary care, and the skills, knowledge and attitudes of primary care workers in regard to the diagnosis and management of mental disorders. Previously, studies of the effectiveness of training primary care workers to deliver mental health care have been criticized for relying on self-reports from these workers (subject to social desirability bias) and failing to look at the sustainability of the

effect of training (12). By examining case records kept by primary care workers (17), some of the subjectivity of assessment can be overcome, although documented practice may not fully accord with actual clinical practice. Some studies incorporating observational methods have yielded important insights (20,24), for example, revealing that the emotional work of dealing with patients with mental disorders may contribute to primary care workers operating in a task-oriented biomedical model of care rather than the more holistic model envisaged by the primary care model (24).

Although several studies included evaluations of the levels of satisfaction with services expressed by patients and their families (e.g., 22), and one study considered patient's social outcomes (17), we did not identify any study that evaluated patients' clinical outcomes using standardized diagnostic or symptom scales, and no study looked at patient experience of side effects of medication or physical health parameters.

Table 3 Synthesis of studies evaluating specialist community mental health services and service interfaces

Evaluated component	Findings
<i>Specialist community mental health services</i>	
Prescription of medications	Unnecessary polypharmacy in 9% of cases (S. Africa) (28); prescription inappropriate for diagnosis in 12-17% of cases (S. Africa) (28)
Psychosocial interventions	Minimal resources available (S. Africa) (15,20)
Referral for frequent relapses	Rarely occurred (S. Africa) (28)
Follow-up	43-46% lost to follow-up (S. Africa) (28); follow-up mostly clinic-based (Botswana) (26)
Service provided	Narrow focus on prescribing by psychiatric nurses (S. Africa) (29); largely biomedical approach by psychiatric nurses (Botswana) (26); minimal resources available for prevention, promotion, training (S. Africa) (15); only 8-10 minutes available for assessment/review (S. Africa) (29)
Staffing	District mental health practitioners diverted to general health care (S. Africa) (15)
<i>Service interfaces</i>	
Sustainability	Difficulty sustaining (e.g., Ghana) (18)
Cost-benefit of service	Demonstrated benefits in Guinea-Bissau (13)
Referral from community	Lack of cooperation from primary care workers; ambiguous role of community workers (S. Africa) (30); community volunteers not sustainable if unpaid (Uganda) (18); community awareness campaigns successful in increasing presentation (Nigeria, Uganda) (23,31)
Referrals upwards	Increased referral to regional not national services (Uganda) (23)
Outreach	Assertive outreach post-admission reduced readmission duration in revolving door patients (33); involvement of service users was successful in decreasing defaulting rates (Uganda) (18)

Only a handful of studies have attempted to evaluate the individual service processes necessary for successful implementation of community mental health care, for example, considering the effectiveness of referral networks (10,30). No studies were identified examining the quality and quantity of supervision required to enable adequate delivery of mental health care by primary care workers, despite the recognized importance of supervision for the success of integration of mental health into primary care (12). The finding that even mental health nurses seem reluctant to revise diagnoses, change medication protocols and proactively discharge patients from follow-up (27) underlines the importance of evaluating supervision arrangements.

There is also an absence of studies evaluating the effectiveness of psychosocial interventions delivered within the constraints of the primary care setting. One exception was the non-randomized study evaluating the incorporation of psychosocial rehabilitation for those with severe mental illness into the role of primary care nurses (19). Understanding whether similar brief interventions are feasible or effective in the primary care setting, or whether primary care workers can collaborate with non-governmental organizations (NGOs) and community-based organizations to provide such interventions is an important topic for future research.

CRITICAL APPRAISAL OF COMMUNITY MENTAL HEALTH SERVICE COMPONENTS

There was evidence of diverse interpretations of the meaning of community care across countries. In the low-income countries of the Africa region, community mental health care

is largely restricted to mental health care delivered by primary care workers, with specialist mental health workers (usually psychiatrists and psychiatric nurses) tending to provide care through hospital-based outpatient clinics. Despite recommendations by WHO and others (23), there are only a few examples of specialist mental health workers being utilized to support mental health care in the primary care setting, through coordination and planning of local mental health care, supervision, in-service training, consultation for complex cases, and prevention and promotion activities.

Although more holistic care is an expected benefit of community mental health services, especially when integrated into primary care, studies have not necessarily shown this to be the case (27,29). Time pressures, a strongly biomedical model of care and limited resources to support non-medication interventions may mean that mental health care is reduced to the dispensing and administration of medication (24).

Without community sensitization and engagement, the detection of untreated patients and take-up of mental health care is unlikely to proceed successfully. Similarly, without strategies in place to deal with patients who default from care, mental health care in primary care may not be sufficiently flexible to respond to the particular needs of patients with mental health difficulties. As more specialist mental health workers tend to be located at regional and district levels of the health system in most African countries, they are limited in their abilities to provide responsive outreach services close to home. A number of countries have made use of trained community-based volunteers to overcome this problem (18,30), but the difficulty of maintaining motivation and sustaining the system when workers are not remunerated has been highlighted (34). Involvement of service user

groups to help support community outreach services has been applied successfully (18).

The potential role of traditional healers and religious leaders in the delivery of community-based care has been much discussed (36,37), but with few examples of this happening in practice. One example of traditional healers providing counselling services in conjunction with a community-based mental health service has been reported, although with no evaluation of patient outcomes (18).

The potential contribution of support groups, composed of service users and caregivers, to improving clinical outcomes and social inclusion, as well as lobbying for improved services, has been described but not formally evaluated (38,39).

Our systematic review of the literature was complemented by a survey of regional experts on their experiences of implementing community mental health care (3). Tables 4 and 5 summarize the challenges and lessons learned.

RECOMMENDATIONS FOR THE AFRICA REGION

The new impetus given to scaling up of mental health services across low- and middle-income countries (40,41) has yet to manifest in terms of published evaluation studies establishing the effectiveness of such services in Africa. None-

Table 4 Challenges in implementing community mental health care in Africa

-
- Competing priorities
 - Waning community engagement
 - Reliance on community volunteers not sustainable
 - Under-funding
 - Paucity of mental health professionals
 - Negative attitudes to mental health
 - Concern about skills of staff and quality of care
 - Difficulty sustaining in-service training
 - Erratic supplies of psychotropic medication
 - Lack of multi-sectoral collaboration, including traditional healers
 - Escalating need and demand for services
-

Table 5 Lessons learned implementing community mental health care in Africa

-
- It can be done
 - Need for patience, perseverance and determination
 - Sustainability requires making best use of existing systems
 - Government commitment, existence of a mental health policy and legislation are crucial
 - International support can greatly help
 - Need to invest time to identify and cultivate allies for support
 - Ensure collaboration between the key stakeholders
 - Advocacy and community groups can influence policy makers
 - A mental health coordinator at the local level is necessary
 - Supervision of primary care workers is critical
 - Importance of proper planning
 - Need to integrate evaluation and monitoring
 - Marginalization of mental health can block progress
-

theless, an opportunity exists to build on the decades of experience, originally initiated by the WHO (42), and the existing evidence base in order to successfully implement models of community mental health care across Africa. Once stakeholders are engaged and political will is present, clear messages emerging from the evidence and experience to date support the importance of:

- Strengthening specialist mental health services at the same time as integrating mental health into primary health care.
- Increasing quality and sustainability of mental health in primary care through adequate supervision, ongoing on-the-job training and reliable referral networks.
- Developing robust mechanisms to ensure reliable supplies of psychotropic medications.
- Supporting the provision of simple and feasible psychosocial interventions to augment medication approaches in the time-pressed primary care setting.
- Evaluative research that considers:
 - a. How the interface between primary and secondary health services affects delivery of mental health care.
 - b. The clinical and social outcomes of individual patients, evaluated in a standardized and systematic way.
 - c. Innovative service models, including collaboration with traditional healers and religious leaders.
 - d. The relative cost-effectiveness of differing models of community care.

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The implementation of the WPA Action Plan 2008-2011

The implementation of the WPA Action Plan 2008-2011, approved by the General Assembly in Prague in September 2008 (1,2), is proceeding very actively. Some of the ongoing activities are summarized below.

The WPA-WHO collaboration

The WPA is collaborating with the WHO in the revision of the ICD-10 (3). As part of this collaboration, the WPA Member Societies are conducting a survey of the views and attitudes of psychiatrists of the world about the diagnosis and classification of mental disorders. Several WPA Scientific Sections are contributing to the Work Groups for the ICD-10 revision: for instance, the Work Groups on Psychotic Disorders, Personality Disorders and Intellectual Disabilities are chaired by officers of the relevant WPA Sections.

The WPA and the WHO are organizing train-the-trainers workshops on the management of the mental health consequences of disasters (e.g., 4). Furthermore, they have collaborated in dealing with the mental health consequences of some recent major emergencies (e.g., Gaza, Haiti).

The WPA programme of fellowships in collaboration with centers of excellence

The WPA is implementing a programme of one-year research fellowships for early-career psychiatrists from low- and lower-middle income countries, in collaboration with internationally recognized centers of excellence in psychiatry. These centers include at the moment: the Western Psychiatric Institute, University of Pittsburgh, USA (coordinator: D. Kupfer); the Institute of Psychiatry, London, UK (coordinators: S. Kapur, M. Prince); the University of Maryland School of Medicine, Baltimore, USA (coordinator: A. Bellack); the Mood Disorders Program, Case Western Reserve Uni-

versity, Cleveland, USA (coordinator: J. Calabrese); the University of Melbourne, Australia (coordinator: P. McGorry). The selected fellows have committed themselves to apply in their country of origin what they have learnt.

WPA-funded research projects

The WPA is funding international research projects dealing with the factors facilitating and those hampering the choice of psychiatry as a career; the factors contributing to the stigmatization of psychiatry and psychiatrists, depression and demoralization in people with cancer, and physical health in people with severe mental disorders.

The WPA guidances

The WPA is producing a series of guidances on issues of great practical relevance, which are being published in *World Psychiatry*, translated in several languages and posted on the WPA website. The guidances deal with: a) steps, obstacles and mistakes to avoid in the implementation of community mental health care (5); b) how to combat stigmatization of psychiatry and psychiatrists (6); c) mental health and mental health care in migrants; and d) protection and promotion of mental health in children of persons with severe mental disorders.

Moreover, the WPA is developing recommendations about best practices in working with service users and carers (7), and an educational module on protection and promotion of physical health in people with severe mental illness (8).

Further documents of clinical interest are being produced by WPA Scientific Sections (e.g., 9,10) and other WPA components (e.g., 11,12).

The WPA programme on depression in persons with physical diseases

The WPA has started a programme

aiming to raise the awareness of the prevalence and prognostic implications of depression in persons with physical diseases. Three books have been produced, dealing respectively with depression and diabetes, depression and cardiovascular disease, and depression and cancer. Three corresponding sets of slides have been developed, which have been translated in several languages and posted on the WPA website.

Production of WPA press releases

The WPA appointed a press agent who is producing press releases on topics relevant to mental health. A press release dealing with the Iraq Mental Health Survey, published in *World Psychiatry* (13), has resulted in a wide media coverage, including articles in the *Herald Tribune*, the *New York Times* and the *Washington Post*. Press releases focusing on presentations delivered at the Florence WPA Congress have resulted in articles published in several newspapers, including the *Guardian* and the *Daily Telegraph*.

WPA educational workshops

The WPA is implementing a programme of high-quality itinerant educational workshops, covering all continents (e.g., 14). Furthermore, it is co-sponsoring a series of workshops on leadership and professional development of young psychiatrists.

The WPA Early Career Psychiatrists Council

The WPA has recently established an Early Career Psychiatrists Council, whose members have been appointed by its Member Societies (15). Among its various activities, the Council will produce papers/documents on psychiatric education, training in psychotherapy, and what happens to young psychiatrists after training in the various regions of the world.

WPA meetings

The WPA had an extremely successful International Congress in Florence, Italy, in 2009, with more than 9,000 participants. In the past two years, WPA Regional Meetings have been held in Asia, Africa, Latin America and Eastern Europe (16).

The 15th World Congress of Psychiatry, to be held in Buenos Aires, Argentina, from 18 to 22 September 2011, will provide a comprehensive overview of those achievements which have stood the test of time (our heritage) and of the most promising current trends (our future) in the various areas of psychiatric research and practice, with the contribution of the most prominent experts of the various topics. An outstanding scientific programme has been built up. The 24 Keynote Lectures and the 18 Core Symposia have been already finalized. In addition, the programme will include Regular Symposia, Workshops, WPA Section and Zonal Symposia, Oral Communication Sessions, Poster Sessions and Sponsored Events. The guidelines for submission can be found on the website of the Congress (www.wpa-argentina2011.com.ar).

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My experience in Haiti: a brief report

KENT RAVENSCROFT

In 1961-62 I had spent a year in Haiti as a Yale undergraduate anthropologist near Leogane, living with a Vodun priest and his family. I was studying the relationship between child rearing practices, psychosocial development, and spirit possession, trying to understand the dynamics and content of Voodoo possession states.

When the earthquake struck, and I finally reached some of my still living friends, the devastation and death stunned me, my tears leading to determination to go to Haiti to help. I contacted the Washington Psychiatric Society, and they, in turn, put me in touch with the World Psychiatric Association efforts around Haiti. I sent a brief resume, including my past experience in Haiti and rusty Creole. Mario Maj responded quickly, asking for my full resume. I was then contacted by Drs. Lynne Jones and Peter Hughes of the International Medical Corp., who interviewed me and arranged my deployment.

We were one of the first commercial flights into Port-au-Prince, and I was one of the first outside child psychiatrists to set foot on Haiti soil. The chaos on the ground as we emerged from the airport was not so beautiful. The few working streetlights revealed collapsed buildings along both sides as far as the eye

could see, with tent cities interspersed with makeshift lean-to's around standing structures for fear of aftershocks. The streets were thronged with people, some nursing, others hawking goods, many on crutches, several with amputations. We passed the collapsed nursing school where 200 souls had perished in seconds, and then the presidential palace, collapsed and lopsided.

After several days I was sent to Petit Goave, to form a mental health team. Like in military psychiatry, we focused on interrupting stress, anxiety, phobic and depression-based symptoms interfering with normal grieving and self-righting so essential after mass trauma. With scarce resources, limited personnel, little time, and often one chance to help people, we had to be practical, and to link and leverage the work through using and strengthening connection with family, friends and community. We also tried to institute and use brief follow-up techniques.

We also taught a basic psychiatric pharmacy. It had to be very basic, not just because of the experience level of the people we were teaching, but because of the very limited supplies we had. But it was adequate and had the virtue of simplifying the treatment options and teaching requirements. Keeping "stress psychophysiology" in mind, we taught patients portable self-help intervention

techniques, like rebreathing in a sac for hyperventilation and palpitation, along with the Valsalva or the childbirth “bearing down” maneuver. We looked for cycles of stress symptoms, and emphasized intervening just as the cycle began, using the above maneuvers, or positive imaging or progressive relaxation techniques to break the cycle. We used behavior and cognitive-behavioral and desensitization techniques to interrupt anxiety and phobic avoidance states. We used journaling and assigned homework, including re-establishing family connections through assigned group discussions of loss, or things blocking grieving. If certain priests refused to give funerals because the loved one’s body could not be found for burial, we recommended finding other more enlightened priests for this important family-unifying, arrested-grief unblocking ritual. And we used brief follow-up clinics to provide the continuity and support of the clinic itself, and its nurses, and doctors to reward and insure that these things were done and that medicines were taken. We only used a “short medication leash”, doling meds out a week at a time to get people back, and to help the Haitian doctors see the value of continuity and supportive follow-up.

This also allowed them to see if their diagnosis was correct, and to learn to adjust the medications and see if and how they worked.

During the first weeks, we saw more acute cases, and more cases having to do directly with the trauma of the earthquake. But as time went on, there were fewer of the acute cases, and more of the chronic or severe cases. Part of this was just a matter of the time course of such conditions as the earthquake receded into the past. Some of the change was just natural resolution of acute stress and trauma reactions, some reflected the good work of the clinic, both medical and psychosocial. In effect, possibly we were draining the acute cases from the “catchment area”; at the same time, the presence and reputation of the clinic were spreading into the mountains and surrounding sugar plains, drawing in more long-standing chronic cases. I’m sure there are other explanations also.

Once our mental health clinics began to function, we went from just a few cases at first, to the word spreading and lots of cases being referred. We were not primarily doing a service mission, since our aim was to train the doctors and the nurses to do more of the work, and

to get them interested and comfortable with it. To this end, I gave all-day Saturday psychosocial seminars and workshops. I also succeeded in getting an initially reluctant hospital medical staff at the Notre Dame Hospital to begin to refer some cases, first by teaching some of their residents invited to our seminar, and then responding quickly to a pair of very psychotic patients that were quite upsetting to the staff. From this we developed a good mutual relationship. But rising expectations in a situation short of psychiatric manpower is always a problem, which is why it is important to emphasize training the front line Haitian personnel to do the work. They will be staying and we will eventually go home. Finally, though it may seem cost-efficient to centralize these kinds of mental health teaching clinics, and they seem to be a luxury with low patient yield, it is always extremely important to do this kind of work on the front line where the teacher as well as the doctors being taught can feel the same pressure and pain, see what the realities are, and where the most staff of all disciplines can see the work being done and the results happening. It supports everyone in the effort.

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