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“Clinical judgment” and the DSM-5 diagnosis of major depression

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The introduction of “explicit diagnostic criteria” in psychiatry – initially only for research purposes and subsequently, with the DSM-III, also for use in ordinary clinical practice – had a main objective: to overcome the “vagueness and subjectivity inherent in the traditional diagnostic process” (1, p. 85), and in particular the variability in the inclusion and exclusion criteria used by clinicians when summarizing patient data into psychiatric diagnoses (“criterion variance”), which was regarded as the main source of the poor reliability of those diagnoses (2).

From the very beginning, however, there was some ambivalence in mainstream American psychiatry about the constraints that the use of fixed diagnostic criteria would pose to the exercise of clinical judgment. Spitzer et al (3), in an early paper reporting on the development of the DSM-III, acknowledged that “the use of specified criteria does not, of course, exclude clinical judgment”. They qualified this statement by adding that “the proper use of such criteria requires a considerable amount of clinical experience and knowledge of psychopathology”, thus giving the impression that clinical judgment was regarded as just instrumental to the proper use of the explicit diagnostic criteria. However, they also stated that “in any case, the criteria that may be listed in DSM-III would be ‘suggested’ only, and any clinician would be free to use them or ignore them as he saw fit” (3, p. 1191).

Spitzer et al’s prediction that operational criteria would appear in the DSM-III “under the heading ‘suggested criteria’” (3, p. 1190) did not come true. However, the DSM-III introduction emphasized that those criteria were provided as “guides for making each diagnosis”, in order not to leave the clinician “on his or her own in defining the content and boundaries of the diagnostic categories” (4, p. 8). As Spitzer commented later on (5, p. 403), the DSM-III diagnostic criteria were intended “as guides, not as rigid rules”.

This is further clarified in the DSM-IV introduction, where it is stated that explicit diagnostic criteria “are meant to serve as guidelines to be informed by clinical judgment and are not meant to be used in a cookbook fashion” (6, p. xxiii). The example is provided of a diagnosis which is made through the exercise of clinical judgment although the clinical presentation falls just short of meeting the full criteria. So, clinical judgment does not only inform the use of explicit criteria; it may also lead the psychiatrist to “force”, to a limited extent, those criteria if he finds this appropriate.

The text of the DSM-IV also mentions clinical judgment when it comes to the assessment of clinical significance, required for the diagnosis of several disorders: “assessing whether this criterion is met, especially in terms of role function, is an inherently difficult clinical judgment” (6, p. 7). The chair of the DSM-IV Task Force, A. Frances, emphasized that “this appeal to clinical judgment is a reminder to evaluate not only the presence of the symptoms in the criteria set, but also whether they are severe enough to constitute mental disorder”, though he acknowledged that an evaluation of clinical significance by using clinical judgment “contains the seeds of tautology” (7, p. 119).

As pointed out by Spitzer and Wakefield (8), there is no reference in the DSM-IV to the exercise of clinical judgment in the differential diagnosis between depression and the “normal” response to a significant loss. The text is very clear in stating that the diagnosis of major depression should be made whenever the severity, duration and distress/impairment criteria for that condition are met, even if the depressive state is the understandable response to a psychosocial stressor (6, p. 326). The only exception is bereavement: if the depressive state follows the loss of a loved one, the diagnosis of major depression should not be made even if the diagnostic criteria are fulfilled, unless some further elements are present (the symptoms persist for longer than 2 months, or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation). So, in any case – whether depression is related to bereavement or not – explicit criteria are provided, and no mention is made of the use of clinical judgment.

Actually, when J. Wakefield proposed to exclude “normal” responses to psychosocial stressors from the diagnosis of major depression, leaving to the clinician the decision on whether the depressive response was proportional or not to the preceding stressor (8,9), the rebuttal by K. Kendler, a protagonist of mainstream American psychiatry (and of the process of development of the DSM-5), was straightforward: this return to “what at basis will be the subjective criteria proposed by Jaspers in his old idea of ‘understandability’” would represent “more a step backward than forward for our field” (10, pp. 149–150).

This “step backward” has to some extent been made in the DSM-5 (11). A note included in the DSM-5 criteria for major depressive disorder states that “responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or

disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite and weight loss noted in Criterion A, which may resemble a depressive episode”, and that the decision about whether a major depressive episode (or just a normal response to the loss) is present “inevitably requires the exercise of clinical judgment based on the individual’s history and the cultural norms for the expression of distress in the context of loss” (11, p. 161).

This solution adopted by the DSM-5 Task Force should be seen within the context of the debate, taking place in both the scientific and the lay press (e.g., 12,13), about the elimination of the bereavement exclusion in the diagnosis of major depression. This development, announced on the DSM-5 website very early in the process (14), raised concerns about a possible trivialization of the concept of depression and consequently of mental disorder, since a depressive response to the death of a significant loved one is normative in several cultures (e.g., 15). It was also pointed out that, contrary to what reported on the DSM-5 website, the ICD-10 does exclude “bereavement reactions appropriate to the culture of the individual concerned” from the diagnosis of depression, and this exclusion is likely to be kept in the ICD-11 (16). The introduction of a note emphasizing the role of clinical judgment in the differential diagnosis between depression and a “normal” response to a significant loss has thus been regarded as a way to mitigate the consequences of the elimination of the bereavement exclusion and to facilitate the harmonization between the DSM-5 and the ICD-11.

As a matter of fact, this re-emphasis on clinical judgment is likely to be welcome by many clinicians worldwide, being perceived as a remarkable acknowledgement of the limitations of the operational approach, which arguably “does not reflect the complex thinking that underlies decisions in psychiatric practice” (17, p. 182). Indeed, in a large international WPA-World Health Organization (WHO) survey of practicing psychiatrists (18), more than two-thirds of respondents expressed the opinion that, for maximum utility in clinical settings, diagnostic manuals should contain flexible guidance allowing for clinical judgment rather than fixed diagnostic criteria.

So, the DSM-5 note does not come out of the blue, and can be seen as a further step in the articulated (and somewhat ambivalent) approach of mainstream American psychiatry to the issue of clinical judgment.

However, the note leaves several questions open. Is it correct to assume that clinical judgment will have priority over operational criteria in determining whether the response to a significant loss is normal or pathological? In other terms, will it be possible not to make the diagnosis of major depression – in cases in which the severity, duration and distress/impairment criteria are completely fulfilled – because the depressive state appears, on the basis of what the clinician knows of the individual and his/her cultural background, a “normal” response to the loss? Or should we assume that the diagnosis of major depression will have to

be made whenever the full criteria are met, and the exercise of clinical judgment be limited to doubtful or subthreshold cases? This is presently unclear, and this uncertainty is likely to introduce an “interpretation variance” in the application of the DSM-5 criteria for major depression which, added to the variance certainly produced by the exercise of clinical judgment, may substantially reduce the reliability of that diagnosis, already found to be “questionable” ($\kappa=0.20-0.35$) in DSM-5 field trials (19) when using an early version of the criteria not including the note.

Furthermore, what will become of epidemiological research using lay interviewers, who by definition are unable to exercise clinical judgment when exploring whether a person has (or has had in the past) a period of “normal” sadness or a depressive episode? Can we afford using two different definitions of major depression, one for clinical purposes and the other for community epidemiological studies? Should we assume that currently available epidemiological data on the prevalence of major depression are biased, due to the fact that clinical judgment was not exercised in the diagnosis?

On the other hand, the emphasis on the role of clinical judgment in the distinction between depression and “normal” responses to psychosocial stressors is likely to increase the burden of responsibility on clinicians in some contexts (e.g., community settings in areas heavily struck by the economic crisis) in which borderline cases are frequent and traditional differential diagnostic skills have become insufficient (see 20). The second note introduced in the DSM-5 definition of major depression – describing differential features between “normal” grief and depression – may be viewed as an attempt to support professionals in the exercise of clinical judgment. No similar guidance, however, is provided for the distinction between a depressive episode and “normal responses” to other psychosocial stressors, so that the clinician may be left again “on his or her own” (4, p. 8), exposed to several biases (see 21), when making a crucial and often delicate differential diagnosis.

Specifying those aspects of mental disorder which “are at present left to the uncertainties of clinical judgment” represents a challenge for psychiatry, since “reliance upon clinical skills implies that some aspects of psychiatric disorder are impossible at the moment to specify in an explicit manner” (22, p. 978). The term “clinimetrics” (23) has indeed been introduced to indicate “a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy” (17, p. 177). One could argue that the DSM-5 re-emphasis on clinical judgment may represent a stimulus to consider and develop this research line, which may be particularly relevant in the case of depression.

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The DSM-5: classification and criteria changes

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The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) marks the first significant revision of the publication since the DSM-IV in 1994. Changes to the DSM were largely informed by advancements in neuroscience, clinical and public health need, and identified problems with the classification system and criteria put forth in the DSM-IV. Much of the decision-making was also driven by a desire to ensure better alignment with the International Classification of Diseases and its upcoming 11th edition (ICD-11). In this paper, we describe select revisions in the DSM-5, with an emphasis on changes projected to have the greatest clinical impact and those that demonstrate efforts to enhance international compatibility, including integration of cultural context with diagnostic criteria and changes that facilitate DSM-ICD harmonization. It is anticipated that this collaborative spirit between the American Psychiatric Association (APA) and the World Health Organization (WHO) will continue as the DSM-5 is updated further, bringing the field of psychiatry even closer to a singular, cohesive nosology.

Key words: DSM-5, ICD-11, diagnosis, classification

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The Diagnostic and Statistical Manual of Mental Disorders (DSM) provides the standard language by which clinicians, researchers, and public health officials in the United States communicate about mental disorders. The current edition of the DSM, the fifth revision (DSM-5) (1), was published in May 2013, marking the first major overhaul of diagnostic criteria and classification since the DSM-IV in 1994 (2).

Historically, the World Health Organization (WHO) has offered its own system of mental disorder classification in Chapter V of the International Classification of Diseases (ICD), largely used for reimbursement purposes and compiling national and international health statistics. However, following a 1982 international conference on mental disorder classification in Copenhagen (3), there was worldwide agreement for the ICD to adopt more explicit diagnostic criteria to define mental disorders that adhered to the 1980 model of DSM-III (4). What followed was a decade of consultation between the American Psychiatric Association (APA) developers of the DSM-IV and the WHO developers of the ICD-10, that was facilitated by a cooperative agreement between the National Institute of Mental Health and the WHO (5).

Although the official ICD-10 (6) contains only a brief definition of each disorder, the WHO Division of Mental Health obtained an agreement with the APA to publish similar Diagnostic Criteria for Research (7) to those in the DSM-IV, as well as more general Clinical Descriptions and Diagnostic Guidelines (8) as part of the ICD-10 Classification of Mental and Behavioural Disorders. Having similar but separate research criteria resulted in a major international convergence of clinical practice communication and research on mental disorders – although the seemingly slight differences in diagnostic criteria for research did produce some differences in prevalence rates and correlates of mental disorders (9,10). Based on this experience, the latest DSM-5 and ICD-11 development processes offered a further opportunity to not only advance the field in terms of diagnostic utility and validity, but to also increase compatibility with

ICD-11 clinical guidelines and the global psychiatric community at large.

DEVELOPMENT OF THE DSM-5

Details of the research development and the review and approval process for DSM-5 are described elsewhere (1,11–14); but briefly, the DSM-5 was constructed with the goal of addressing limitations in the DSM-IV while integrating the latest scientific and clinical evidence on the empirical basis of psychiatric disorders. The priority was to ensure the best care of patients possible and, in the process, improve usability for clinicians and researchers. Through the contribution of more than 400 experts from 13 countries, representing disciplines of psychiatry, psychology, neurology, pediatrics, primary care, epidemiology, research methodology and statistics, a series of 13 international research conferences was held (2003–2008), in cooperation with the WHO Division of Mental Health and Substance Abuse – with support from a 5-year National Institutes of Health (NIH) cooperative agreement with the American Psychiatric Institute for Research and Education, the research component of the APA (15). The resulting monographs were produced to identify gaps in the then-current nosology and diagnostic criteria, providing a starting point from where members of the DSM-5 Task Force and Work Groups would begin building their proposals for DSM-5.

One of these monographs, jointly produced by the APA and the WHO, was specifically focused on public health considerations in psychiatric diagnosis and classification in the United States and internationally (16), but nearly all of the monographs included explicit discussion of cultural implications of assessment and nosology, including cultural influences on the expression of anxiety and depression (17), the classification of psychotic disorders in Western and non-Western countries (18), and socio-cultural factors relevant to somatic syndromes (19). The additional monographs developed

under this cooperative agreement were used by the specific Work Groups responsible for the relevant disorders covered (20-25).

Membership in the DSM-5 Task Force and Work Groups was determined in part by the range of knowledge needed and also by diversity of representation. Nearly every DSM-5 Work Group included at least one international member. To ensure that cultural factors were included in early revision proposals, a DSM-5 Culture and Gender Study Group was appointed to provide guidelines for the Work Group literature reviews and data analyses that served as the empirical rationale for draft changes. Recommendations to the Work Groups included consideration of possible evidence of racial, ethnic, or gender bias in diagnostic criteria; the emergence of new data about gender or cultural differences, like discrepancies in prevalence or symptom presentations; and the presence of gaps in the literature signaling the need for field trial testing or secondary data analyses. Given his unique knowledge of international diagnostic issues from his leadership of the ICD-10 development, the former Director of WHO's Division of Mental Health, Norman Sartorius, was nominated and served as an international consultant to the DSM-5 Task Force.

Although the subfield of transcultural psychiatry has firmly established the relevance of culture and social context to individual help-seeking behaviors, clinical presentation, and response to treatment, the DSM leadership recognized that these issues would only increase in importance for both clinical care and research applications. As the social environment becomes more strongly linked to epigenetic mechanisms, heritability, disease risk, and resiliency factors, attention to these matters in the DSM-5 text was encouraged. As a result, in developing the chapter outline of text accompanying each diagnostic criteria set, it was determined that culture, as well as age and gender, warranted separate discussion of variances in symptom expression, risk, course, prevalence, and other aspects of diagnosis, where evidence was available. Although not included for every disorder, a substantial proportion of disorders include text that references such findings. This is a notable improvement from the DSM-IV, which more explicitly recognizes cultural context than the DSM-III (4), but relegates culture, gender, and age to sporadic discussion and collectively, rather than as separate topics. Symptom expression among different cultures is also referenced in revisions of certain disorder criteria. For instance, the B criterion for social anxiety disorder (Criterion A in the DSM-IV) has been expanded beyond just fear of embarrassment or humiliation of oneself to now include anxiety symptoms about offending others – a nod to the cultural syndrome *taijin kyofusho* and an acknowledgment of the fact that this presentation might be observed more in individuals from non-Western cultures (particularly Japan and Korea).

DSM-5 CLASSIFICATION

Despite the fact that the DSM is a US classification system for the diagnosis of mental disorders, in conjunction with the

use of official ICD statistical code numbers, international interest in the manual has flourished since the DSM-III was published in 1980. The DSM-5 is based on explicit disorder criteria, which taken together constitute a “nomenclature” of mental disorders, along with an extensive explanatory text that is fully referenced for the first time in the electronic version of this DSM. Although there is a more limited ICD-10 set of criteria for research, the current WHO proposal for ICD-11 will be to provide more general clinical descriptions and guidelines without the adoption of separate research criteria. The intent of joint APA and WHO collaborative efforts to date has been to develop a common research base for the revision of both DSM-5 and ICD-11, through the NIH supported conference meetings and a series of “harmonization meetings”. The developers of the DSM-5 sought to maintain and, where possible, enhance the consistency of DSM and ICD revisions for clinical guidance – a challenging task given that revisions to each were not entirely concurrent (the publication of the ICD-11 is projected for 2015). However, a DSM-ICD harmonization coordinating group was organized early in the development process, under the direction of Steven Hyman, chair of the WHO's International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders and a DSM-5 Task Force member. The group convened by teleconference and at several in-person meetings to facilitate the sharing of information on development processes for each publication and reduce discrepancies between the two. Of note, several of the chairs or members of the ICD revision Working Groups were also DSM-5 Work Group members.

At the outset, it was clear that one of the primary strategies would be to develop a joint approach to organizing the “metastructure” or organizational framework by which disorders are grouped into similar clusters based on shared pathophysiology, genetics, disease risk, and other findings from neuroscience and clinical experience. The DSM-IV's descriptive and phenomenological approach to classification was outdated and, in the framework of research from science that had emerged over the previous two decades, also inaccurate. Likewise, the organizational structure for the ICD-10 was open to a major restructuring, with the expectation that a new numbering system for ICD-11 codes would be initiated to accommodate a major expansion in the number of codes available for all medical disorders.

As a result, a DSM-5 initiative to develop a more valid basis for the organization of a mental disorder classification was rapidly converted into a joint effort of the DSM-5 Task Force and the ICD-10 revision (ICD-11 development) Advisory Committee. Using an expanded set of “validity criteria” from those originally proposed by Robins and Guze in 1970 (26), a series of analyses and papers were developed that were published in an international psychiatric journal (27-34). It was rapidly recognized that the application of such “validators” was much more meaningful for larger groups or disorder spectra than for individual categorical diagnoses. This resulted in a new organizational

Table 1 DSM-5 diagnostic chapters

Neurodevelopmental disorders
Schizophrenia spectrum and other psychotic disorders
Bipolar and related disorders
Depressive disorders
Anxiety disorders
Obsessive-compulsive and related disorders
Trauma- and stressor-related disorders
Dissociative disorders
Somatic symptom and related disorders
Feeding and eating disorders
Elimination disorders
Sleep-wake disorders
Sexual dysfunctions
Gender dysphoria
Disruptive, impulse-control, and conduct disorders
Substance-related and addictive disorders
Neurocognitive disorders
Personality disorders
Paraphilic disorders
Other mental disorders

structure for the DSM-5 and the ICD-11, that is reflected in Table 1. The linear structure of this organization is intended to better reflect the relative strength of relationships between disorder groups, whereas the internal organization of disorder groups is intended to reflect more of a child-adult developmental perspective.

Much of the research from genetics and psychiatry over the past 20 years points to an overlapping genetic liability between psychotic and mood disorders, particularly bipolar disorder, that belie DSM-IV's separation of these as distinctive (35). In the DSM-5 classification, the chapter on schizophrenia and other psychotic disorders is sequenced with that of bipolar and related disorders (which are now separated from unipolar mood disorders), which is then followed by the chapter on depressive disorders. This also is consistent with recent findings from the largest genome-wide study of mental disorders to date (36), which identified shared polymorphisms between select neurodevelopmental disorders (autism spectrum disorder, ASD and attention-deficit/hyperactivity disorder, ADHD), schizophrenia, bipolar disorder, and major depressive disorder. Incidentally, these comprise the first four chapters of the DSM-5.

A similar pattern – grouping based more so on neuroscience and less on symptom expression – also occurs within the diagnostic categories. As noted above, ASD and ADHD are now grouped together in neurodevelopmental disorders, with some of the former DSM-IV “disorders first diagnosed in

infancy, childhood, or adolescence” distributed throughout DSM-5. In the obsessive-compulsive and related disorders chapter are body dysmorphic disorder (previously classified in DSM-IV's “somatoform disorders”) and trichotillomania (hair-pulling disorder), which belonged to DSM-IV's chapter on “impulse-control disorders not elsewhere classified”. For trichotillomania, similarities to obsessive-compulsive disorder and to other body-focused, repetitive pathologies (e.g., excoriation [skin-picking] disorder) in terms of symptom expression, comorbidity, and familial patterns suggested a closer resemblance to the obsessive-compulsive and related disorders than to its DSM-IV neighbors of pathological gambling, intermittent explosive disorder, kleptomania, or pyromania (37). Like the pediatric disorders, DSM-IV's anxiety disorders too are distributed into separate chapters of fear circuitry-based anxiety disorders (e.g., phobias); anxiety disorders related to obsessions and compulsions (e.g., obsessive-compulsive disorder); those that arise from trauma or extreme stress (e.g., post-traumatic stress disorder, PTSD); and those characterized by dissociation (e.g., dissociative amnesia).

Furthermore, the DSM-5 organization also reflects a broader clustering among groups of diagnostic categories, with those that tend to have similar premorbid personality traits and/or co-occur being placed proximally to one another, including neurodevelopmental disorders, schizophrenia and other psychotic disorders. As indicated in the series of “metastructure” papers, bipolar disorder occupies an intermediary position between the schizophrenia and other psychotic disorders and the emotional or internalizing disorders – exhibiting high levels of disinhibition, psychoticism, and negative affectivity (31). The internalizing disorders, with high levels of negative affectivity, include depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma and stressor-related disorders, and dissociative disorders. Somatic disorders also frequently co-occur with the emotional or internalizing disorders, that include somatic symptom and related disorders, feeding and eating disorders, sleep-wake disorders, and sexual dysfunctions. Externalizing disorders include disruptive, impulse control, and conduct disorders, and the substance-related and addictive disorders (38).

INTEGRATION OF DIMENSIONS

Despite the statement in the DSM-IV that “there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders” (2, p. xxxi), the use of strict categorical boundaries has given the impression of psychiatric disorders as unitary, discrete phenomena. Throughout general medicine, conditions are frequently conceptualized on a continuum from “normal” to pathological, without relying on a singular threshold to distinguish the presence or absence of disease, as in serum cholesterol and glycated hemoglobin. In evolving toward a structure that more closely follows this

approach, the DSM-5 includes dimensional aspects of diagnosis along with categories. Although, ultimately, diagnosis is still largely dependent on a “yes or no” decision, use of specifiers, subtypes, severity ratings, and cross-cutting symptom assessments help clinicians better capture gradients of a disorder that might otherwise be hindered by a strict categorical approach.

For instance, the new “with anxious distress” specifier, applied to depressive disorders and bipolar and related disorders, includes symptoms that are not a part of the criteria for most mood disorders (e.g., difficulty concentrating because of worry) but nonetheless may describe a particular variant of mood disorder that causes impairment and/or distress and warrants intervention. It also yields clinically useful information for treatment planning and tracking outcomes that would likely be masked under a residual diagnosis of “not otherwise specified” in the DSM-IV, and may bring greater awareness to clinicians and researchers about the importance of assessing anxiety in the presence of mood symptoms. The DSM-5’s inclusion of severity specifiers contributes important details about the presentation and may be particularly informative for promoting more appropriate treatment, as treatment for certain mild disorders should differ from treatment regimens for moderate-to-severe presentations (39).

Some DSM-IV disorders were combined to form spectra disorders in the DSM-5. The most notable example is ASD, which includes symptoms that characterize previous DSM-IV autism disorder, Asperger’s disorder, child disintegrative disorder, and pervasive developmental disorder NOS. This proposed revision was developed because of the presence of very poor reliability data, that failed to validate their continued separation (40). Although the DSM-5 describes all of these presentations under one rubric, specifiers are provided to account for ASD variations, including specifiers for the presence or absence of intellectual impairment, structural language impairment, co-occurring medical conditions, or loss of established skills. A child previously diagnosed with Asperger’s disorder under the DSM-IV could therefore be diagnosed under the DSM-5 with ASD, with the specifiers “without intellectual impairment” and “without structural language impairment”.

Finally, integration of dimensions in the DSM-5 is encouraged for further study and clinical experience. Such dimensional assessment can be applied *across* disorders through use of cross-cutting quantitative assessments. These patient/informant- and clinician-completed measures prompt clinicians to assess symptom domains relevant to most, if not all, mental disorders, like mood, anxiety, sleep, and cognition, with a second level of measures specified for more in-depth assessment when a particular domain is endorsed. If criteria for a diagnosis are fulfilled, a third level of dimensional assessment can help establish severity. For example, the first level of cross-cutting assessment of a given patient indicates the presence of depressed mood; the clinician then administers the Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress – Depression –

Short Form. The score suggests the possible presence of major depressive disorder, and after a clinical interview that assesses the presence of diagnostic criteria, a depression diagnosis may be given. The Nine-Item Patient Health Questionnaire can then be administered to establish baseline severity, with repeated administration at regular intervals as clinically indicated for monitoring course and treatment response. While the first level cross-cutting measure is provided in the printed DSM-5, all three levels of dimensional measures are provided in the electronic version of the manual for downloading and clinical use without additional charge.

REVISIONS TO DIAGNOSTIC CRITERIA

By and large, there were not sweeping changes in the diagnostic criteria for most disorders. An abbreviated description of the major deviations from the DSM-IV can be found in the Appendix of the manual itself, with a more detailed version online (www.psychiatry.org/dsm5). What follows below is a select summary of revisions.

Combining and splitting DSM-IV disorders

Some disorders were revised by combining criteria from multiple disorders into a single diagnosis, as in instances where there was a lack of data to support their continued separation. The most publically discussed example of this is ASD. As noted previously, the addition of behavioral specifiers indicates variants of ASD that account for the DSM-IV disorders it subsumed. Somatic symptom disorder largely takes the place of somatization disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder, although many individuals previously diagnosed with hypochondriasis will now meet criteria for illness anxiety disorder (new to DSM-5). Substance use disorder is a combination of DSM-IV’s substance abuse and substance dependence, the latter of which was deemed inappropriate due to the pejorative nature of the term *dependence* used to describe normal physiological responses of withdrawal from certain substances and medications. Further, the addition of severity ratings for substance use disorder enables a diagnosis of mild substance use disorder, that will be coded separately (with the ICD code for substance abuse in DSM-IV) from moderate-to-severe levels (coded with the ICD codes previously used for substance dependence).

Alternately, in some instances, a DSM-IV disorder was split into independent disorders under the DSM-5. DSM-IV’s reactive attachment disorder included the subtypes “emotionally withdrawn/inhibited” and “indiscriminately social/disinhibited”. Despite a shared etiology (i.e., lack of a consistent, emotionally supportive caregiving environment), the reactive attachment subtype (reactive attachment disorder) is a manifestation of incomplete, insecure social attachments and is more similar to internalizing disorders, like

major depressive disorder, whereas the social disinhibition subtype (disinhibited social engagement disorder) is evident in children without secure social attachments but is more similar to externalizing disorders, including ADHD. The two subtypes also demonstrate disparities in course and treatment response; thus, each was elevated to a separate full disorder in the DSM-5 (41). Similarly, the DSM-5 now lists the DSM-IV subtypes of breathing-related sleep disorder as independent disorders with separate criteria (i.e., obstructive sleep apnea hypopnea syndrome, central sleep apnea, and sleep-related hypoventilation), which is more consistent with the International Classification of Sleep Disorders, 2nd Edition.

Specifiers and subtypes

Specifiers and subtypes delineate phenomenological variants of a disorder indicative of specific subgroupings, which impact, among other outcomes, on treatment planning and treatment developments. The numbers of specifiers and subtypes in the DSM-5 has been expanded to account for efforts to dimensionalize disorders more so than in the DSM-IV. Within the depressive disorders and bipolar and related disorders, a specifier of “with mixed features” replaces the diagnosis of bipolar I, mixed episode in the DSM-IV, given that subthreshold mixed states of major depressive and manic episodes are much more common and may have specific treatment implications (42,43) but would be excluded from diagnosis by continuing DSM-IV’s requirement that full criteria are met for both syndromes. The “with mixed features” specifier, therefore, now applies to unipolar as well as bipolar conditions. A specifier of “with limited prosocial emotions” is added to conduct disorder for children displaying extreme callousness and negative affectivity, different severity (e.g., more frequent and severe patterns of aggression), and poorer treatment response than children who do not qualify for the specifier (44). Specific treatment interventions have been developed that are more successful with this subgroup.

DSM-5’s major neurocognitive disorder (NCD) is roughly equivalent to DSM-IV’s dementia, although criteria for dementia have been revised to also form a separate and new diagnosis of mild NCD, representing the presence of neurocognitive disturbance that has not risen to the level of severity to warrant significant impairment or disruption in functioning, akin to DSM-IV’s mild cognitive impairment that was included in the Appendix. In addition to the core criteria for major and mild NCD, ten etiological subtypes are now provided, with separate criteria and text for each. Other than the explicit link to specific known etiologies, most of these subtypes’ criteria are largely similar to one another. However, there are important and often subtle differences between these disorders, as greater information on post-mortem laboratory correlations and clinical progression has become available over the past two decades. Many, but not all, of these subtypes were described briefly in the DSM-IV, but the DSM-5 recognizes each separately and in greater detail

to give clinicians more guidance in determining possible etiology.

New disorders

A rigorous review process was established for assessing all proposed revisions to the DSM-5, and those suggesting inclusion of new disorders were among the most stringently assessed. Based on a review of existing evidence from neuroscience, clinical need, and public health significance, a handful of new disorders are included, many of which were elevated from DSM-IV’s chapter on “conditions for further study”. Hoarding disorder addresses the excessive collection of often useless items, including garbage, which frequently results in hazardous living conditions for patients and/or dependents. Disruptive mood dysregulation disorder (DMDD) was proposed in response to a decade-long debate about whether or not chronic irritability in children is a hallmark symptom of pediatric bipolar disorder. With the prevalence of childhood bipolar disorders growing at an alarming rate, the DSM-5 Childhood and Adolescent Disorders Work Group compared evidence from natural history and treatment studies of classic bipolar disorder versus bipolar disorder diagnosed using non-episodic irritability as a criterion, and determined that separate disorders based on episodic versus persistent irritability were justified (45). Therefore, children with extreme behavioral dyscontrol but non-episodic irritability no longer qualify for a diagnosis of bipolar disorder in the DSM-5 and instead would be considered for DMDD. Other notable new disorders (which were elevated from DSM-IV’s appendix) include binge eating disorder, premenstrual dysphoric disorder, restless legs syndrome, and REM sleep behavior disorder.

Removal from DSM-IV

One of the most controversial proposals for the DSM-5 concerned the removal of the bereavement exclusion for major depressive episodes. Under the DSM-IV, individuals exhibiting symptoms of major depressive disorder were excluded from diagnosis if also bereaved within the past 2 months. The intention was to prevent individuals experiencing normal grief reactions to loss of a loved one from being labeled as having a mental disorder. Unfortunately, this also prevented bereaved individuals who were experiencing a major depressive episode from being appropriately diagnosed and treated. It also implied an arbitrary time course to bereavement and failed to recognize that experiences of major loss – including losses other than the death of a loved one, like job loss – can lead to depressive symptoms that needed to be distinguished from those associated with a major depressive disorder. Although symptoms of grief or other losses can mimic those of depression and do not necessarily suggest a mental disorder, for the subset of individuals whose loss *does* lead to a depressive disorder (or for whom a

depressive disorder was already present), appropriate diagnosis and treatment may facilitate recovery. As a result, the bereavement exclusion was lifted and replaced with much more descriptive guidance on the distinction between symptoms characteristic of normal grief and those that are indicative of a clinical disorder (46).

Changes in naming conventions

Revisions in commonly used terminology required an evaluation of the most appropriate terms for describing some mental disorders – an issue of particular concern for consumer-advocate organizations. The term “mental retardation” underwent several draft changes before the name “intellectual disability (intellectual developmental disorder)” was approved. The joint naming convention reflects use of the term “intellectual disability” in US law (47), in professional journals, and by some advocacy organizations, while the parenthetical term maintains language proposed for ICD-11 (48). As described previously, the terms “substance abuse and substance dependence” have been removed and are now replaced jointly by “substance use disorder”. The name of the substance chapter itself (“substance-related and addictive disorders”) was altered to include the term “addictive”, matching a proposed ICD-11 naming convention, which refers to inclusion of gambling disorder as a behavioral syndrome with symptoms and pathophysiology (e.g., reward system activation) largely mirroring those in substance-related disorders. Also in keeping with ICD language, the “not otherwise specified” categories in the DSM-IV have been renamed and reconceptualized as “other specified” and “unspecified” categories in the DSM-5.

CONCLUSIONS

Final determination of DSM-5’s impact must await judgment until after the manual has been in use for some time. Epidemiological studies will aid in detecting changes in prevalence and comorbidities from the DSM-IV, including implementation of cross-national surveys of disorders with high public health relevance worldwide, such as schizophrenia, major depressive disorder, and substance use disorders. The more immediate next steps for the DSM-5 include the development of materials that may assist in its use in primary care settings, adaptation of assessment instruments to DSM-5, and documenting the evidence base for revision decisions in the DSM-5 electronic archives. There will also be further testing and development of the dimensional assessments in the manual, including that of a pediatric version of the internationally used WHO Disability Assessment Schedule 2.0.

By continuing collaboration with the WHO in future editions of the DSM, we can assure a more comparable international statistical classification of mental disorders and move closer to a truly unified nosology and approach to diagnosis.

Such a collaborative effort should assist the 200,000 psychiatrists worldwide to better care for individuals with these life-altering and potentially destructive conditions, and advance a more synergistic and cumulative international research agenda to find the causes and cures for these disorders.

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Future perspectives on the treatment of cognitive deficits and negative symptoms in schizophrenia

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Drug discovery based on classic models for cognitive impairment and negative symptoms of schizophrenia have met with only modest success. Because cognitive impairment and negative symptoms may result from disruptions in neurodevelopment, more complex developmental models that integrate environmental and genetic risk factors are needed. In addition, it has become clear that biochemical pathways involved in schizophrenia form complex, interconnected networks. Points at which risk factors converge, such as brain-derived neurotrophic factor (BDNF) and protein kinase B (AKT), and from which processes involved in neuroplasticity diverge, are of particular interest for pharmacologic interventions. This paper reviews elements of neurodevelopmental models for cognitive deficits and negative symptoms of schizophrenia with the aim of identifying potential targets for interventions.

Key words: Schizophrenia, negative symptoms, cognition, neurodevelopment, neuroplasticity, drug development

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The mechanisms responsible for cognitive impairment and negative symptoms in schizophrenia continue to be poorly understood and, as a result, these highly disabling deficits remain relatively refractory to current treatments. Two decades of efforts at drug discovery based on commonly-employed animal models have been largely disappointing, suggesting that new models for these symptom domains are needed. The large literature on previous clinical trials with existing compounds has been reviewed elsewhere (1,2). This paper outlines current etiologic theories for cognitive deficits and negative symptoms, potential animal models, and novel treatment strategies suggested by these models.

Traditional theories of cognitive deficits and negative symptoms in schizophrenia have focused on single neurotransmitters or receptor subtypes and have employed animal models in which the targeted receptor is dysregulated by pharmacological manipulation or genetic engineering. In contrast, emerging theories posit a neurodevelopmental or neurodegenerative diathesis, involving complex interactions between environmental factors and integrated networks of biochemical pathways. The goal of newer models is to identify points of convergence among the many implicated environmental risk factors, genes, and neurochemical pathways that can account for course and symptoms of the illness. This approach assumes that schizophrenia is a single biologically-valid syndrome, although different paths may lead to the development of the illness. If, instead, schizophrenia represents a heterogeneous collection of brain disorders without overlapping etiologies or mechanisms, then multiple models will be necessary to support a personalized approach to treatment.

RISK FACTORS AND NEUROPATHOLOGICAL FINDINGS

Established risk factors for schizophrenia include *in utero* exposure to infection, stress or malnutrition, as well

as a large number of common alleles that individually contribute very small incremental risk (3). Many of these risk genes are modulators of brain development, are involved in response to infection or inflammation, or are regulators of synaptic connectivity. Within the category of neurotransmitters, genes involved in glutamatergic, GABAergic and dopaminergic transmission are over-represented (4). In addition to genetic and early environmental risk factors, daily use of cannabis in adolescence also appears to increase risk (5,6).

At the time of onset of symptoms in young adulthood, comparisons with healthy controls have identified elevated serum levels and gene expression of inflammatory markers, increased glucocorticoid response to stress, enhanced oxidative load, and decreased activity of brain-derived neurotrophic factor (BDNF) (7,8). These factors have been associated with loss of gray matter, cognitive deficits and negative symptoms (7,9).

An optimal model for drug discovery should also account for cardinal neuropathological findings in schizophrenia, including gray matter loss (10) and loss of inhibitory interneurons expressing GAD67 (an enzyme required for synthesis of GABA) (11), as well as for dysregulated dopamine release (12) and hypofunction of N-methyl-D-aspartate (NMDA) receptors (13). Intact inhibitory input from GABAergic interneurons is believed to be important for the synchronization of neuronal activity and related cognitive processes (14).

Finally, the study of schizophrenia is complicated by medication effects, which may be both protective and toxic. For example, early treatment of psychosis with antipsychotics has been found to improve functional outcomes (15); however, treatment of nonhuman primates for roughly 18 months (16,17) and rats for 8 weeks (18) with antipsychotics has been shown to result in decreased brain volume with loss of neuropil and cognitive deficits believed to reflect frontal D1 receptor down-regulation (19).

NEUROINFLAMMATION

Exposure to inflammation during early development has emerged as an important component of neurodevelopmental models for schizophrenia. Exposure to acute maternal infection *in utero* is a well-established risk factor for schizophrenia; for example, maternal influenza infection increased risk in offspring 3–8 fold in prospective studies with serologic documentation of infection (20,21). Elevated levels of the inflammatory cytokine, interleukin-8 (IL-8), in second trimester blood samples from pregnant women doubled risk for schizophrenia in offspring (22). While early infection is a far greater contributor to risk than any single susceptibility gene, it has been estimated that 48% of schizophrenia susceptibility genes are directly involved in response to infection (23). Genes comprising the HLA region in particular are strongly implicated (3). Elevated levels of neuroinflammation represented by microglial activation have been demonstrated in post-mortem schizophrenia brain (24,25) and, by positron emission topography (PET) imaging studies, in early and chronic schizophrenia subjects (26–28). A recent meta-analysis clarified that peripheral cytokine elevation is most apparent in medication naïve patients and during periods of relapse (29).

Animal models that simulate maternal viral infection during pregnancy have unique ecological validity, since they duplicate a process known to increase risk for schizophrenia in humans. The injection of polyinosinic:polycytidylic acid (PolyI:C) stimulates maternal release of inflammatory cytokines, mimicking response to viral infection. Offspring exhibit many characteristics similar to the neurodevelopmental abnormalities found in schizophrenia (30). These include increased volume of lateral ventricles, decreased temporal lobe volume, abnormal prepulse inhibition, increased behavioral sensitivity to dopamine agonists and impairments in memory. These deficits are not observed until young adulthood, roughly the age at which humans first exhibit symptoms of schizophrenia (30).

NEUROINFLAMMATION, OXIDATIVE STRESS, AND EXCITOTOXICITY

From a therapeutic perspective, it is important to establish the mechanisms by which early exposure to inflammation may produce neurobehavioral effects suggestive of schizophrenia in adulthood. Equally important is the determination of whether these consequences of early exposure to inflammation are potentially reversible. *In utero* exposure to PolyI:C is associated with decreased density of D1 and D2 receptors in the frontal cortex and of NMDA receptors in the hippocampus (30). In the hippocampus, PolyI:C administration also was shown to lower concentrations of protein kinase B (AKT) and decrease axonal diameter, myelination, and markers of neurogenesis in

adolescent offspring (31,32). The changes in AKT, axonal size and myelination returned to normal in adulthood (31), possibly representing a specific period of vulnerability during adolescence. Jukel et al (33) also examined the brains of adolescent offspring exposed to PolyI:C *in utero* and found increased numbers of abnormally activated microglia in the hippocampus and striatum, suggesting that, following exposure to inflammation *in utero*, an active inflammatory state persists later in life at the time of vulnerability for onset of symptoms. The potential reversibility of some of the effects of early neuroinflammation was demonstrated by the administration of clozapine during adolescence (postnatal days 34–47) in PolyI:C-exposed mice, which prevented the development of structural and behavioral changes in adulthood (34).

Neuroinflammation in adulthood may be particularly relevant to cognitive impairment and negative symptoms in schizophrenia, since these deficits have been associated with elevation of C-reactive protein (CRP), a marker for inflammation, in medication-naïve and chronic schizophrenia samples (35–37). Serological evidence of infection with herpes simplex virus has also been associated with impaired cognitive function and gray matter loss in individuals with schizophrenia (38,39).

Inflammatory effects on brain development may be mediated in part by a cytokine-induced increase in oxidative stress and reduction in BDNF release. In both developing and adult brain, administration of the inflammatory cytokine, IL-6, has been shown to increase oxidative stress and inhibit the expression of GABA in inhibitory interneurons (40), consistent with findings in post-mortem schizophrenia brain (11). Maturation of inhibitory circuits continues through adolescence, as reflected in changes in brain oscillations with increased gamma rhythms and improved capacity for executive function (41). Inflammation-associated oxidative stress could disrupt this process in late adolescence, producing cognitive deficits that might be reversible with targeted anti-inflammatory or anti-oxidant therapy early in the course of illness. In chronic schizophrenia patients, elevated markers for oxidative stress have been associated with negative symptoms (42).

An additional consequence of early exposure to neuroinflammation may be a compensatory, protective down-regulation of factors that promote neurotoxicity in the presence of neuroinflammation. For example, the NR2C subunit of the NMDA receptor is down-regulated following exposure to the inflammatory cytokine, IL-6 (43). This down-regulation of the NR2C subunit is associated with a marked reduction in neurotoxicity in response to activation of the receptor by NMDA (43). The expression of the NR2C subunit was found to be selectively decreased post-mortem in the frontal cortex of schizophrenia patients (44). Timing of inflammatory exposure is an important determinant of neurodevelopmental impact; for example, exposure to PolyI:C in adolescence produced elevated expression of NMDA NR2A subunits, along with lowered

seizure threshold and memory deficits in rats; these effects of neuroinflammation in adolescence were reversed by minocycline (45).

BDNF AND AKT

Both inflammation and environmental stress reduce the release of activated BDNF from axons. The effect of environmental stress on BDNF is mediated by cortisol secretion acting on glucocorticoid receptors. BDNF facilitates neuroplasticity by the stimulation of dendritic growth, synapse formation and neurogenesis (46). The BDNF Val66Met genotype is associated with reduced BDNF activity and has been linked to diminished synaptic plasticity in the hippocampus (47). BDNF activity declines with age; this decline has been linked to the reduction in hippocampal volume and cognitive decline in the elderly (48,49). In first episode schizophrenia subjects, BDNF genotype significantly predicted longitudinal change in hippocampal volume (50) and BDNF gene expression predicted cross-sectional volume (7).

BDNF in turn activates (phosphorylates) AKT, a second point of convergence of several risk factors, since AKT activation is also influenced by dopamine D2 receptors, cannabinoid CR1 receptors and metabolic status (51). It has recently been shown that AKT genotype predicts the likelihood that cannabis abusers will develop a psychotic disorder (5). Like BDNF, AKT modulates neurogenesis, neuronal survival, dendritic growth and, in addition, selectively phosphorylates NMDA receptors (NR1 and NR2C subunits) and GABA receptors (A beta2 subunits). While the role of hippocampal neurogenesis in humans remains uncertain, BDNF and AKT may play a role in gray matter volume loss, decreased neuropil, and associated negative symptoms and cognitive deficits. Deficits in neuroplasticity have been found on several cognitive and electrophysiological measures in schizophrenia (52,53).

A NEURODEVELOPMENTAL MODEL

In summary, a complex interplay between environmental factors of inflammation and stress seems to interact with a large number of genes to shift biochemical pathways in the brain from states of neuroplasticity and neurogenesis in the presence of a “benign” environment to a defensive state with reduced neuroplasticity and decreased vulnerability to neurotoxicity under conditions of environmental stress. Dysregulation of this process may underlie the neurodevelopmental origins and expression of several psychiatric conditions, including schizophrenia.

While many parallel and interactive pathways contribute to this regulation of brain equilibrium, the modulation of BDNF by inflammation and by stress-induced elevation of glucocorticoids represents one important point of convergence. Similar to BDNF, AKT functions like a “thermostat”,

since its level of activity represents a summation of BDNF levels, D2 receptor activation and activity at the cannabinoid receptor. BDNF and AKT both represent a point of convergence of risk factors for schizophrenia and a point of divergence for factors controlling neuroplastic and NMDA/GABAergic regulation that may contribute to phenotypic expression of cognitive and negative symptoms of schizophrenia.

Many schizophrenia genes are involved in pathways involved in these diverse networks, consistent with an “epistatic” combination of multiple genetic factors in determining risk. In addition, the functional state of inflammatory and glucocorticoid pathways is influenced by early environmental exposure, thereby contributing an epigenetic component to this model. Given the multiple developmental, genetic and environmental factors interacting in a highly complex and interactive network, the development of therapeutic targets for cognitive impairment and negative symptoms of schizophrenia involves identification of “druggable” factors that can be manipulated to correct pathological imbalances at key developmental stages of the disorder. Non-pharmacologic approaches are also quite promising, such as cognitive behavioral therapy (CBT) to reduce stress, and cognitive remediation, repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to stimulate neuroplasticity and enhance brain functioning in schizophrenia.

THERAPEUTIC IMPLICATIONS

Studies of offspring exposed to PolyI:C *in utero* predict that neurodevelopmental abnormalities associated with schizophrenia risk factors may be reversible during adolescence or early adulthood. This model might be used to test potential interventions during the prodromal phase of schizophrenia. Whether interventions targeting factors, such as inflammation and oxidative stress, believed to influence neurodevelopment can be effective later in the course of the illness is unknown, but preliminary findings suggest that efficacy tends to be less robust with increasing chronicity.

Anti-inflammatory agents

One example of a therapy based on this neurodevelopmental approach is the use of omega 3 fatty acids (fish oil) in the schizophrenia prodromal phase. Omega 3 fatty acids possess potent anti-inflammatory activity (54). Fish oil is an ideal agent for anti-inflammatory prophylaxis, since it is well tolerated and quite benign. In a placebo-controlled 12-week trial in 81 ultra-high risk (prodromal) subjects, fish oil significantly reduced the rate of conversion to psychosis over a 52 week period (55). A large, multi-center trial is currently in progress to attempt to replicate this finding. Trials of omega 3 fatty acids in chronic

patients have not produced consistent results, however (56).

Several placebo-controlled add-on trials of standard anti-inflammatory agents, including COX-2 inhibitors (57,58) and aspirin (59), have demonstrated efficacy in schizophrenia for positive and negative symptoms, but not for cognitive deficits. A recent meta-analysis of studies of non-steroidal anti-inflammatory agents revealed a moderate therapeutic effect size of 0.4 for total symptom response (60). In general, response to anti-inflammatory agents has been observed most consistently in individuals within the first five years of illness onset (61). In a placebo-controlled study of add-on aspirin treatment, peripheral levels of inflammatory cytokines predicted response of symptoms (59). The use of inflammatory biomarkers to identify patients most likely to benefit and the targeting of early stage patients are two strategies that may improve outcomes in future studies.

Minocycline is also of interest, given that it is well tolerated and has been shown in mice to decrease expression of activated microglia (62) and release of inflammatory cytokines (63). Minocycline significantly improved negative symptoms at 6 months compared to placebo in two studies of early-stage schizophrenia subjects (64,65). Working memory also improved in one of these studies (65).

Anti-oxidants

Strategies to reduce oxidative stress are also promising (66). The best-studied agent is N-acetyl-cysteine (NAC), the glutathione precursor, which is a potent antioxidant and also increases glutamate levels by competing for the cysteine/glutamate transporter (67). In a placebo-controlled trial, NAC significantly improved negative symptoms in chronic schizophrenia patients, producing a moderate effect size that was detected after 6 months but not at 2 months (68). In a 60-day placebo-controlled cross-over study in chronic schizophrenia patients, NAC significantly improved response to mismatch negativity (an evoked potential test of auditory discrimination) (69) and resting-state EEG synchronization (70). Additional studies are needed in early course subjects, ideally with biomarkers for oxidative load. Studies of NAC in early-stage psychosis are currently in progress.

BDNF

Another therapeutic approach suggested by the neurodevelopmental model involves the targeting of BDNF. As described previously, environmental factors such as stress and inflammation that lower BDNF expression and a Met66Val genotype that results in diminished BDNF activity are both associated with loss of brain volume in schizophrenia. Antidepressants appear to act primarily via release of BDNF; this mechanism may account for both antidepressant effects and protection against hippocampal volume loss (71–73). Release of BDNF by antidepressants has been shown to increase neurogenesis and survival of immature

neurons in rodent dentate gyrus (74,75). Whereas antidepressants enhance BDNF activity in hippocampus, first generation antipsychotics may decrease BDNF expression (76) and second generation antipsychotics either have no effect (77) or may increase it (78). Effects of selective serotonin reuptake inhibitors (SSRIs) on BDNF have been shown to decrease with age in humans and were diminished in mice with the Val66Met BDNF genotype (79). In chronic patients, antidepressant treatment has been associated with improvement of negative symptoms (80,81). In an open trial, Cornblatt et al (82) found that antidepressant treatment prevented conversion from prodrome to psychosis, whereas treatment with second generation antipsychotics did not. A multi-center placebo-controlled trial (DECIFER) is currently in progress to evaluate the effects of a 12-month trial of an SSRI in first-episode schizophrenia.

Physical exercise and hippocampal-dependent cognitive exercises also enhance neurogenesis in rodent models by stimulating BDNF release (83). A recent controlled study in which schizophrenia subjects exercised on a stationary bicycle found improvement in memory and increased hippocampal volume (84). Cognitive remediation has been reported to elevate peripheral BDNF levels, although this increase did not correlate with cognitive benefit (85).

Folate

Another treatment suggested by the neurodevelopmental model is folate supplementation. Folate deficiency results in elevation of homocysteine, which at high concentrations may be neurotoxic via oxidative stress and activity at NMDA receptors (86,87). Maternal folate deficiency and elevated homocysteine concentrations during pregnancy have been identified as risk factors for schizophrenia (88,89). Risk for schizophrenia is also increased in individuals with a genotype of methylenetetrahydrofolate reductase (MTHFR) associated with reduced availability of activated folate (90), and in offspring of mothers with a similar genotype (91). In chronic patients, MTHFR genotype, in combination with blood folate concentration and other genes related to folate absorption and activation, has been found to predict negative symptoms and cognitive deficits (92–94). In a placebo-controlled pilot trial, MTHFR genotype predicted improvement of negative symptom severity in response to folate supplementation (95). In a large multi-center study, MTHFR and related genes predicted negative symptom response to supplementation with folate and vitamin B12 (96). Cognitive deficits did not improve, however. In a third placebo-controlled study, folate and B12 supplementation improved positive and negative symptoms in schizophrenia subjects with elevated homocysteine levels at baseline (97).

The mechanism by which folate improves symptoms and enhances neuroplasticity is not clear, since it serves multiple roles in brain development and function, including synthesis of neurotransmitters, maintenance of DNA, modulation of prefrontal dopamine concentrations by

methylation of catechol-O-methyl-transferase (COMT), and modulation of gene expression and neurogenesis (98). The potential therapeutic value of folate supplementation in early-phase schizophrenia has not yet been studied.

Other targets

Whereas treatments designed to counter inflammatory response, oxidative stress, glucocorticoid elevation and folate deficiency may be most effective as preventive measures or early in the course of illness, treatment of cognitive impairment and negative symptoms in chronic patients may require a focus on targets that are ultimately impacted by these factors and which are more proximal to symptomatic expression of the illness. Most clearly implicated are dysregulation of dopamine (D1) and glutamate (NMDA) receptors. These factors influence many relevant brain functions, including neuroplasticity, attention, and cortical synchronization. Both D1 receptors and NMDA receptors, along with BDNF, are key elements of neuroplasticity as described by Kandel (99) in his classic studies of the molecular biology of memory. If schizophrenia involves aberrant neurodevelopmental processes that produce defects in connectivity, approaches that facilitate neuroplasticity may be the most effective to improve cognitive efficiency. Non-pharmacologic approaches, such as cognitive remediation and tDCS, may also facilitate neuroplasticity.

As it becomes increasingly clear that neurochemical pathways in the brain are extremely complex and interconnected, many other potential targets may exist that can alter the overall function of these networks in beneficial ways. Prediction of such effects has proven very difficult, however, although network analysis may facilitate this process in the future (100). The reader is referred to other reviews providing descriptions of the rationale and clinical trial results for various additional targets, including GABAergic, cholinergic and serotonergic receptors (1,2).

Dopamine D1 receptors

Dopamine D1 receptor activity in the prefrontal cortex is crucial for attention and working memory. Dopamine levels are determined in part by ventral tegmental dopamine neuronal firing (regulated by D2 and NMDA receptors) and by the rate of dopamine metabolism by COMT. Optimal prefrontal functioning requires precise control of dopamine concentrations – too little or too much may both reduce cognitive functioning.

Several approaches have been suggested to enhance dopaminergic function. In monkeys, Castner et al (19,101) demonstrated that chronic treatment with antipsychotic drugs produced a gradual impairment of cognitive functioning, attributable to a compensatory down-regulation of frontal D1 receptors. Intermittent treatment with a psychostimulant was found to “sensitize” dopamine transmission and

improve cognitive functioning (19,101). In individuals with schizophrenia, addition of psychostimulants to antipsychotic medication may enhance frontal D1 receptor activation, while potential psychotomimetic effects of dopamine release are attenuated by D2 blockade. Single dose administration of amphetamine was shown to improve memory in medicated schizophrenia subjects and in healthy controls (102). The COMT inhibitor, tolcapone, has been shown to improve cognitive function in healthy subjects, predicted by COMT genotype (103), and may represent a potential therapeutic approach in schizophrenia. Finally, direct agonists for D1 receptors are under development, but clinical trials have been complicated by problems with tolerability (104).

NMDA receptors

For over two decades, glutamate transmission has been a focus for drug discovery in schizophrenia (105). NMDA receptors in particular have been implicated, since they are involved in many relevant processes: those on ventral tegmental neurons modulate dopamine release, those on inhibitory interneurons modulate brain oscillations, and those on hippocampal and prefrontal neurons modulate neuroplasticity and memory. As has been noted, many of the genes that have been linked to schizophrenia are involved in glutamate signaling. Furthermore, density of certain NMDA receptor subunits has been found to be decreased in the prefrontal cortex of patients with schizophrenia (44). Most impressively, NMDA receptor blockade produces manifestations similar to the psychotic symptoms, negative symptoms and memory deficits characteristic of schizophrenia (106).

In early studies, agonists at the glycine site of the NMDA receptor (glycine, D-serine and D-alanine) and the partial agonist D-cycloserine (DCS), added to first generation antipsychotics, improved negative symptoms and, in some trials, positive symptoms and cognition (107). However, when added to second generation antipsychotics in the CONSIST trial, glycine and DCS produced no effect (108). While the explanation for this failure to replicate results from earlier studies is not clear, it is possible that second generation antipsychotics may enhance glutamate release via 5HT₂ antagonism and hence may mask therapeutic effects of glycine site agonists (109). When added to clozapine, DCS worsened negative symptoms, suggesting that clozapine may act, in part, via effects on NMDA receptors (110,111).

Another approach to facilitate activity at the glycine site of the NMDA receptor is the inhibition of glycine reuptake. Sarcosine, an endogenous precursor of glycine which competes with glycine for reuptake, was shown in a preliminary study to improve negative symptoms (112). The selective glycine transporter 1 (GlyT1) inhibitor, RG1678 (bitopertin), produced a modest improvement in negative symptoms in an initial multi-center clinical trial and is currently on registration trials as potentially the first agent to gain Food and Drug Administration approval for negative symptoms.

High doses of D-serine are being investigated; in an unblinded study, high dose D-serine improved cognitive function (113). D-serine concentrations can also be increased by inhibition of D-aminoacid oxidase (DAO); this approach is also currently under study.

D-cycloserine may offer additional therapeutic options as a highly potent agonist at NMDA receptors containing the NR2C subunit (114,115). NMDA receptors containing this subunit have been linked to memory and thalamic oscillations (116,117), although activation by D-cycloserine produces rapid tolerance for memory consolidation (118). Recent work suggests that intermittent (once-weekly) dosing with D-cycloserine may produce persistent improvement of negative symptoms in addition to memory enhancement (119). When combined with CBT in a placebo-controlled cross-over pilot trial, a single dose of D-cycloserine was associated with a large improvement in delusion severity in subjects who received the drug with the first session (120). D-cycloserine has demonstrated efficacy as a facilitator of CBT for anxiety disorders (121) and, by enhancing neuroplasticity and memory, may have a role in facilitating psychosocial interventions in schizophrenia.

CONCLUSIONS

In summary, classical models for drug discovery have been only modestly successful in identifying therapeutic agents for cognitive impairment and negative symptoms of schizophrenia. The evidence from epidemiological and genetic studies suggests that schizophrenia is a complex neurodevelopmental disorder for which modulation of a single neurotransmitter is unlikely to produce full symptomatic response. Analysis of the many environmental and genetic risk factors may identify points of convergence that may contribute to disease expression, such as neuroinflammation, stress, and folate deficiency. These environmental risk factors, in combination with genetic vulnerability, may disrupt normal brain development and produce cognitive deficits and negative symptoms by effects on neuroplasticity, apoptosis and neurogenesis, in part mediated by reduced activity of BDNF and AKT.

Interventions targeting these factors may be effective early in the course of illness, including use of anti-inflammatory agents, anti-oxidants, antidepressants and CBT. In chronic patients, facilitation of neuroplasticity via cognitive remediation, rTMS and tDCS, perhaps combined with agents acting via NMDA and D1 receptors, are also promising approaches for the treatment of cognitive deficits and negative symptoms.

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Cognitive and social factors influencing clinical judgment in psychiatric practice

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M. Gladwell, in his popular book *Blink: The Power of Thinking Without Thinking*, stated that the “important task of this book is to convince you that our snap judgments and first impressions can be educated and controlled. . . Just as we can teach ourselves to think logically and deliberately, we can also teach ourselves to make better snap judgments” (1, p. 15). To help determine if psychiatrists should make snap judgments and rely on first impressions, one can turn to research on cognitive and social factors that influence clinical judgment (2).

COGNITIVE FACTORS

A number of studies have described how mental health professionals, including psychiatrists, make judgments. Results will be described for three of these factors: the primacy effect, cognitive heuristics, and confirmatory hypothesis testing.

Primacy effect

Gladwell (1) encouraged people to make snap judgments. Surprisingly, to a large degree, people already do this. In everyday life, people often make judgments about other people very quickly. This phenomenon is called the primacy effect, and it is also true of clinical practice. For example, as described by Kendell, “accurate diagnoses can often be reached very early in an interview, even within the first two minutes, and after five or ten minutes further expenditure of time is subject to a law of rapidly diminishing returns” (3, p. 444).

Making judgments quickly saves time and energy. And judgments made quickly may frequently be correct. Still, on a personal level, we might be hurt if someone formed a negative impression of us while barely getting to know us. And when clients seek help, they might object if they learn that the psychiatrist very quickly formed impressions that were unlikely to change.

Cognitive heuristics

Cognitive heuristics are simple rules for making judgments (4). They describe cognitive processes that allow us to efficiently process vast amounts of information, but they can cause us to make characteristic types of mistakes. As with research on the primacy effect, studies on cognitive heuristics suggest that people, including psychiatrists, will often make

judgments quickly. One of the cognitive heuristics, the affect heuristic, will be discussed here.

The affect heuristic refers to the effect of emotions on judgments. The impact of the affect heuristic may be especially pronounced when a judgment is based on first impressions or intuition. The affect heuristic has grown in importance for the understanding of judgments made in everyday life, but its role in the cognitive processes of mental health professionals has rarely been studied, perhaps because the effect of emotions on judgments can lie outside of our awareness.

Gladwell (1) argued that people can make better snap judgments by trusting their emotions. For example, he described how several art experts had a strong negative emotional response upon seeing a statue that had been bought by the Getty Museum (a response that Gladwell labeled “intuitive repulsion”). It later became clear that the experts were right to attend to their emotional reactions as the statue was found to be a forgery.

Can psychiatrists be trained to make better judgments by relying on their emotions? Everyone, including psychiatrists, already makes judgments and decisions that are based, in part, on their feelings. A training intervention for helping psychiatrists make better judgments by changing the way they rely on their emotions has not yet been described and evaluated.

Research on clinical judgment supports strategies that can run counter to attending to one’s emotions to guide judgments. People often become overconfident and, to counter their overconfidence, they are not told to attend to their emotions. Rather, they are typically advised to: a) consider more alternatives, b) ask more questions, and c) adhere to criteria when making diagnoses (5).

Confirmatory hypothesis testing

Confirmatory hypothesis testing refers to seeking and remembering information that can confirm, but not refute, a hypothesis. Although it does not describe how snap judgments are made (or how initial hypotheses are generated), it does help to explain Kendell’s finding that “accurate diagnoses can often be reached very early in an interview, even within the first two minutes, and after five or ten minutes further expenditure of time is subject to a law of rapidly diminishing returns” (3, p. 444). One should not encourage psychiatrists to make snap judgments if they tend to not seek or remember information that could refute those judgments.

SOCIAL FACTORS

Several of the most famous studies on clinical judgment have described how social factors affect it. Social factors include client characteristics (e.g., race) and context effects (e.g., clinical setting).

Client characteristics

Judgments and decisions made by psychiatrists are said to be biased when their accuracy varies as a function of group membership. For example, if diagnoses of schizophrenia are more accurate for White than for Black clients, then race bias is said to be present. Bias may not be present when a diagnosis is made more frequently for one group than another, because prevalence rates for the disorder may differ across groups. Biases, including gender, race, and social class biases, will not be less likely to occur if psychiatrists rely on their emotions to make snap judgments. To illustrate this point, the effect of race bias on clinical judgments will be briefly described.

Research on clinical judgment suggests that race bias is more pervasive than gender bias and social class bias (2,6). This is an especially important area of research in psychiatry, particularly with regard to the use of psychotropic medication. The methodology of the research has been sound, with race bias occurring for judgments made in real-life settings.

Race bias is of gravest concern for the treatment of psychotic patients. Results from one study (7) demonstrate that it is due in part to a failure to collect information that would lead clinicians to consider additional hypotheses about their clients. This is quite different from arguing that clinicians should rely on their first impressions and make snap judgments. In this study, Black patients, compared to other patients, received a significantly larger number of psychotropic medicines, a significantly larger number of injections of antipsychotic medicine, and a significantly larger number of doses of antipsychotic medication. These differences in treatment were obtained even though the research investigators controlled for the following factors: a) level of functioning, b) presence of a psychotic disorder, c) danger to self or others or severely disabled, d) history of mental disorder, and e) whether physical restraints were used. Psychiatrists spent significantly less time with the Black patients than the other patients. When they spent more time evaluating the Black patients, the dosage of antipsychotic medicine decreased.

Context effects

Setting has a strong influence on treatment. For example, in a study of 338 patients treated for major depressive disorder (8), clinical setting was a better predictor of treatment than severity of depression. Large differences in the amount and type of treatment (medicine, electroconvulsive therapy, psychotherapy) were found across five medical centers.

Even admission to a hospital depends in part on context. When 96 clinicians made 432 different emergency room assessments, the strongest predictor of both admission and involuntary commitment was whether the individual was self-referred, accompanied by the police, or accompanied by a family member or friend (9). As noted by the authors, “the presence of violence against others or suicide appear to have considerable influence, but even these do not appear as strong as who accompanies the patient” (9, p. 50). For example, when individuals were accompanied by the police, they were almost always hospitalized.

IMPLICATIONS FOR CLINICAL PRACTICE

Can we teach ourselves to make better snap judgments, as hoped for by Gladwell? In the clinical judgment literature, there is no evidence that this can be done. Gladwell argued that one can become better at making snap judgments by attending to one’s emotions (which clinicians already do) and by gaining a variety of experiences. For example, Gladwell recounted how an expert recognized that a statue was a forgery because it did not resemble long-buried statuary that the expert had unearthed. However, one of the most interesting findings on clinical judgment is that it can be very difficult to learn from clinical experience (10), in part because clinicians often do not receive accurate feedback on whether their judgments are right or wrong, but also because clinicians are not always aware of how social factors affect their judgments, and because cognitive processes are imperfect.

Forming sudden impressions and being influenced by one’s emotions are an ingrained part of the process of how we make judgments. This is unlikely to change. Nor should it change. But after quickly forming an impression of a client, clinicians should collect additional information and consider alternative hypotheses. Our goal should be to think logically and deliberately – not to become better at making snap judgments.

Disclaimer

The views expressed in this article are those of the author and are not the official policy of the Department of Defense or the United States Air Force.

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The past, present and future of psychiatric diagnosis

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Modern descriptive psychiatry was born two centuries ago in the classification of Pinel, was later systematized in the textbook of Kraepelin, and was then expanded by Freud to include outpatient presentations previously seen by neurologists. Brain science also flourished in the second half of the 19th century and has enjoyed a second revolutionary advance during the past thirty years. Unfortunately, however, the attempt to explain psychopathology using the remarkable findings of neuroscience has thus far had no impact on psychiatric diagnosis or treatment. The crucial translation from basic science to clinical practice is necessarily even more difficult in psychiatry than in the rest of medicine, because the human brain is the most complicated thing in the known universe and reveals its secrets slowly and in small packets.

Psychiatric diagnosis must therefore still rely exclusively on fallible subjective judgments, not on objective biological tests. In the not too distant future, we will finally have laboratory methods for diagnosing Alzheimer's disease, but there is no pipeline of promising tests for any of the other mental disorders. Biological findings, however exciting, have never been robust enough to become test-worthy, because the within-group variability always drowns out the between-group differences. It appears certain that we will be stuck with descriptive psychiatry far into the distant future.

There have been two crises in confidence in descriptive psychiatry: the first was in the early 1970s, the second is occurring right now with the publication of DSM-5. The earlier crisis was occasioned by two highly publicized studies that exposed the inaccuracy of psychiatric diagnosis and threw into serious question the credibility of psychiatric treatment. A landmark study proved that British and US psychiatrists came to radically different diagnostic conclusions when viewing videotapes of the same patient (1). And Rosenhan (2) exploded a bombshell when his graduate students were kept in psychiatric hospitals for extended stays after claiming to hear voices, despite the fact that they behaved completely normally once they were admitted. Was psychiatry entitled to a place among medical specialties if its diagnoses were so random and its treatments so nonspecific, especially when the other specialties were just then becoming increasingly scientific?

Psychiatry's response was dramatic and effective. The DSM-III, published in 1980, featured detailed definitions of mental disorders that, when used properly, achieved reliabilities equivalent to much of medical diagnosis. The DSM-III soon stimulated its own revolution, quickly transforming psychiatry from research stepchild to research

darling; in most medical schools, the department of psychiatry now ranks behind only internal medicine in research funding.

But psychiatric diagnosis is now facing another serious crisis of confidence, this time caused by diagnostic inflation. The elastic boundaries of psychiatry have been steadily expanding, because there is no bright line separating the worried well from the mildly mentally disordered.

The DSMs have introduced many new diagnoses that were no more than severe variants of normal behavior. Drug companies then flexed their powerful marketing muscle to sell psychiatric diagnoses by convincing potential patients and prescribers that expectable life problems were really mental disorders caused by a chemical imbalance and easily curable with an expensive pill.

We are now in the midst of several market-driven diagnostic fads: attention-deficit/hyperactivity disorder (ADHD) has tripled in rates in the past twenty years; bipolar disorder has doubled overall, with childhood diagnosis increasing forty-fold; and rates of autistic disorder have increased by more than twenty-fold (3). In the US, the yearly prevalence of a mental disorder is reported at 20–25%, with a 50% lifetime rate (4), and Europe is not far behind (5). A prospective study of young adults in New Zealand has reported much higher rates (6) and another of teenagers in the US found an astounding cumulative 83% rate of mental disorders by age 21 (7).

The expanding concept of mental disorder brings with it unfortunate unintended consequences. Only about 5% of the general population has a severe mental disorder; the additional 15–20% have milder and/or more temporary conditions that are placebo responsive and often difficult to distinguish from the expectable problems of everyday life. Yet an amazing 20% of the US population now takes a psychotropic drug (8) and psychotropic drugs are star revenue producers – in the US alone \$18 billion/year for antipsychotics, \$12 billion for antidepressants, and \$8 billion for ADHD drugs (9). And 80% of psychotropic drugs are prescribed by primary care physicians with little training and insufficient time to make an accurate diagnosis (10). There are now more overdoses and deaths from prescribed drugs than from street drugs.

And the investments in psychiatry are badly misallocated, with excessive diagnosis and treatment for many mildly ill or essentially normal people (who may be more harmed than helped by it), and relative neglect of those with clear psychiatric illness (whose access to care in the US has been sharply reduced by slashed mental health budgets) (11). It is no accident that only one third of

people with severe depression get any mental health care or that a large percentage of the swollen US prison population consists of psychiatric patients with no place else to go (12). A recent meta-analysis shows the results of psychiatric treatment to equal or surpass those of most medical specialties (13), but the treatments must be delivered to those who really need them, not squandered on those likely to do as well or better on their own.

This disparity between treatment need and treatment delivery is about to get much worse. The DSM-5 has introduced several new disorders at the fuzzy and populous border with normal and has also loosened requirements for many of the existing disorders. The biggest problems are removing the bereavement exclusion for major depressive disorder, adding a very loosely defined somatic symptom disorder, reducing the threshold for adult ADHD and post-traumatic stress disorder, adding a diagnosis for temper tantrums, introducing the concept of behavioral addictions, combining substance abuse with substance dependence, and adding mild neurocognitive disorder and binge eating disorder.

The DSM-5 has been prepared without adequate consideration of clinical risk/benefit ratios and has not calculated the large economic cost of expanding the reach of psychiatry. It has been unresponsive to the widespread professional, public, and press opposition that was based on the opinion that its changes lacked sufficient scientific support and often defied clinical common sense. And a petition endorsed by fifty mental health associations for an independent scientific review, using methods of evidence based medicine, was ignored.

There will be no sudden paradigm shift replacing descriptive psychiatry with a basic explanatory understanding of the pathogenesises of the different mental disorders. This will be the gradual and painstaking work of many decades. In the meantime, we must optimally use the tools of descriptive psychiatry to ensure reliable and accurate diagnosis and effective, safe, and necessary treatment. It is time for a fresh look. The preparation of the ICD-11 provides an opportunity to re-evaluate

psychiatric diagnosis and to provide cautions against its over-inclusiveness.

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Beyond DSM and ICD: introducing “precision diagnosis” for psychiatry using momentary assessment technology

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In medicine, a diagnostic system should ideally be mechanism-based rather than symptom-based. Although attempts to create diagnostic entities in psychiatry that are based on specific *biological* mechanisms have failed (1), new evidence suggests that an alternative mechanistic approach, based on *mental* mechanisms, can be readily implemented in psychiatry, complementing the widely criticized categorical systems of DSM and ICD.

Below, we describe the contours of a novel system of diagnosis in psychiatry based on: a) the need for a more individualized approach, based on causal influences in symptom circuits (“precision diagnosis”); b) the need to take into account the fact that symptoms reflect responses to context (“context diagnosis”); c) the need to take into account that syndromes develop over time and have recognizable stages of expression (“staging diagnosis”) (2); and d) the need for the diagnostic process to become collaborative rather than unidirectional, reflecting the first stage of collaboration between patient and professional, and the first stage of treatment.

The proposed diagnostic system is based on novel digital momentary assessment technology, which allows the patient to collect data on symptoms and contexts in the flow of daily life, from which detailed contextual symptom circuits can be constructed, that serve as a diagnostic and therapeutic tool, as well as an instrument to assess change.

THE PRINCIPLE OF CONTEXTUAL PRECISION DIAGNOSIS

The main problem with psychiatric diagnosis is that groups identified by a common label, for example schizophrenia, in fact have little in common. The level of heterogeneity in terms of psychopathology, need for care, treatment response, illness course, cognitive vulnerabilities, environmental exposures and biological correlates is so great that it becomes implausible that these labels can provide much clinical utility.

In other areas of medicine, unexplained heterogeneity was addressed by the introduction of precision (or personalized) diagnosis. For example, blood pressure, plasma glucose, cardiac rhythm, electroencephalogram, muscle tone and other somatic outcomes can now be monitored in daily life, allowing for a diagnosis that yields individualized information about the pattern of *variation* of the parameter in question in

response to daily life circumstances. This diagnostic information is *precise*, as it reflects highly personal patterns of variation, and is *contextual*, as it traces variation related to daily life circumstances of, for example, stress, sleep, medication and life style. It is also *collaborative*, as the patient is actively involved in collecting and interpreting the diagnostic data. This not only enables precise indexing of treatment needs (diagnosis), but also precise monitoring of treatment response (prognosis). A similar system of contextual precision diagnosis may be useful in psychiatry.

PRECISION: DIAGNOSING MENTAL CAUSATION IN SYMPTOM CIRCUITS

How can diagnosis based on psychopathology be similarly individualized? To date, the most commonly used attempt at individualization is based on assigning individuals to diagnostic categories, in combination with personalized ratings of psychopathology across different dimensions. In theory, this system of “dimensionalized categories” ought to yield acceptable precision, given that two individuals within the same diagnostic category will nearly always have different psychopathological profiles.

Recent research, however, indicates that this system is based on the false premise that symptoms always vary together as a function of a latent underlying dimension or category – which does not appear to be the case (3,4). Instead, it has been argued that mental “disorders” in fact may represent sets of symptoms that are connected through a system of causal relations, which may explain individualized co-occurrence of different symptoms (4,5). For example, the negative and positive symptoms of schizophrenia have largely independent courses (6), and etiological factors appear to operate at the symptom level rather than the diagnostic disorder level (7-9).

Therefore, there is increasing interest in how multiple symptoms in individuals arise not as a function of a latent construct, but as a function of symptoms impacting on each other, for example insomnia impacting on depressive symptoms (10) or on paranoia (11), depressive symptoms impacting on anxiety symptoms (12), affective disturbance giving rise to psychosis (13,14), negative symptoms predicting psychosis (15), and hallucinations impacting on delusions (16,17). Not only between-symptom dynamic relationships

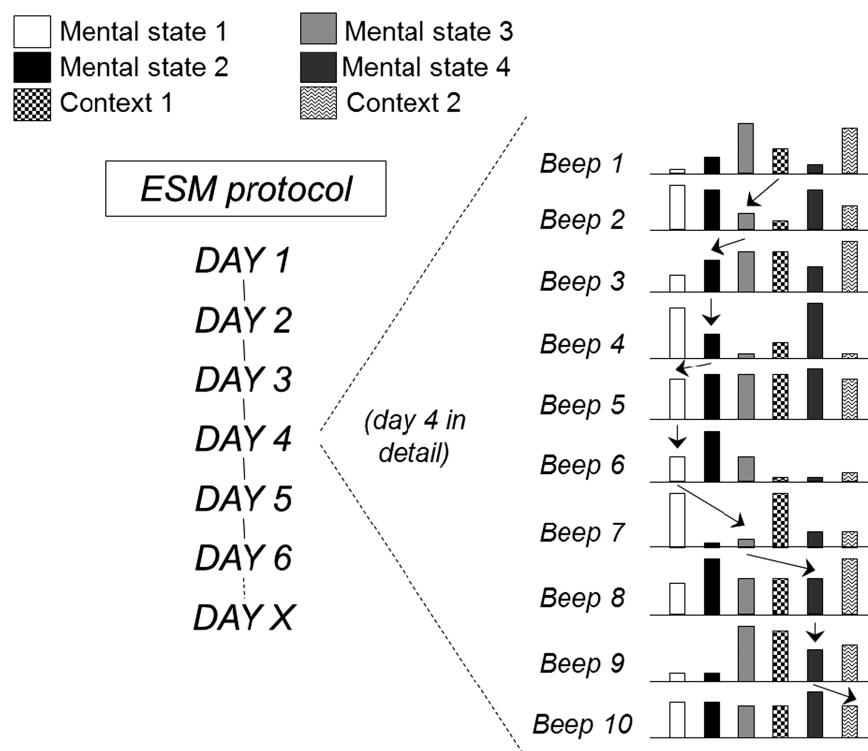


Figure 1 Momentary assessment with the Experience Sampling Method (ESM). At 10 random moments during the day, mental states (e.g., anxiety, low mood, paranoia, being happy) and contexts (stress, company, activity, drug use) are assessed. The arrows represent examples of prospectively analyzing the impact of mental states and contexts on each other over time.

have been described, but intra-symptom temporal dynamics resulting in *persistence* or, in momentary assessment technology terms, *momentary transfer* of symptoms have been observed. For example, intra-symptom dynamics over time, in the form of intra-symptom feedback loops, have been described in the area of psychosis, both at the momentary “micro-level” over the course of a single day in daily life (18), or over the course of months or years (19,20), under the influence of genetic and non-genetic risk factors (21-23).

The notion that traditional diagnostic categories and dimensions need to be transformed to represent the dynamics of symptoms impacting on each other over time in a model of mental mechanisms or mental causation is tantalizing. It implies that special methodology is required to collect repeated measures of symptoms over time in the flow of daily life, both at the momentary level and over more extended periods (24). This type of information allows for a detailed analysis and systematic presentation (25) of how symptoms impact each other (4,5,18).

CONTEXT: DIAGNOSING ENVIRONMENTAL REACTIVITY

Although it is widely believed that mental disorders have their origin in altered cerebral function, disease categories

as defined in DSM and ICD do not map on to what the brain actually does: mediating the continuous flow of meaningful perceptions of the social environment that guide adaptive behaviour. The use of *ex-cathedra* static diagnostic categories appears distal from the neural circuits that mediate dynamic adaptation to social context.

Therefore, reformulation of the basic psychopathological unit towards capturing dynamic reactivity, modelled on the role of neural circuits in mediating adaptive functioning to social context, may be productive in the context of diagnosis. Momentary assessment technology phenotypes capturing dimensional variation in mental states in response to other mental states in the symptom circuit on the one hand, and to environmental variation on the other, are well placed to fill these requirements (Figure 1), resulting in a diagnosis that is both contextual and precise.

It is proposed that momentary assessments of contextual symptom circuits, using the Experience Sampling Method (ESM), will provide a fertile model for investigation of psychopathology, encompassing phenotypes at multiple levels of neurofunctional organization (26). For example, momentary assessment technology studies of exposure to early trauma in humans have yielded replicated evidence that early environmental exposures predict altered momentary response to stress in adulthood that increase the risk of mental disorder (27-29). There is a

suggestion that these ESM phenotypes of behavioural sensitization (30) can be linked to biological models of sensitization (31,32), thus suggesting that the momentary environmental reactivity may represent a key variable in linking mental and neurobiological phenotypes (33). Also, several ESM mental state measures have shown that connections between momentary mental states and environments are sensitive to genetic effects, not just in terms of heritability and familial resemblance (34,35), but particularly in terms of the genetics underlying environmental sensitivity (36-43), a mechanism referred to as gene-environment interaction.

EMPOWERMENT: A COLLABORATIVE DIAGNOSTIC PROCESS

In the momentary assessment paradigm of diagnosis as described above, patients collect their own data in daily life, and not only assist in observing variation in mental states, but also learn about daily environments likely to induce changes therein. Their experiences are assessed and translated in the diagnostic paradigm. For example, tracking aberrant salience can be explained as “let’s follow how you tend to put some issues under a magnifying glass”, or “let’s see what kind of environment helps you to generate positive affect”. This stimulates awareness and involves patients in making their own diagnosis, both at the level of psychopathology and at the level of functioning, relevant for both treatment and rehabilitation. During treatment, patients can directly observe how treatment impacts their dynamically varying mental states in response to environmental challenges in the flow of daily life. Patients thus become empowered to evaluate their own diagnosis and treatments in daily life, outside the doctor’s office. Doctors, in turn, are given access to a much more accurate, prospective measurement of the phenotype of mental disorder: rather than a static cross-sectional measure that is not representative of what the patient experiences outside the doctor’s office, they now have access to the true phenotype of continuous and dynamic variation in response to environmental challenges in the flow of daily life, allowing them to not only prescribe treatments, but also life style alterations targeting challenging environments.

PRECISION DIAGNOSIS IN CLINICAL PRACTICE

An example of contextual precision diagnosis is depicted in Figure 2. “Diagnosis” here refers to the visual display of causal relationships between symptoms and environment (in the example: stress) in the circuit. The circuit not only focuses on environment and symptoms, but also includes positive affective states, thus increasing therapeutic relevance.

Previous work has shown that contextual precision diagnosis is highly sensitive to longitudinal development

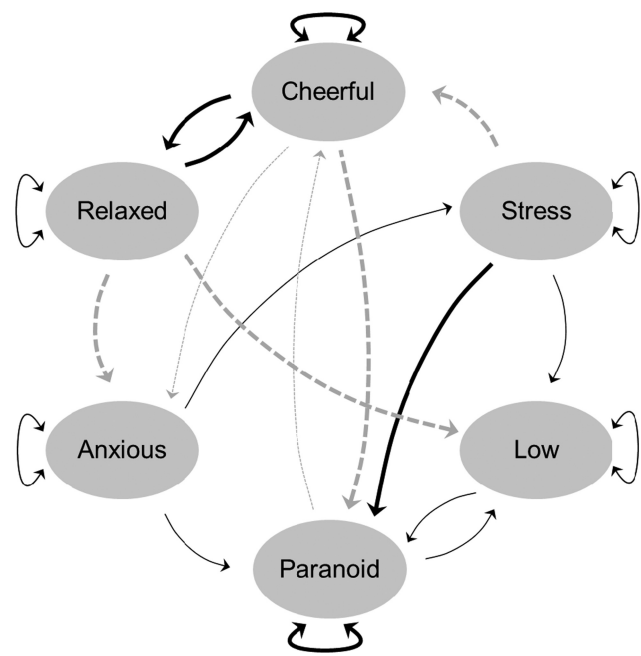


Figure 2 Contextual precision diagnosis. Thicker lines indicate stronger associations. The (simulated) patient in this example did 6 days of experience sampling in order to determine circuit patterns of stress and mutually impacting mental states. The resulting causal circuit is depicted. A strong positive (black lines) feedback loop exists between positive states (relaxed and cheerful) and a negative (dotted grey lines) feedback loop exists between the opposite mental states of being cheerful and being paranoid. Stress occasions paranoia and impacts negatively on cheerfulness. Being relaxed helps reducing low mood and anxiety. Both cheerfulness and paranoia have a strong tendency to persist over time, increasing the probability of stable symptoms (18).

of phenotypes across definable stages; in that connection strength and connection variability between mental states differ in a predictable fashion across different stages of psychopathology (44). In addition, there is evidence that symptom circuit dynamics based on momentary assessment technology is sensitive to genetic variation and neural function (45-47), and can be used to predict dynamic transitions from a state of vulnerability to illness (48).

Contextual precision diagnosis is idiographic and sensitive to stages of psychopathology, replacing the need for nomothetic approaches that lack validity and practical utility (49). Finally, there is emerging evidence that the process of contextual precision diagnosis using ESM has therapeutic effects by itself (50-52).

CONCLUSIONS

Although it may be useful to retain some of the higher order syndromal groupings, such as common mental disorder and severe mental disorder, the focus of contextual precision diagnosis is on the individual, neutralizing the forces of stereotyping and treatment irrelevance. The summary

presented above suggests that novel momentary assessment diagnostic systems delivering patient- and treatment-relevant information represent a welcome addition to the diagnostic toolbox in psychiatry.

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Pediatric psychopharmacology: too much or too little?

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This paper provides a selective overview of the past, present and future of pediatric psychopharmacology. The acceptance of medication use in child psychiatry was based on the results of double-blind, placebo-controlled trials documenting the efficacy of drug treatments for attention-deficit/hyperactivity disorder, enuresis, depression, anxiety disorders, obsessive-compulsive disorder and psychoses. This period of success was followed by a series of challenges, including a growing awareness of the long-term adverse effects of medications and of the inadequacy of long-term drug surveillance. There is great concern today that children are being overtreated with medication, especially in the US. Further advances in pediatric psychopharmacology may come from examination of large medical data sets including both pharmacological and psychiatric information, which could lead to drug repurposing, as well as from preclinical translational studies such as those using human induced pluripotent stem cells.

Key words: Pediatric psychopharmacology, stimulant drugs, child psychiatry, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, drug toxicity

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It has been an extraordinary personal and professional experience to see the development of the field of pediatric psychopharmacology across the last four decades, and to work throughout the successive challenges.

Initially, there was a strong climate against medication for children with mental disorders. In the US, the psychiatrists and psychologists interested in pharmacological research formed a small group clearly out of the “main stream”. Psychoanalytically oriented psychotherapy was the generally preferred treatment for children and adolescents.

Suspicion of medication was only overcome by the focus on double-blind trials and validated clinical measures. The assembly of large relatively homogeneous populations for those trials had a strong overall impact on the field by permitting a variety of clinical studies. The eventual acceptance of medication use in child psychiatry was based on the growing evidence of efficacy of drug treatments with large effect sizes for disorders that had been resistant to psychological treatments.

This period of success has been followed by a series of challenges. The acceptance of drug treatment has been often uncritical, including a drastic increase in polypharmacy. There has been a growing awareness of the long-

term adverse effects of medications and of the inadequacy of long-term drug surveillance. With the transition to managed care in the US, medication has shifted to more of a business model. Because non-medical therapists are less costly, psychiatrists in most insurance plans have been assigned exclusively to medication clinics. This may have increased the likelihood that they would prescribe drugs to children.

Also relevant to the backlash against the use of drugs in children is the growing alienation of the media from psychiatric illness. Not only are medications often described as unnecessary, but the diagnoses themselves, such as that of attention-deficit/hyperactivity disorder (ADHD), are sometimes perceived as unscientific and even harmful.

Finally, there is the awareness that most of our drugs still act on the monoaminergic and glutaminergic targets that have been known for decades. As our current medications are only partially successful, with 40–50% of patients having incomplete response and/or intolerance, the field still has a great deal to accomplish. Yet, the complexity of the search for new targets has made many pharmaceutical companies leave the field.

This paper provides a selective overview of the past, present and future of pediatric psychopharmacology.

THE EXCITEMENT OF DISCOVERY

As in adult psychopharmacology, several discoveries of psychotropic drugs for pediatric use have been serendipitous. This was the case for the use of stimulants for “minimal brain dysfunction” (1) and the use of antidepressants for enuresis (2). The funding of systematic case recruitment for clinical drug trials brought about a profound change in the field of child psychiatry, because of the increased scale of observations.

Stimulant medications were responsible for the actual “start” of pediatric psychopharmacology, as the patients of greatest interest were children with ADHD, one of the most common disorders in childhood, accounting for almost half of pre-adolescent contacts. The results of the studies concerning these drugs were electrifying. The clear and immediate benefits for the child and the family were particularly welcome as ADHD did not respond well to traditional psychotherapy.

A variety of double-blind, placebo-controlled studies demonstrated that stimulants improved on-task behavior in both healthy and hyperactive children (3,4). Stimulants did not merely make hyperactive children move less (3). For example, during athletic activities such as basketball or soccer,

hyperactive children on stimulants actually moved *more*, because their attention was focused on the immediate task, which was playing the active game (5). When the task was a quiet one, such as classroom learning, the stimulants decreased motor activity (5).

Because stimulant drug effects can be seen within 15–20 min, and since the effect on the behavior of hyperactive children is striking, a series of studies were able to compare *parent and teacher behavior* between periods when the child was on placebo or on stimulant (6,7). Parents were rated as highly critical and controlling during the placebo periods compared to when the child was on stimulant (8) and teachers received higher “teaching grades” when their hyperactive students were on medication compared to placebo (9).

More recently, the development of long-acting agents has provided a smoother treatment throughout the day, avoiding school involvement in drug administration. Long-term prospective follow-up studies of children with documented ADHD have showed that a substantial group of patients continue to have significant symptoms, with only about 40% truly remitting (10,11). This has led to studies of adult ADHD and a debate on stimulant drug treatment of the adult disorder and the problematic clinical cases of adult onset ADHD (12). These remain important controversies today.

Antidepressant treatments were initially studied in children with enuresis (13), but later extended to children with depression and anxiety disorders (14). There has been considerable controversy over how to define childhood depression, with many clinicians feeling that several symptoms (behavioral problems, anxiety, enuresis) could be an expression of underlying depression (15). For clinical medication trials, more operational definitions were required and an active experimental field compared various definitions in relation to family history, treatment response, long-term follow-up and so forth (16). The answer was complex, as some behavioral dyscontrol with

chronic irritability in fact *did* predict depression in later life (17,18), but a core group could be identified of about 1% of pre-pubertal children with similar symptoms to those seen in adult depressed patients, and such children did respond to treatment (19,20), although effect sizes varied widely across studies.

Later studies extended antidepressant treatment to pediatric anxiety disorders (21,22). These are now drug treatments of documented efficacy for pediatric generalized anxiety disorder, separation anxiety, social anxiety and panic disorder (23,24).

Studies of childhood onset obsessive-compulsive disorder (25) led to the development of specialty clinics for these children in several countries and to the recognition of the close association of this disorder with Tourette’s disorder (26). Again, double-blind, placebo-controlled drug treatment trials required assembly of large numbers of children, and the recognition that obsessive-compulsive disorder could best be diagnosed and assessed using the child as informant (27). Because a subgroup of patients appeared to have a very sudden onset of a severe variety of the disorder (as well as of motor tics and ADHD) in relation to streptococcal infection, highly innovative treatments using plasmapheresis or intravenous gamma globulin were introduced (28). The interest in infection-related acute psychiatric disorders remains high based on these studies and is an important area of future research.

Antipsychotics have been a mainstay of treatment for childhood, adolescent and adult onset psychosis (29). Low-dose antipsychotic medications are used even more frequently in child psychiatry for the treatment of Tourette’s disorder and for repetitive motor behaviors generally (30). The clinical indication for antipsychotics has been also extended to conduct disorders, although with only moderate efficacy rates (31,32).

Clinical trial publications in pediatric psychopharmacology paired with the satisfaction of extended treatment

options in ordinary clinical practice. Trainees were attracted to psychiatry by the treatment advances. The use of rating scales and double-blind design introduced the evidence-based approach that changed the field forever. More recently, initial research comparing behavior therapy and drug treatment has revealed that the *combination* of medication and non-drug treatment is the most effective in childhood depression, anxiety and obsessive-compulsive disorder (e.g., 33). This has led to an increased use and acceptance of these approaches.

PEDIATRIC PSYCHOPHARMACOLOGY: TOO MUCH?

There is great concern today that children are being overtreated with medication, especially in the US. The rapid shift to managed care has resulted in a split in mental health care-giving. Because of the higher cost, psychiatric care is primarily allotted to medication clinics. Non-drug therapies are provided primarily by psychologists, social workers and counselors. It is possible, and I speculate that it is probable, that the increase in medication use results in part from the desire of physicians to be helpful with what they have at hand given their lack of flexibility with respect to alternate treatment delivery.

The rates of increase of pediatric psychotropic drug prescription in the US are alarming (30,34). Multiple psychotropic treatments have also become more common. There is extensive use of atypical antipsychotics for non-psychotic children. An increased prescription of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), particularly for ADHD, has been reported. The duration of stimulant drug treatment has also greatly increased (34–36). Particularly worrisome is the trend to prescribing medications (particularly stimulants) for pre-school children (37). An additional concern is that children in institutional

or foster care seem to receive higher doses and multiple medications to a particularly high extent (35).

It is clear that the rate of stimulant treatment exceeds that of strictly diagnosed ADHD (38,39). Since stimulants improve cognitive function irrespective of diagnosis (4), it is probable that individual troubling symptoms are being treated in children who do not meet full diagnostic criteria for ADHD. This remains a highly controversial issue.

While childhood treatment of ADHD with stimulants does not increase substance abuse at a later age (40), it is also true that longer-term treatment of the disorder is more usual today. This has raised complex clinical and ethical issues (12). While short-term administration of stimulants with drug holidays did not have a long-term influence on height, the more sustained and longer use of these drugs has raised this issue once more (41). The identification and treatment of ADHD in adults, particularly those without clear childhood history, has generated further controversy; this remains a clinical dilemma of great regulatory concern in the US (42). One bright spot is the probability that long-acting stimulant preparations in wide use today may be less prone to abuse (43).

First-generation antipsychotics carry a high risk for tardive dyskinesia following long-term use (44). This was a particular issue in institutionalized patients, and several US states legislated a yearly drug holiday with observation for movement disorders.

Today, the increased use of atypical antipsychotics in children and adolescents is also a major issue. Originally thought safer because of decreased risk of tardive dyskinesia, these drugs are now known to be at increased risk for cardiometabolic syndrome, particularly in adolescents (45). These medications remain of major importance, including clozapine, the most effective (and toxic) of all for childhood psychosis (46,47). However, the physician now has to weigh the lower risk of akathisia and tardive dyskinesia against the greater risk of obesity

and cardiometabolic syndrome. In the childhood schizophrenia studies, weight gain with clozapine appeared at a high rate, possibly higher than that of adult onset patients (48).

The use of low-dose antipsychotic medications is widespread in child psychiatry for conduct disorders, as augmentation of SSRIs for pediatric obsessive-compulsive disorder, and for Tourette's disorder and motor tic disorders (29). Collectively, these cases are far more common than those of childhood psychoses, and the problems of obesity and the cardiometabolic syndrome are even more alarming. One of the most disturbing aspects of drug-related obesity in children is that weight loss occurs slowly and incompletely when the drug is stopped.

Antidepressant drug treatment in children has also come under criticism (49). Initial trials with tricyclic antidepressants have not been replicated (50). Results of double-blind trials of SSRIs have been more compelling in adolescents (51), but the effect sizes vary widely, with possibly better responses with fluoxetine (52).

Suicidality in children on antidepressants became a major concern in 2004, when the Food and Drug Administration (FDA) issued a warning (53). This controversial move raised concerns that these effective agents might not be prescribed for severely depressed children (54). The FDA action both reflected and fueled public suspicion and backlash against pediatric psychopharmacology. Part of the issue was the failure to distinguish between suicidality and actual self-harm, but everyone involved in this issue agreed that current post-marketing surveillance of drugs is inadequate (55).

PEDIATRIC PSYCHOPHARMACOLOGY: WHAT IS THE FUTURE?

In the early history of our field, serendipitous discoveries led to treatment trials of medications with large effect sizes. Building on these accidental approaches, further advances

in psychopharmacology may come from examination of large medical data sets through single payer medical systems including both pharmacological and psychiatric information. This could lead to drug repurposing, that is, drugs given for other medical purposes may be found to influence the course of some psychiatric conditions. This form of "psychopharmacological epidemiology" has not been systematically pursued for treatment effects in child or adult mental disorders, although epidemiology has been of major importance for studies of adverse drug events.

Clinically, there has been interest in repurposing riluzole for psychiatric use (56). This is a glutamate antagonist approved for treatment of amyotrophic lateral sclerosis (57), which had theoretical support as an alternative treatment for obsessive-compulsive disorder in children and adolescents. In spite of promising pilot results (58,59), however, a double-blind trial did not show significant efficacy (60).

Rapamycin, a commercially available immunosuppressant, has been found highly effective in the treatment of tuberous sclerosis, a rare genetic disorder associated with widespread brain and somatic abnormalities and with autism spectrum disorder (61). This rare disease model is leading to proposals of new treatment targets (62,63) related to the role of mTOR (mammalian target of rapamycin) in pathways affecting protein synthesis, cell division and cell growth.

Mutations in the FMR1 (fragile X mental retardation) gene can cause cognitive deficits, ADHD, autism and other social-emotional problems. Studies of metabotropic glutamate receptor (mGluR5) pathway antagonists in multiple animal models of fragile X syndrome have demonstrated benefits in various behaviors (64). Several trials of mGlu5 antagonists have been designed (65). There is considerable optimism about the ultimate usefulness of the study of this and other rare single gene disorders that cause autism, as the pathways and targets that are revealed may inform treatment

development for wider patient populations (66).

Genetic-based animal models of autism, ADHD, obsessive-compulsive disorder and schizophrenia have generated putative candidates, but this has not led to successful clinical trials. This failure may be due to the complexity of human disorders, for which animal models may prove unsuccessful. It may be that the dramatic changes underlying human brain evolution make us vulnerable to mental disorders that are uniquely human. Post-mortem human brain studies may ultimately generate new targets, as gene expression studies of post-mortem brains in autism have implicated pathways for both brain development and immune responses (67).

An obstacle to drug discovery is our limited understanding of human brain development. The tools that we have for measuring brain functioning and connectivity are growing, but only recently sizeable multimodal normative brain developmental data have become available, with large prospective studies ongoing in Rotterdam (68), San Diego (69) and Philadelphia (70). The Rotterdam studies will extend from the prenatal period through adolescence (68), but the perspective for new drug treatments is remote.

Clinically, there is a growing dissatisfaction with existing diagnostic entities, which are perceived as being too heterogeneous and thus not helpful to drug development (71). The DSM-5 is going to place emphasis on psychopathological dimensions, and this may be a useful step forward (72). Other approaches in treatment development have been based on intermediate phenotypes or specific biomarkers, including genetic variables, as in the glutamate trial mentioned above. The Research Domain Criteria project (73,74) involves measurement of common physiological, neuropsychological, or brain imaging markers to identify a patient subgroup or alternately be themselves a target for treatment. Examples of this approach could include sensory gating such as pre-pulse inhibition, or specific cognitive tests such as the Continuous Performance Test or the California Test of

Verbal Learning (75). In children with anxiety disorders, newer treatments are being proposed in relation to patterns of brain activation in response to emotionally loaded stimuli as well as to cognitive bias associated with these disorders (22).

Human induced pluripotent stem cells would seem ideal for the study of neurodevelopmental disorders. Using Rett syndrome as a model, neurons derived from human induced pluripotent stem cells from people with the syndrome have been found to have fewer synapses and some electrophysiological defects (76). Identification of cellular mechanisms for schizophrenia and for autism with the attendant possibility of *in vitro* treatment trials to normalize developmental trajectories is under study at several centers (77).

The development of real translational clinical neuroscience will hopefully be the ultimate answer, but this does not address the critical shortage of new drugs in development.

CONCLUSIONS

Pediatric psychopharmacology has historically been a vibrant field. The excitement of new treatments, such as stimulants and more recently the SSRIs, not only brought help to otherwise treatment-refractory patients but inspired two generations of academicians. These academics leveraged the treatment trials into complex pharmacological and clinical studies.

Looking back, it is apparent that there was over-acceptance of drug treatment, leading to reductionist biology. Market forces in health care delivery also drove the process of over-prescribing (78).

There are now imaginative new approaches to psychiatric diagnosis (such as the Research Domain Criteria project) and astonishing preclinical translational studies (such as the study of human induced pluripotent stem cells), but new treatments remain unfortunately remote.

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Pediatric psychopharmacology: too much and too little

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Rapoport's lucid overview points to overmedication in children in the USA, especially for attention-deficit/hyperactivity disorder (ADHD) and irritability. By contrast, many countries make so little use of medication that it seems probable that children who could profit do not receive it. Undertreatment is perhaps a bigger problem globally than overmedication.

In Europe, stimulants are used increasingly, but rates are very much lower than the 73 per 1,000 in the USA that was described by Angold et al (1) in 2000. In a UK national database report from years 2003–2008, the prevalence rose from 4.8 to 9.2 per 1,000 in the 6–12 age range, and from 3.6 to 7.4 per 1,000 at ages 13 to 17 (2). In France, the rate was 1.8 per 1,000 in 2005 (3). In Italy, stimulant use was almost unknown until a few centres were recently licensed to prescribe. In all these countries, preschool use was too rare for an accurate estimate. As to other types of medication, some (e.g., antipsychotics in schizophrenia) are uncontroversial; others (e.g., antipsychotics for irritability) are used much less in Europe than in USA. What factors influence these startling differences?

A first factor is availability of prescribers. Rapoport emphasizes the market forces confining US psychiatrists to "medication clinics"; if some clinics use only medication for ADHD, one must doubt whether adequate practice is being followed. By contrast, parent training is widely available and free in the UK, while prescribers are in shorter supply – which may well limit the need for, and the use of, medication. In many countries, lack of child psychiatric services in general, and of professionals qualified to prescribe in particular, restrict all therapeutic services

including medication. Good training of paramedical staff could allow both medication and behavioural interventions to be included in therapy.

A second factor is perceived efficacy of drugs and alternatives. In some low-prescribing countries, non-pharmaceutical interventions are regarded as more or less equivalent to drugs. European Guidelines and those in the UK from the National Institute for Clinical Excellence (NICE, 4) recommend both medication and psychological approaches (especially behavioural) as being effective and cost-effective, at least for cases of mild or moderate severity. Similarly, UK guidelines for the treatment of childhood depression recommend that selective serotonin reuptake inhibitors should only be used after three months of psychological therapy – advice that has perhaps been outdated by recent studies arguing that the combination of both is more effective and safer than either treatment alone.

Furthermore, a recent meta-analysis of non-pharmacological interventions in ADHD casts some doubt on the value of treatments such as behaviourally oriented parent training – and indeed most dietary interventions (5). Evidence for efficacy depends on ratings from parents who have themselves been involved in delivering the therapy, and may therefore not be unbiased. Teacher ratings and assessments by blinded observers suggest much smaller effect sizes. This does not, of course, mean that parent-delivered therapies are useless. Even if the good effects are situation-specific, and even if they represent more positive parental attitudes rather than a profound change in the children, they may still be very worthwhile.

Nevertheless, there may need to be some re-evaluation of the power of medication relative to psychological interventions. If, in line with European

recommendations, medication were to be provided for most of those with the World Health Organization's definition of hyperkinetic disorder (about 1% of school-age children) and those children with ADHD that falls short of hyperkinetic disorder (about 4%) who fail to respond to behavioural interventions (perhaps half of that 4%), then there would be approximately 30 per 1,000 children eligible for treatment. Of course, not all children would or should be presented for treatment, but it is hard to escape the conclusion that countries such as England and France are using less psychopharmacology than would be optimal for child health.

A third factor is cultural. The perceived overuse of medication in the USA has generated widespread media criticism in Europe, amounting in some cases to hostile campaigns against individual doctors. The fire is fed by opposition to biological psychiatry, e.g., from sociological and psychoanalytic perspectives and from anti-American political positions. The resulting polarization can get in the way of balanced and discriminating use.

A fourth factor is represented by adverse effects. Differing perceptions of drug dangers influence regulatory authorities and prescribers. Clozapine, for instance, is statutorily regulated in some countries for its haematological risks; in others, such as some ex-Soviet countries, it may be prescribed in the same way as other antipsychotics. The metabolic and obesity-inducing effects of second-generation antipsychotics are sometimes taken to debar their use for non-psychotic aggression in all but the most severe cases (6), while their wide use for this purpose in parts of the USA implies that they are considered to be manageable with low doses and good monitoring.

Detailed European recommendations for ADHD based on systematic review (7) have indicated that the hazards of stimulants are few and manageable. Oral

administration (especially of extended-action preparations) is unlikely to lead to misuse. Nevertheless, the fear of inducing dependence has led some countries to limit availability.

A final factor is uncertainty of indications. Most of the problems of child mental health are distributed in the population as continuous dimensions. It is therefore a real difficulty to decide where to place cut-offs for the use of medication, or how to decide on the balance between medication and psychological therapy. For ADHD, NICE (4) used a reanalysis of a large US trial to recommend a cut-off for the use of medication as first therapy, corresponding to the ICD-10 definition of “hyperkinetic disorder” (severe, pervasive and impairing ADHD).

In summary, great international differences in the use of psychopharmaca stem from professional and cultural attitudes. The evidence base on clinical outcomes should be extended and applied.

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What's next for developmental psychiatry?

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J. Rapoport provides an accurate and thoughtful overview of the history and current state of pediatric psychopharmacology. Since Bradley's report in 1937 concerning the use of benzedrine in children with behavior problems (1), pediatric psychopharmacology has been with us. However, psychoanalytically oriented psychotherapy was the generally preferred treatment for children and adolescents in the USA until the late 1970s, when things began to change. By 2002, with the publication of the first edition of *Pediatric Psychopharmacology* (2) and the advent of *Journal of Pediatric Psychopharmacology*, the use of psychoactive medications in children had become main stream in the USA, although remaining problematic for large segments of the general population in Europe and other areas of the world, including South America.

There is no doubt that for many children the use of psychoactive drugs has been beneficial. So, from my perspective, pediatric psychopharmacology is here to stay. Rapoport

summarizes many of these advances. Sadly, however, there are many children for whom the benefits are modest at best.

We need new agents, but the pharmaceutical industry has become cautious. For the most part they are content to develop analogs of successful compounds. How many derivatives of stimulant medications are on the market, to say nothing of the serotonin reuptake inhibitors and antipsychotics?

As noted by Rapoport, attempts at “repurposing” of existing compounds initially developed for other indications also make sense. Here, it is of interest to recall that antipsychotics were first developed by surgeons to potentiate the effects of anesthetics and analgesics, and cycloserine was initially used as an antibiotic to treat tuberculosis.

A significant portion of my research and clinical practice is focused on Tourette's syndrome (TS), where we do not have ideal agents (efficacious with minimal side effects). Consequently, we are in the midst of trying a number of agents, some of which are novel and others have been in development for other indications. For example, recent genetic findings indicating a

role for central histamergic pathways (3,4) have led to the development of a clinical trial for histamine H3 receptor antagonists, using an agent first developed for the treatment of obesity. We are also evaluating the evidence base for the use of nutritional supplements. Caution is warranted here as well. Once nutritional companies recognize the commercial potential of their products, financial as well as clinical pressure will likely drive the development of ever more aggressively marketed products.

More importantly, we need to develop and sustain efforts to build on the strengths and interests of children and adolescents with behavioral and emotional difficulties and find ways to take advantage of advances in developmental neuroscience to enhance their cognitive and emotional development. This echoes the recent forum in *World Psychiatry* on “Positive mental health: models and clinical implications” (5). When seeing a new case in our clinic, I frequently ask the parents “to brag” about their child and indicate what his/her favorite activities are and what skills he/she is developing. In the case of TS, engaging in activities that require

focused attention and motor control, e.g., playing a musical instrument or practicing a martial art, markedly diminishes motor and vocal tics (6). Consequently, encouraging parents to build on those interests and the child's innate abilities can be a path to a more positive future. For example, success in sports activities can enhance a child's physical fitness, self esteem and social connectedness. This, along with the extensive animal literature indicating that exercise enhances neural development, including the survival, growth and differentiation of neurons, synaptogenesis and myelination, provides a strong rationale to evaluate interventions including regular physical exercise programs (7).

Building on the work of Klingberg and associates, there is also a growing body of evidence that computer games focused on working memory and other cognitive capacities can reduce inattentive symptoms in young children with attention-deficit/hyperactivity disorder (ADHD) as well as enhance fluid intelligence in typically developing preschoolers (8,9). It is too early to tell how efficacious will be more advanced cognitive training programs designed to expand the horizon beyond working memory to include other cognitive skills (e.g., sustained attention, inhibitory control, cognitive flexibility, category formation, pattern recognition and inductive thinking), synergistically combined with aerobic sports activities designed to enhance the same cognitive abilities. Such trials are currently underway. One other neuroscience based intervention, neurofeedback, also shows promise for ADHD, but further evidence is required to guide its use (10,11).

It is possible that such interventions will emerge as adjunctive, if not possible alternatives, to pharmacological treatment options (12). Time will tell, but there is a real possibility that they will have positive effects on neurodevelopment as well as the subjective well-being of children and adolescents.

In closing let me briefly point to areas of concern. First, with the advent of pediatric psychopharmacology we have seen a shift away from viewing the

"whole child" and his/her strengths and weaknesses across various domains and contexts to a greater attention to his/her "symptoms". This has led to a reification of diagnostic entities and comorbidities. Our diagnostic classification systems are far from perfect. Each child is unique and not simply a child with ADHD or TS or autism spectrum disorder or obsessive-compulsive disorder. Often the boundaries between specific disorders are indistinct, at best. Next, this refocusing on diagnosis and the successes of pediatric psychopharmacology have led many programs to train developmental psychiatrists to become essentially experts in "medication management" rather than clinicians for the whole child and his/her family.

Last but not least, as noted by Rapoport, many psychopharmacological agents have undesirable side effects. Most of the acute and initially appearing adverse effects are reasonably well known, but in many instances the long-term effects of these agents on neurodevelopment have not been a major focus of research. For example, a recent systematic review clearly indicates that a substantial proportion of children and youth with depressive (11.2%) and anxiety (13.8%) disorders being treated with antidepressants experience behavioral side effects including excessive arousal activation (13). These rates are 3- to 10-times higher than seen during treatment with a placebo. There are also data from the Danish registries suggesting that for a subset of children the use of high doses of psychostimulants may have long-term adverse effects on cardiac function (14). Another area of concern is the use of psychotropic agents during gestation and their long-term effects on the fetus' neurodevelopment. Animal models may help to clarify these risks but the ethical dilemmas faced by the treating clinician will remain (15).

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Prescribing of psychotropic medications to children and adolescents: *quo vadis?*

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Childhood and adolescence is a period of extraordinary biological, psychological and social growth. However, at such times, individuals are also vulnerable to disruptions of healthy development. In fact, a staggering 50% of all adult psychiatric disorders have manifested by age 14, with 75% manifesting by age 24 (1). Moreover, two thirds of pediatric-onset psychiatric disorders are moderate or severe (2), and most continue into adulthood (3). Such patterns clearly indicate the importance of identifying and appropriately treating psychiatric disorders as early as possible to preserve healthy development and to reduce individual suffering and societal burden.

As eloquently described by J. Rapoport, there have been a number of groundbreaking developments in the management of pediatric psychiatric disorders. After decades of nearly exclusive reliance on psychological and behavioral interventions, psychopharmacologic advances have provided important biological management tools for severe pediatric psychiatric disorders. The advent of modern psychopharmacology, with its focus on parallel group, randomized controlled trials in large samples, has further informed the

efficacy and tolerability of major psychotropic drug classes in youth (4). This progress has been facilitated by regulatory agencies encouraging and, more recently, requiring adequate studies of pharmacologic agents in pediatric patients.

Yet, as outlined by Rapoport, many challenges remain. There has been a far too narrow focus on short-term trials, with a lack of sufficient information on distal and lower frequency, but potentially serious adverse effects. Insufficient attention has also been devoted to the effects of commonly prescribed psychotropic medications on development, and too little is known about the safety and effectiveness of common off-label prescribing. Moreover, psychiatric drug development has been limited to relatively few and non-specific mechanisms of action, and much less is known regarding the efficacy of treatments for early illness manifestations compared to more chronic conditions. The rational development of psychotropic medications is impeded by limited pathophysiological understanding of the disorders we aim to treat. In this context, the Research Domain Criteria project and other recent initiatives described by Rapoport may help to structure inquiries into underlying disease processes needed to identify new drug targets.

Although psychiatric disorders are now understood as having biological, psychological and social origins, requiring interventions in all domains, unilateral treatment approaches dominate in many countries and settings. Especially in the US, great concern has been raised about reductionist treatment approaches that focus too narrowly on pharmacologic management (5). Potential reasons include local and regional shortage of personnel trained in evidence-based psychosocial treatments, the absence of powerful and

well-financed advocates for psychosocial treatments, ideological disagreements among psychotherapists, financial disincentives to providing psychotherapy under many public and private insurance plans, and the added time burden associated with psychological interventions. Many families are not willing to engage in therapy or are unable to attend appointments on a regular basis. Criticism has also focused on the tendency of some physicians to reach for a “quick fix”. Yet, all too often children and adolescents are brought to see a pediatric mental health clinician only at times of great distress and when urgently requiring interventions that reduce burdensome symptoms, improve disrupted functioning, or allow youth to stay in the current educational system or to advance to the next grade. In these instances, parents and school personnel may demand rapid results. Waiting lists for psychosocial treatment and longer periods to initial symptom control may further diminish the attractiveness of psychotherapy.

Although rising prescriptions do not permit distinguishing adequate treatment from overuse, concerns remain regarding overprescribing of psychotropic medications in youth, especially to those with behavioral symptoms and to pre-schoolers (5). These concerns focus on adverse drug effects, especially potentially life shortening cardiometabolic effects (6) that are only inadequately monitored and addressed, insufficient utilization of psychosocial treatments before, during or after psychotropic drug treatment, and use of psychotropic medications for conditions with a particularly underdeveloped evidence base.

Despite increasing private and public investments in research, the number of new drug classes entering clinical trials has fallen over the past two decades, as have overall new drug introductions

worldwide (7). Many pharmaceutical companies have recently discontinued research on central nervous system disorders. While this is an understandable reaction to the availability of generic drugs, failed attempts at discovering new mechanisms of action, and narrowing profit margins, such decreased investment minimizes opportunities for much needed new treatments. In addition to the cutting-edge academic initiatives outlined by Rapoport, more emphasis should be paid to prevention targets and treatments in youth and adults. Given that first-onset disorders generally occur during childhood and adolescence, agents with neurotrophic, neuro-modulatory, anti-apoptotic and anti-inflammatory capacity and those countering oxidative stress should be investigated.

The move from immediate to intermediate phenotypes and the focus on biomarkers of illness as well as of treatment response will be important in realizing the critical goal of more personalized matching of patients to interventions. The decision by regulatory agencies to allow pharmaceutical companies to

market companion tests if they can identify patient subgroups that are particularly likely to benefit from their treatments is a welcome step toward incentivizing the development of treatments for identifiable patient subgroups. Nevertheless, most of the next-generation progress in psychopharmacology and pediatric psychopharmacology will likely depend on the identification of mechanisms for illness development, persistence and progression.

It is hoped that increasingly sophisticated technological tools and neuroscientific methods will deliver new breakthroughs. Likewise, large registry data sets are as much needed to assess long-term safety in naturalistic settings, as are high-quality characterization of patients and clinical trial execution in order to successfully test and transfer new pharmacologic treatments into clinical care.

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Child neuropsychopharmacology: good news... the glass is half full

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J. Rapoport nicely illustrates the past and present of paediatric neuropsychopharmacology and – what is even more interesting – also speculates about the future of this field. She posits the debate as either more or less prescription of psychotropic drugs to children and adolescents than needed, with the relevant clinical implications and diagnostic controversies linked to it. I will address the debate from a complementary view, that of hazards and opportunities for child neuropsychopharmacology.

Let's start with the empty part of the glass. I agree with Rapoport that we are far from discovering new drugs that cure or dramatically change the course of psychiatric disorders in children and adolescents. We first have to discover what needs to be fixed or repaired, i.e. the pathophysiology of psychiatric conditions at the molecular level. Only then will we be able to develop drugs targeted to altering *a priori* known biological mechanisms. This makes the field of neuropsychopharmacology a risky business: the old paradigms (e.g., monoamine release, dopamine blockade) seem to be exhausted, while the search for new mechanisms of action is uncertain, since in most cases we lack the

science that should drive the development of such new drugs. This is even more true in times of economic crisis, when drug companies gravitate toward more secure markets, such as cancer and cardiovascular disease. This is a clear threat to the search for new treatments for very prevalent and disabling mental disorders. Big Pharma's pull-out from neuropsychopharmacology is a consequence of some of these problems (1).

Turning now to the half-full part of the glass, we have to acknowledge that, while the field of child neuropsychopharmacology has always lagged behind that of adult neuropsychopharmacology, this has been changing in the last decade, as both the US Food and Drug

Administration (Pediatric Research Equity Act, 2003) and the European Medicines Agency (regulations 1901/2006 and 1902/2006) have not only provided extension patents for drug companies that have pediatric plans, but also required companies to conduct clinical trials in children, if their drugs have the potential to be used in that population, when they are seeking approval for an indication in adults. For many years, drugs with proven efficacy in adults have been used in children with no evidence either for efficacy or safety and tolerability. This is not going to be the case anymore if these rules stay in place. The flip side of the coin is the difficulty drug companies face in recruiting patients for such clinical trials, and the economic burden added to the already extremely high cost of drug development. While it is clear that data from pediatric populations are needed, this should not come at the expense of making the business of developing drugs for mental disorders unaffordable. Nevertheless, we as a field should take advantage of the enormous amount of data generated by these pediatric clinical trials conducted for many psychiatric disorders (2). Some data are also valuable for assessing non-drug-related hypotheses, such as those concerning the clinical course and predictive markers in pediatric mental disorders provided by longitudinal trials with large patient samples.

The high rate of prescription of drugs such as antipsychotics and stimulants in children reported in the US (3,4) is in no way the rule in Europe, although prescription rates of psychotropics have also increased, to a much lesser extent, in some European Union countries (5). It is worrisome to see that the prescription rate of antipsychotics in the US is approximately five times the prevalence of psychotic disorders in the pediatric population. This clearly means that such drugs are prescribed without evidence or with only marginal evidence

of efficacy, as is the case for conduct disorders without mental retardation.

As many of these drugs are out of patent, more clinical trials need to be funded with public money. Since many patients need to be recruited for these trials and this is not an easy task, it seems very important to prioritize this type of studies among those launched at the initiative of the European Commission or the National Institute of Mental Health. Networks such as that on child and adolescent neuropsychopharmacology established by the European College of Neuropsychopharmacology are also a good way to improve recruitment at centres with a solid background in this field.

Although mostly discovered by serendipity, as we lack the knowledge of the pathophysiology needed to direct the targets, some drugs used in child psychiatry have larger effect sizes than those used in other areas of medicine. For instance, drugs prescribed for asthma, headache or atopic dermatitis have lower effect sizes than those used to treat attention-deficit/hyperactivity disorder. Still, they are much less controversial. We should not allow the stigma related to mental disease to preclude us from providing the right treatment to our patients. If that were to happen, the stigma would have the dual deleterious effect of marginalizing our patients and depriving them of the benefit of drugs that have been shown to improve their quality of life and functioning.

We are under close scrutiny, and some recent movements in the US (prescription of drugs to children under 7 years of age diagnosed as bipolar) work against us as a field. It has taken great effort and excellent professionals like J. Rapoport to arrive where we are now. We should take advantage of new opportunities, such as translational psychiatry studies that allow us to assess the behavioural effects of genetic variants or molecular induced changes. These include large cohort studies that will shed light

on normal and abnormal development or the wealth of data on short- and long-term efficacy, safety and tolerability of new drugs that pharmaceutical companies are now requested to generate.

One further opportunity is the increasingly accepted view that we should move towards early intervention and prevention and that most psychiatric conditions develop during childhood and adolescence (6). That should shift the target, not only of drug discovery but also of therapeutic approaches in general, toward a younger population than is typically included in clinical trials.

We should not waste these opportunities or cook our own goose by diverging from evidence-based treatment algorithms. It is our children's mental health that is at stake.

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From too much and too little towards stratified psychiatry and pathophysiology

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As J. Rapoport points out in her incisive commentary, pediatric psychopharmacology stands now at the crossroads of both too much and too little. Certainly, the number of options now available to clinicians far exceeds the resources physicians could draw on even two decades ago. However, appreciation of this apparent cornucopia is tempered by awareness of how limited therapeutic benefits tend to be when examined in controlled studies and by increasing insight into the numerous secondary adverse effects that inevitably accrue. Too little benefit, too many adverse effects.

Rapoport eloquently echoes the observation that all of our present psychopharmacological options emerged as a result of serendipity based on conditions that no longer exist – chiefly the ability to carefully observe patient responses to systematic treatment trials during long-term inpatient hospitalizations (1). To advance the field, she urges us to seek ways of recapturing opportunities that may once again lead to fortuitous discovery. One benefit of the extension of health care benefits in the United States, dubbed “Obamacare”, is the requirement for the universal adoption of electronic medical records. Such systems could provide the basis for “psychopharmacological epidemiology” in what is arguably the most adventuresome health care system in the industrialized world. Heretofore, much of the clinical experimentation conducted under conditions of apparent necessity has been inaccessible to investigators. Adoption of harmonized medical record systems that can be searchable, while protecting patient privacy and confidentiality, could provide the essential infrastructure for recapturing serendipity (1).

However, simply trolling large data sets is unlikely to yield much clinical bounty. The needle of occasional therapeutic benefit is too slender to detect within the haystack of clinical complexity and the Tower of Babel of existing clinical records. As Rapoport notes, the optimism regarding repurposing older medications for psychiatric disorders has not been matched by much evidence of success to date. The answer, we hope, lies in shifting from the illusory distant goal of “personalized medicine” to the more modest and attainable one of “stratified psychiatry”, as recently advocated in the context of developing clinical tests (2). As shown by the example of human epidermal growth factor subtype 2 (HER2) in breast, ovarian, endometrial, non-small-cell lung and even gastric cancer (2), identification of effective means of stratifying on the basis of prognosis can lead to the development of effective novel therapeutic agents, in that case, the monoclonal antibody trastuzumab, also known as Herceptin.

So, what lessons can we glean from the molecular therapeutic advances being attained in oncology? Chiefly, that we must reinvigorate our efforts to understand pathophysiology. As psychiatrists cannot access brain tissue with the same facility as oncologists probe tumor samples, we will need to further develop indirect methods, such as those based on human induced pluripotent stem cells, as noted by Rapoport in her conclusion. Regardless of the method, the overarching goal needs to be to understand physiology, and the many ways it goes awry in pathophysiology. We must think in terms of systems, networks, and above all, functions. Fortunately, many of the elements and components required to carry out this endeavor are close at hand. Human brain function is increasingly being appreciated in terms of large-scale neural systems, i.e., spatially defined networks, which capture and condense complexity

which would otherwise remain unimaginable (3–5).

In the dazzling field of molecular genetics, simplistic notions that common variants would account for much of the substantial heritability of psychiatric disorders have been replaced by a focus on biological pathways and their underlying genetic networks (6). Genetic markers are no longer sought as sufficient clues to pathogenesis, but rather as indicators of the relevant physiological processes which can become targets for intervention. An illustration of our near-term objective was provided two decades ago by D. Klein in his seminal consideration of “false suffocation alarms, spontaneous panics, and related conditions” (7). Klein arrayed myriad clinical and laboratory observations in light of an evolutionarily motivated theory of the etiology of panic disorder, i.e., that spontaneous panic attacks result from dysfunction of an inborn suffocation alarm system. This formulation made sense of seemingly inconsistent observations and has motivated hundreds of subsequent reports, many of them relevant to anxiety disorders in children and adolescents. However, the greater lesson is encoded in the conclusion, which would be well adopted in pediatric psychopharmacology and clinical neuroscience: “The history of medicine amply demonstrates the value of the splitting diagnostic approach as well as the dangers of hardening of the categories. An active experimental, therapeutic, and physiologic challenge approach to psychopathology may move us from symptoms to a grasp of deranged circuitry” (7).

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A European perspective on paedo-psychiatric pharmacoepidemiology

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J. Rapoport's paper confronts the reader with the central statement that in the recent past some over-acceptance of drug treatment for children and adolescents with mental disorders has emerged, contributing to the development of a reductionist psychobiology. This may be regarded as a major current threat to the identity of child and adolescent psychiatry. The present commentary concentrates on findings indicating that this over-prescribing of psychotropic medications in children and adolescents differs in magnitude in the various countries. More detailed analyses are needed for a better understanding of these differences.

International studies have shown that the prescription rates of psychotropic medications in children and adolescents vary substantially across countries. The prevalence of any prescription of psychotropic drugs in youth in the year 2000 was substantially greater in the US (67 per 1,000 people) than in the Netherlands (29 per 1,000) and in Germany (20 per 1,000) (1). Marked differences among countries have been observed also for individual groups of drugs. For instance, the utilization of antidepressants in 0–19 year olds in the year 2000 in an US dataset (16.3 per

1,000) largely exceeded that of three Western European countries (1.1–5.4 per 1,000) (2).

There have been also changes over time in both the total number of prescriptions and the utilization of the various drugs. The number of all psychotropic prescriptions for children has risen between the years 2000 and 2002 in Europe, South America, and North America (3). In the Netherlands, the prescription rate of all antipsychotics, benzodiazepines, antidepressants, and psychostimulants increased from 11.1 per 1,000 in 1995 to 22.9 per 1,000 in 2001 (4). These time trends have been also observed for individual groups of drugs, including stimulants, the most widely prescribed psychotropics in children and adolescents, but also antidepressants and antipsychotics.

However, most of the data on time trends are biased by the unrepresentativeness of the study populations and the short and rather accidental observation periods. The long-standing tradition and quality of Scandinavian registers, including data on prescriptions, allow studies which are not affected by these biases. Our own recent study (5) based on the Danish register, analyzing all dispensed prescriptions in the population aged 0–17 years between the years 1996 and 2010, allowed a consistent analysis of patterns of psychotropic medication over fifteen consecutive years. The major findings were the following. First, the prevalence of all dispensed psychotropic medications over these fifteen years showed a nine-fold increase. This increase was much re-

duced after adjustment for the increasing number of patients seeking help from public health services. However, even after adjustment, there was still a two-fold higher rate of dispensed prescriptions over the observation period. Secondly, this trend was most pronounced for stimulants, with a twenty-three-fold increase in non-adjusted prevalence rates and a still eight-fold increase in adjusted prevalence rates. For antidepressants, there was a 9.5-fold increase (1.8-fold increase after adjustment). For antipsychotics, there was a 6.6-fold increase (two-fold increase after adjustment). Despite increasing numbers, these Danish rates were lower than in many other European countries and particularly in the US.

Vitiello (6) suggested that many factors affect prescription of medications in children, including variations in health service organization, differences in diagnostic systems, adherence to clinical practice guidelines, drug regulations, availability and allocation of financial resources, and cultural attitudes towards child and adolescent mental disorders. It remains unclear whether the Danish public health system counteracts to some extent the impact of market forces on prescriptions. However, given the similar organization of health services in Scandinavian countries and some indication of markedly different prescription rates for psychotropic medications in these countries (7), there is not much room for the argument that public health services *per se* unfold strong control of market processes through strict drug

regulations and restrictive allocations of financial resources. Differences in diagnostic systems, with Denmark using the ICD-10 rather than the DSM-IV classification, and a potentially less strict adherence to clinical guidelines in most European countries compared to the US, may have exerted some impact.

The main factor involved may still be represented by the different cultural attitudes towards child and adolescent mental disorders among both lay people and experts. Without having solid studies and data in this respect, one may only argue that some characteristics of the Danish society, including no marked social gradients, a stable large middle class, free public health services for citizens, and a predominant feeling of a high quality of life, may have had an impact against the tendency to over-

prescribe psychotropic medications to children and adolescents. It is also possible that the current status of Danish and European child and adolescent psychiatry is encouraging a patient-oriented assessment and treatment, beyond evidence-based guidelines. However, more detailed analyses are needed in order to understand inter-country differences in drug prescriptions in young people with mental disorders.

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Do we face the same dilemma on pediatric psychopharmacology in low and middle income countries?

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Children and adolescents constitute almost a third of the world's population, and almost 90% live in low and middle income countries (LMIC), where they form up to 50% of the population (1). Available data strongly suggest that child mental disorders occur in different cultures at the same rates as those detected in developed countries (1,2). Thus, the majority of children suffering from mental disorders live in LMIC.

Can we extend the dilemma proposed in Rapoport's paper ("too much or too little psychiatric medication?") to those children? I am afraid the answer would be no. Some years ago, we documented that a substantial proportion of children with the diagnosis of attention-deficit/hyperactivity disorder (ADHD) do not receive any kind of

treatment in several countries of Latin America (3). As an example, we studied around 100 children with ADHD presenting clear impairment from a huge non-referred school sample in Brazil. Less than 5% of them had ever received any treatment for their condition (4).

We recently highlighted a phenomenon that we called the 90/10 paradigm: only about 10% of randomized clinical mental health trials for children and adolescents come from LMIC, while almost 90% of children and adolescents live in those countries. Almost all trials assess psychopharmacological interventions, while there is a complete lack of high quality studies assessing combined treatments (1). Finally, less than 2% of the items published in child psychiatry have an author from a low or low-middle income country (5).

There is a shortage of child psychiatrists in LMIC, and the great majority of them do not have access to training in evidence-based mental health. So,

differently from the US, children with ADHD, obsessive-compulsive disorder, tics, anxiety or depressive disorders receiving medication represent a small minority in those countries. In fact, ordinarily, only those from middle-high to high-income class families have access to the few child psychiatrists in these regions by paying out of their pockets (1).

What kind of child psychopharmacology is found in LMIC? Outside the few university settings, we see children with inadequate diagnosis, being treated with ineffective doses for short periods of time, with medications not supported by empirical evidence, and frequently with polypharmacy. Most of these children are treated by non-specialists (this is not a problem *per se* in our reality; the problem is the lack of adequate training). So, the future of pediatric psychopharmacology in LMIC lies not only in the development of new drugs, but also in training more child psychiatrists and in educating more child mental health

professionals in evidence-based treatments, so that they can use appropriately the tools we already have. However, Rapoport's view that child psychiatrists are being reduced to a mechanistic role of prescribing medication should be taken as a word of advice for the kind of training to be offered globally.

Moving away from the role of a LMIC clinician and taking the perspective of a researcher in the field, I cannot be in more agreement with Rapoport's description of a sense of frustration in the field of child psychopharmacology in recent years. Despite some initiatives like testing drugs acting on the glutamatergic system for different child mental disorders, we are living in a moment of "me too" drugs. Nothing really new and effective seems to be visible in the horizon.

I share with Rapoport the excitement and expectations on potential discoveries from studies using brain cells derived from human induced pluripotent stem cells of individuals with both typical development and child neuropsychiatric conditions. However, as she points out, in order to develop new drug targets, we need to expand our knowledge on the normal trajectories of brain development and how child mental disorders impact on it (6). We need to pursue effective ways to

interfere on these trajectories as early as possible, addressing the so-called "at risk" conditions, as other medical specialties do. Some initiatives along this line are flourishing in the area of psychosis (7).

Combining the research and the clinical perspectives, one additional issue that is worth to mention is the lack of real functional outcomes as dependent variables in child psychopharmacology. The field needs to move beyond studies only documenting statistically significant reductions in psychopathological scale scores. What we really want to know, as in other areas of medicine, is how our treatments impact on the natural history of the disorders. Do antidepressants decrease suicides in adolescence? Do ADHD medications reduce school repetitions and accidents at home? Some findings are just now appearing in the literature (8).

Finally, as wisely mentioned by Rapoport, we cannot forget that child psychopharmacology means prescribing medication for individuals with a developing brain and, most of the time, for long periods. Thus, we need to improve our long-term drug surveillance by well-designed post-marketing psychopharmacology epidemiological studies.

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Child psychopharmacology: how much have we progressed?

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Since its inception, pediatric psychopharmacology has been a point of clinical interest as well as concern. While a constant attempt has been made to find the "magic pill" for psychiatric disorders, concerns regarding safety have often overshadowed new drug development. However, with double blind randomized placebo controlled trials becoming the norm, pediatric psychopharmacology has

come of age to certain extent. Rapoport reviews the evolution, current practices and future of child psychopharmacology. However, there are other important issues relevant to clinical practice across the world that we would like to discuss briefly.

To begin with, a large part of pediatric psychopharmacological literature comes from the US and European countries. Most drug trials are on homogenous populations of Caucasian individuals, often to the exclusion of other ethnic and cultural groups. However, studies

have shown that different ethnic groups metabolize drugs differently, and hence safety and efficacy in one group cannot be easily generalized to the other (1,2). This is especially important given that a huge population of today's children reside in Asia and Africa. Ideally, in the future, we should design large scale multicentric or multicountry trials to generate data which can be applicable to children and adolescents throughout the world. Additionally, diagnostic criteria for various psychiatric disorders have been developed in the Western

world and may not be valid in their entirety in other populations. Even in the Western world, diagnostic criteria for most severe and common mental illness are developed for adult populations. Researchers and clinicians often apply adult criteria to children and adolescents, which is at times not appropriate. For example, evidence shows that childhood depression has phenomenological differences from adult depression. Until we develop sufficient culture as well as age based evidence, child psychiatrists must tread with caution while making decisions regarding prescription.

Next, even in a homogenous population, most of the psychopharmacological evidence is for a particular disorder and for a particular age group. Evidence of efficacy for one diagnosis does not imply efficacy for other related diagnoses. Additionally, the available evidence should not be taken as applicable across all ages during the childhood and adolescence, as the current level of evidence based on randomized controlled trials is limited to certain age groups. For example, the US Food and Drug Administration has approved the use of stimulants for children above 6 years only, based on randomized controlled trial data (3). In contrast, available data suggest that in certain cases stimulants are used in children as young as 2 years (4). It must be remembered that organ systems (including and especially the central nervous system) in children are in a state of constant development and any form of pharmacology may impact this. Safety data that are available for most drugs do not extend beyond 6 months to 1 year, with studies that follow up participants for 2 years being labeled as "long term". While constraints of the investigators and the study itself are understandable, the clinician needs to remember that we just do not have enough information about how a particular drug will impact a child as he/she grows towards adulthood.

Evidence is accumulating that, like in adults, second generation antipsychotics cause significant weight gain and

dyslipidemia in children and adolescents (5). Cardiovascular diseases are the most common cause of mortality and morbidity worldwide, and lack of long-term surveillance data on cardio-metabolic side effects in those receiving antipsychotics is an important limitation of current evidence. The increase in the prevalence of obesity, diabetes mellitus and cardiovascular events in younger age groups may significantly impact on the health expenditures in the years to come.

Additionally, the growing practice to use different agents for various symptoms rather than treating disorders leads to polypharmacy, further adding to the safety conundrum. As pointed out by Rapoport, polypharmacy and off-label use of medications must be strongly discouraged.

One issue which is not discussed by Rapoport is the dearth of research on the attitudes of patients and their parents (who are often the decision makers) toward use of medications, both for short and long term. Some studies suggest that parents are usually fearful of administering psychotropics to their children and often prefer psychological treatments over pharmacological agents (6). Medication compliance rates in patients with disorders like attention-deficit/hyperkinetic disorder vary from 56 to 75% (7) and attitudes towards medication certainly contribute to reduce adherence to treatment. Hence, the clinician should not ignore the need to assess patients' and caregivers' attitudes and concerns. Clinicians should work with them to clarify possible erroneous beliefs and misconceptions associated with use of medications in childhood and adolescence.

Finally, a problem that plagues almost all of psychopharmacology, and particularly child psychopharmacology, is that, while we have a great deal of efficacy data, true real-world effectiveness data are sorely missing.

Despite all these problems, the future of pediatric psychopharmacology seems

bright. With the recognition of financial conflicts of interests and increased governmental funding to test various psychotropics for different conditions in children and adolescents, we can soon expect to have much better quality data from neutral sources which can strengthen the confidence of use of medications in children and adolescents. Further, with the development of psychiatric pharmacogenomics, we can hope that we will soon be able to develop more targeted drugs and understand genetic variations which influence treatment response, thus moving from empirical selection of medications to personalized medicine in true sense.

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Psychopharmacological treatments in children and adolescents. Adequate use or abuse?

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J. Rapoport's article is a comprehensive and well-balanced review of pediatric psychopharmacology over four decades. Without any doubt we are now experiencing, not only in the US but in many other countries in the world, an overdiagnosis and overtreatment of mental disorders in children and adolescents. Some authors speak of a "dramatic expansion of the use of psychotropic medications in children in recent years" (1).

This might have different causes: medications are easy to prescribe and to apply, treatments are less time consuming compared to psychotherapy, and in some disorders (such as attention-deficit/hyperactivity disorder, ADHD) there is a large group of quick responders. But it might also have to do with a switch from a categorical to a dimensional model of disease, facilitating the treatment of less severe cases by using lower cut-off points and not taking so much into account the burden of suffering. In this context, the question of cognitive enhancement in young people becomes more and more relevant. The Internet is full of advertisements of "brain doping as a quiet revolution".

Psychopharmacological treatments in children should always consider the developmental perspective. It is true that our knowledge in that field is still limited. However, the existent knowledge is sometimes not taken into consideration. For example, the ineffectiveness of tricyclic antidepressants in children has to do with the incomplete maturation of the transmitter systems at that age.

Related to the knowledge about brain maturation is the question of qualification of doctors for prescribing psychotropic drugs in children. Due to the uneven distribution of child and adolescent psychiatrists and other specialists

with expertise in this field, a significant number of children in need for psychopharmacological treatment receive their medication from general practitioners and other prescribers with varying degrees of interest and training (2).

Not much is known regarding the long-term effects of most psychotropic medications when administered in childhood. In this respect, it is a source of concern that so-called preschool bipolar children are treated with compounds which are not even sufficiently tested in adults, and that new categories like bipolar spectrum disorders are created (3,4). There are also other new labels like "deficient emotional self regulation" still waiting for convincing empirical validation, but already used in medication studies.

Studies like these raise the question of validity of diagnoses. We see a tendency to make diagnoses on the basis of rating scales and checklists, missing the important information which can be collected by thorough interviews and observation of the patients. Even standardized interviews miss major elements of the disorder when not combined with a detailed family history and individual history of the patient.

A further major issue in pediatric psychopharmacology is comorbidity. This applies more or less to all psychopathological disorders in childhood and adolescence. For instance, in a study on autism spectrum disorders, 95% of the patients had three or more psychiatric disorders and 47% had more than five (5). This is a great challenge for medication, since it leads to polypharmacy, with all its consequences.

There is a remarkable shortage of studies on combined treatments (for instance, medication plus cognitive-behavioural therapy, or family interventions, or specific school programs), though it is well known that environmental factors interact significantly with pharmacological treatment. There is also a complete

absence of studies on the placebo effect in pediatric psychopharmacology, although clinical experience indicates that this effect is significant also in children.

Interestingly enough, the majority of studies in pediatric psychopharmacology come from a few very productive centers. This raises the question of funding by the pharmaceutical industry and possibly also of conflicts of interests. In this context, the importance of ethical guidelines, such as those produced by the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP), should be emphasized.

As to future perspectives, those which appear most promising to me are the reclassification of syndromes in terms of endophenotypes, allowing a more carefully tailored approach to pharmacological treatment; combined treatment approaches (medication and non-medication treatment); and the development of new medications after clarification of the brain developmental trajectories for different endophenotypes.

There is still in the public, as Rapoport mentions, "a climate against medication for children with mental disorders". This has to do with widespread misunderstandings, such as that behaviourally defined syndromes are not real disorders and cannot be treated by medication, and that psychotropic drugs poison the brain and cause dependence. Both statements are wrong in this general formulation, but difficult to disprove. The best arguments against these misunderstandings are a clear and restrictive indication for psychopharmacological treatments and their integration into a comprehensive treatment plan, including other treatment components (e.g., psychotherapy, family and school interventions). Medication alone is not sufficient in most cases.

Psychopharmacological treatment in children was and is still a long

journey. J. Rapoport and her co-workers have made a remarkable contribution along this way.

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The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons

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Although psychotherapy and antidepressant medication are efficacious in the treatment of depressive and anxiety disorders, it is not known whether they are equally efficacious for all types of disorders, and whether all types of psychotherapy and antidepressants are equally efficacious for each disorder. We conducted a meta-analysis of studies in which psychotherapy and antidepressant medication were directly compared in the treatment of depressive and anxiety disorders. Systematic searches in bibliographical databases resulted in 67 randomized trials, including 5,993 patients that met inclusion criteria, 40 studies focusing on depressive disorders and 27 focusing on anxiety disorders. The overall effect size indicating the difference between psychotherapy and pharmacotherapy after treatment in all disorders was $g=0.02$ (95% CI: -0.07 to 0.10), which was not statistically significant. Pharmacotherapy was significantly more efficacious than psychotherapy in dysthymia ($g=0.30$), and psychotherapy was significantly more efficacious than pharmacotherapy in obsessive-compulsive disorder ($g=0.64$). Furthermore, pharmacotherapy was significantly more efficacious than non-directive counseling ($g=0.33$), and psychotherapy was significantly more efficacious than pharmacotherapy with tricyclic antidepressants ($g=0.21$). These results remained significant when we controlled for other characteristics of the studies in multivariate meta-regression analysis, except for the differential effects in dysthymia, which were no longer statistically significant.

Key words: Psychotherapy, antidepressant medication, depressive disorders, anxiety disorders, dysthymia, obsessive-compulsive disorder, meta-analysis

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Depressive and anxiety disorders are highly prevalent (1,2) and associated with high levels of service use, a considerable disease burden (3), substantial economic costs (4–6), and a significant loss of quality of life for patients and their relatives (7,8). Several efficacious treatments for depressive and anxiety disorders are available, including different forms of psychotherapy and antidepressant medication (9–11). Although both types of treatment have been found to be efficacious, it is not known whether they are equally efficacious for all types of depressive and anxiety disorders. There is evidence from meta-analyses of studies comparing psychotherapy and pharmacotherapy directly that they are about equally efficacious in depression (12) and generalized anxiety disorder (GAD) (13). It is not clear whether this is true for all depressive and anxiety disorders. For example, for obsessive-compulsive disorder (OCD) and social anxiety disorder (SAD), no meta-analyses of direct comparisons between psychotherapy and pharmacotherapy have been conducted yet, even though a considerable number of such comparative trials have been carried out.

Furthermore, it remains unclear whether all types of psychotherapy and all types of antidepressant medications have comparable effects. In one previous meta-analysis, we found that treatment with selective serotonin reuptake inhibitors (SSRIs) was somewhat more effective than treatment with psychotherapy (12), whereas tricyclic antidepressants (TCAs)

and psychotherapy were equally effective. A re-analysis of those data, however, showed that there were no significant differences between psychotherapy and SSRIs after adjusting for differential drop-out from both treatments. Another meta-analysis confirmed that psychotherapy and SSRIs were equally effective, when only *bona fide* psychotherapies were included (14).

It is also possible that there are differences between different forms of psychotherapy. There are some indications from meta-analytic research that interpersonal psychotherapy (IPT) may be somewhat more efficacious than other psychotherapies in the treatment of depression (15,16), although this is not confirmed in all meta-analyses (17). There are also some indications that psychodynamic psychotherapy (18) and non-directive supportive counselling (19) may be somewhat less efficacious than other psychotherapies. Given these potential differences between psychotherapies, it is conceivable that the differential effects of psychotherapy and pharmacotherapy may depend on the type of psychotherapy. Earlier meta-analyses may have failed to detect these differential effects because of the small number of included studies and the resulting lack of statistical power.

We report here the results of an overall meta-analysis of the studies in which psychotherapy and antidepressant medication for depressive and anxiety disorders were directly compared with each other.

METHODS

Identification and selection of studies

Several strategies were used to identify relevant studies. We searched four major bibliographical databases (PubMed, PsycInfo, EMBASE and the Cochrane database of randomized trials) by combining terms indicative of each of the disorders with terms indicative of psychological treatment (both MeSH terms and text words) and randomized controlled trials. We also checked the references of 116 earlier meta-analyses of psychological treatments for the included disorders. Details of the searches and exact search strings are given in Figure 1.

We included randomized trials in which the effects of a psychological treatment were directly compared with the effects of antidepressant medication in adults with depressive disorder, panic disorder with or without agoraphobia, GAD, SAD, OCD, or post-traumatic stress disorder (PTSD). Only studies in which subjects met diagnostic criteria for the disorder according to a structured diagnostic interview – such as the Structured Clinical Interview for DSM-IV (SCID), the Composite International Diagnostic Interview (CIDI) or the Mini International Neuropsychiatric Interview (MINI) – were included. Comorbid mental or somatic disorders were not used as an exclusion criterion. Studies on inpatients, adolescents and children (below 18 years of age) were excluded. We also excluded maintenance studies, aimed at people who had already recovered or partly recovered after an earlier treatment, and studies on other types of medication, such as benzodiazepines for anxiety disorders. Studies in English, German, Spanish and Dutch were considered for inclusion.

Quality assessment and data extraction

We evaluated the quality of included studies using the Cochrane Collaboration “risk of bias” assessment tool (20). This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence, the concealment of allocation to conditions, the prevention of knowledge of the allocated intervention (masking of assessors), and dealing with incomplete outcome data (this was rated as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses). The assessment was conducted by two independent researchers, and disagreements were solved through discussion.

We also coded the participant characteristics (disorder, recruitment method, target group); the type of antidepressant which was used (SSRI, TCA, monoamine oxidase inhibitor (MAOI), other or protocolized treatment including several antidepressants); and the characteristics of the psychotherapy (format, number of sessions, and type of psychotherapy). The types of psychotherapy we identified were

cognitive-behavioral therapy (CBT), IPT, problem-solving therapy, non-directive supportive counselling, psychodynamic psychotherapy, and others. Although CBTs used a mix of different techniques, we clustered them together in one group. We rated a therapy as CBT when it included cognitive restructuring or a behavioral approach (such as exposure and response prevention). When a therapy used a mix of CBT and IPT, we rated it as “other”, along with other therapeutic approaches.

Meta-analyses

For each comparison between a psychotherapy and a pharmacotherapy, the effect size indicating the difference between the two groups at post-test (Hedges' g) was evaluated. Effect sizes were calculated by subtracting (at post-test) the average score of the psychotherapy group from the average score of the pharmacotherapy group, and dividing the result by the pooled standard deviation. Because some studies had relatively small sample sizes, we corrected the effect size for small sample bias (21).

In the calculations of effect sizes in studies of patients with depressive disorders, we used only those instruments that explicitly measured symptoms of depression. In studies examining anxiety disorders, we only used instruments that explicitly measured symptoms of anxiety. If more than one measure was used, the mean of the effect sizes was calculated, so that each study provided only one effect size. If means and standard deviations were not reported, we used the procedures of the Comprehensive Meta-Analysis software (version 2.2.021) to calculate the effect size using dichotomous outcomes; and if these were not available either, we used other statistics (such a t value or p value). To calculate pooled mean effect sizes, we also used the Comprehensive Meta-Analysis software. Because we expected considerable heterogeneity among the studies, we employed a random effects pooling model in all analyses.

We only examined the differential effects at post-test and did not look at the longer-term effects. The types of outcomes reported at follow-up and the follow-up periods differed widely between studies. Furthermore, some studies reported only naturalistic outcomes, while others delivered booster sessions and maintenance treatments during the whole follow-up period or part of it. Because of these large differences, we decided it was not meaningful to pool the results of these outcomes.

As a test of homogeneity of effect sizes, we calculated the I^2 statistic. A value of 0% indicates no observed heterogeneity, and higher values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (22). We calculated 95% confidence intervals around I^2 (23) using the non-central chi-squared-based approach within the Heterogi module for Stata (24).

We conducted subgroup analyses according to the mixed effects model, in which studies within subgroups are pooled

	Depression	GAD	SAD	Panic	OCD/PTSD	Total
<i>21,729 references identified by literature search</i>						
Pubmed	3320	547	296	849	91	5103
Cochrane	2988	1309	752	1436	128	6613
PsycInfo	2710	337	246	424	32	3749
Embase	4389	372	661	764	78	6264
Total	13407	2565	1955	3473	329	21729
⇓						
<i>After removal of duplicates</i>						
	9860	1562	1228	2032	221	14903
⇓						
<i>Earlier meta-analyses checked for references</i>						
	42	7	14	26	27	116
⇓						
<i>Full-text papers retrieved</i>						
	1344	136	247	493	58	2278
⇓						
<i>Reasons for exclusion</i>						
No correct comparison	235	49	83	169	27	563
Duplicate study	306	32	24	52	5	419
No diagnosis	165	32	52	112	2	363
No control group	167	7	39	33	3	249
No psychotherapy	151	7	1	76	3	238
Other reason	280	8	41	40	10	379
Total	1304	135	240	482	50	2211
⇓						
<i>Included in meta-analysis</i>						
	40	1	7	11	OCD: 6 PTSD: 2	67

GAD – generalized anxiety disorder, SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder

Figure 1 Selection and inclusion of studies

with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model. For continuous variables, we used meta-regression analyses to test whether there was a significant relationship between the continuous variable and the effect size, as indicated by a Z value and an associated p value.

We tested for publication bias by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure (25), which yields an estimate of the effect size after the publication bias has been taken into account. We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant.

Multivariate meta-regression analyses were conducted with the effect size as the dependent variable. To decide which variables should be entered as predictors in the regression

model, we first defined a reference group within each category of variables. To avoid collinearity among the predictors of the regression model, we first examined whether high correlations were found among the variables that could be entered into the model. Next, we calculated the correlations between all predictors (except the reference variables). Because no correlations were higher than $r=0.60$, all predictors could be entered in the regression models. Multivariate regression analyses were conducted in STATA MP, version 11 for Mac.

RESULTS

Selection and inclusion of studies

After examining a total of 21,729 abstracts (14,903 after removal of duplicates), we retrieved 2,278 full-text papers for

Table 1 Selected characteristics of included studies

Study	Disorder	Psychotherapy	Medication	Quality*	Country
Bakhshani et al (26)	GAD	CBT (n=7)	TCA (n=7)	- - - +	Iran
Bakker et al (27)	PAN	CBT (n=35)	SSRI (n=32)	- - - +	Europe
			TCA (n=32)		
Barber et al (28)	MDD	DYN (n=51)	Mixed/other (n=55)	- - + +	USA
Barlow et al (29)	PAN	CBT (n=65)	TCA (n=83)	- - + +	USA
Barrett et al (30)	Mood	PST (n=80)	SSRI (n=80)	+ + + +	USA
Bedi et al (31)	MDD	Counseling (n=39)	Mixed/other (n=44)	+ + - -	Europe
Black et al (32)	PAN	CBT (n=25)	SSRI (n=25)	- - - -	USA
Blackburn & Moore (33)	MDD	CBT	Mixed/other	- - - +	Europe
Blanco et al (34)	SAD	CBT (n=32)	MAOI (n=35)	+ + + +	USA
Blomhoff et al (35)	SAD	BT (n=98)	SSRI (n=95)	+ + + +	Europe
Browne et al (36)	DYS	IPT (n=122)	SSRI (n=117)	+ + + -	Canada
Clark et al (37)	PAN	CBT (n=16)	TCA (n=16)	- - + -	Europe
Dannon et al (38)	PAN	CBT (n=23)	SSRI (n=27)	- - - -	Israel
David et al (39)	MDD	CBT (n=56)	SSRI (n=57)	- - + +	Europe
		REBT (n=57)			
Davidson et al (40)	SAD	CBT (n=42)	SSRI (n=39)	+ + + +	USA
Dekker et al (41)	MDD	DYN (n=59)	Mixed/other (n=44)	- - + -	Europe
Dunlop et al (42)	MDD	CBT (n=41)	SSRI (n=39)	+ + + +	USA
Dunner et al (43)	DYS	CBT (n=9)	SSRI (n=11)	- - + -	USA
Elkin et al (44)	MDD	IPT (n=61)	TCA (n=57)	+ + + +	USA
		CBT (n=59)			
Faramarzi et al (45)	MDD	CBT (n=29)	SSRI (n=30)	- - + -	Iran
Finkenzeller et al (46)	MDD	IPT (n=23)	SSRI (n=24)	+ - + +	Europe
Foa et al (47)	OCD	BT (n=19)	TCA (n=27)	- - + -	USA
Frank et al (48)	MDD	IPT (n=160)	SSRI (n=158)	- - + +	USA
Frommberger et al (49)	PTSD	CBT (n=10)	SSRI (n=11)	- - - -	Europe
Hegerl et al (50)	Mood	CBT (n=52)	SSRI (n=76)	+ + + +	Europe
Heimberg et al (51)	SAD	CBT (n=28)	MAOI (n=27)	- - + +	USA
		Counseling (n=26)			
Hendriks et al (52)	PAN	CBT (n=20)	SSRI (n=17)	+ + + +	Europe
Hoexter et al (53)	OCD	CBT (n=13)	SSRI (n=13)	+ - + -	Brazil
Hollon et al (54)	MDD	CBT (n=25)	TCA (n=57)	- - + +	USA
Jarrett et al (55)	MDD	CBT (n=36)	MAOI (n=36)	+ + + +	USA
Keller et al (56)	MDD	CBASP (n=226)	SNRI (n=220)	+ + + +	USA
Kolk et al (57)	PTSD	EMDR (n=24)	SSRI (n=26)	- - + +	USA
Koszycki et al (58)	PAN	CBT (n=59)	SSRI (n=62)	+ + + +	Canada
Lesperance et al (59)	MDD	IPT (n=67)	SSRI (n=75)	+ + + +	Canada
Loerch et al (60)	PAN	CBT (n=14)	MAOI (n=16)	- - + +	Europe
Markowitz et al (61)	DYS	IPT (n=23)	SSRI (n=24)	- - + +	USA
		Counseling (n=26)			
Marshall et al (62)	MDD	CBT (n=37)	Mixed/other (n=30)	- - - -	Canada
		IPT (n=35)			
Martin et al (63)	MDD	IPT (n=13)	SNRI (n=15)	- - - +	Europe

Table 1 Selected characteristics of included studies (*continued*)

Study	Disorder	Psychotherapy	Medication	Quality*	Country
McBride et al (64)	MDD	CBT (n=21)	Mixed/other (n=21)	— — — —	Canada
McKnight et al (65)	MDD	CBT	TCA	— — — —	USA
McLean & Hakstian (66)	MDD	DYN (n=44) BT (n=42)	TCA (n=49)	— — + —	Canada
Miranda et al (67)	MDD	CBT (n=90)	Mixed/other (n=88)	+ + + +	USA
Mohr et al (68)	MDD	CBT (n=20) Supp Ex (n=19)	SSRI (n=15)	— — — +	USA
Mörtberg et al (69)	SAD	CBT ind (n=32) CBT grp (n=35)	Mixed/other (n=33)	+ + + +	Europe
Murphy et al (70)	MDD	CBT (n=22)	TCA (n=24)	+ + — +	USA
Murphy et al (71)	MDD	PST (n=29)	TCA (n=27)	+ + + +	Europe
Mynors-Wallis et al (72)	MDD	PST gp (n=39) PST n (n=41)	SSRI (n=36)	+ + + +	Europe
Nakatani et al (73)	OCD	BT (n=10)	SSRI (n=10)	— — + —	Japan
Nazari et al (74)	OCD	EMDR (n=30)	SSRI (n=30)	— — + —	Iran
Oosterbaan et al (75)	SPH	CBT (n=28)	MAOI (n=27)	— — + +	Europe
Prasko et al (76)	SPH	CBT (n=22)	MAOI (n=20)	— — + —	Europe
Ravindran et al (77)	DYS	CBT (n=24)	SSRI (n=22)	+ + + —	Canada
Reynolds et al (78)	MDD	IPT (n=16)	TCA (n=25)	— — + +	USA
Rush et al (79)	MDD	CBT (n=19)	TCA (n=22)	— — + +	USA
Salminen et al (80)	MDD	DYN (n=26)	SSRI (n=25)	— — — +	Europe
Schulberg et al (81)	MDD	IPT (n=93)	TCA (n=91)	— — + +	USA
Scott & Freeman (82)	MDD	CBT (n=29) Counseling (n=29)	TCA (n=26)	+ + + +	Europe
Shamsaei et al (83)	MDD	CBT (n=40)	SSRI (n=40)	+ — + —	Iran
Shareh et al (84)	OCD	CBT (n=6)	SSRI (n=6)	— — — —	Iran
Sharp et al (85)	PAN	CBT (n=29)	SSRI (n=29)	— — — —	Europe
Sharp et al (86)	Mood	Counseling (n=112)	Mixed/other (n=106)	+ + + +	Europe
Sousa et al (87)	OCD	CBT (n=25)	SSRI (n=25)	— — + —	Brazil
Spinhoven et al (88)	PAN	CBT (n=20)	SSRI (n=19)	— — — +	Europe
Thompson et al (89)	MDD	CBT (n=36)	TCA (n=33)	— — — +	USA
Van Apeldoorn et al (90)	PAN	CBT (n=36)	Mixed/other (n=37)	+ + + +	Europe
Weissman et al (91)	MDD	IPT (n=23)	TCA (n=20)	— — + —	USA
Williams et al (92)	Mood	PST (n=113)	SSRI (n=106)	+ + + +	USA

*A positive or negative sign is given for four quality criteria: allocation sequence, concealment of allocation to conditions, blinding of assessors, and intention-to-treat analysis

GAD – generalized anxiety disorder, PAN – panic disorder with or without agoraphobia, MDD – major depressive disorder, Mood – mixed mood disorder, SAD – social anxiety disorder, DYS – dysthymic disorder, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder, CBT – cognitive-behavioral therapy, DYN – psychodynamic therapy, PST – problem-solving therapy, BT – behavior therapy, IPT – interpersonal psychotherapy, REBT – rational emotive behavior therapy, CBASP – cognitive behavioral analysis system of psychotherapy, EMDR – eye movement desensitization and reprocessing, Supp Ex – supportive-expressive therapy, ind – individual format, grp – group format, gp – delivered by a general practitioner, n – delivered by a nurse, TCA – tricyclic antidepressant, SSRI – selective serotonin reuptake inhibitor, MAOI – monoamine oxidase inhibitor, SNRI – serotonin-norepinephrine reuptake inhibitor

further consideration. We excluded 2,211 of the retrieved papers. The flow chart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. A total of 67 studies met the inclusion criteria for this meta-analysis. Selected characteristics of the included studies (26–92) are reported in Table 1.

Characteristics of included studies

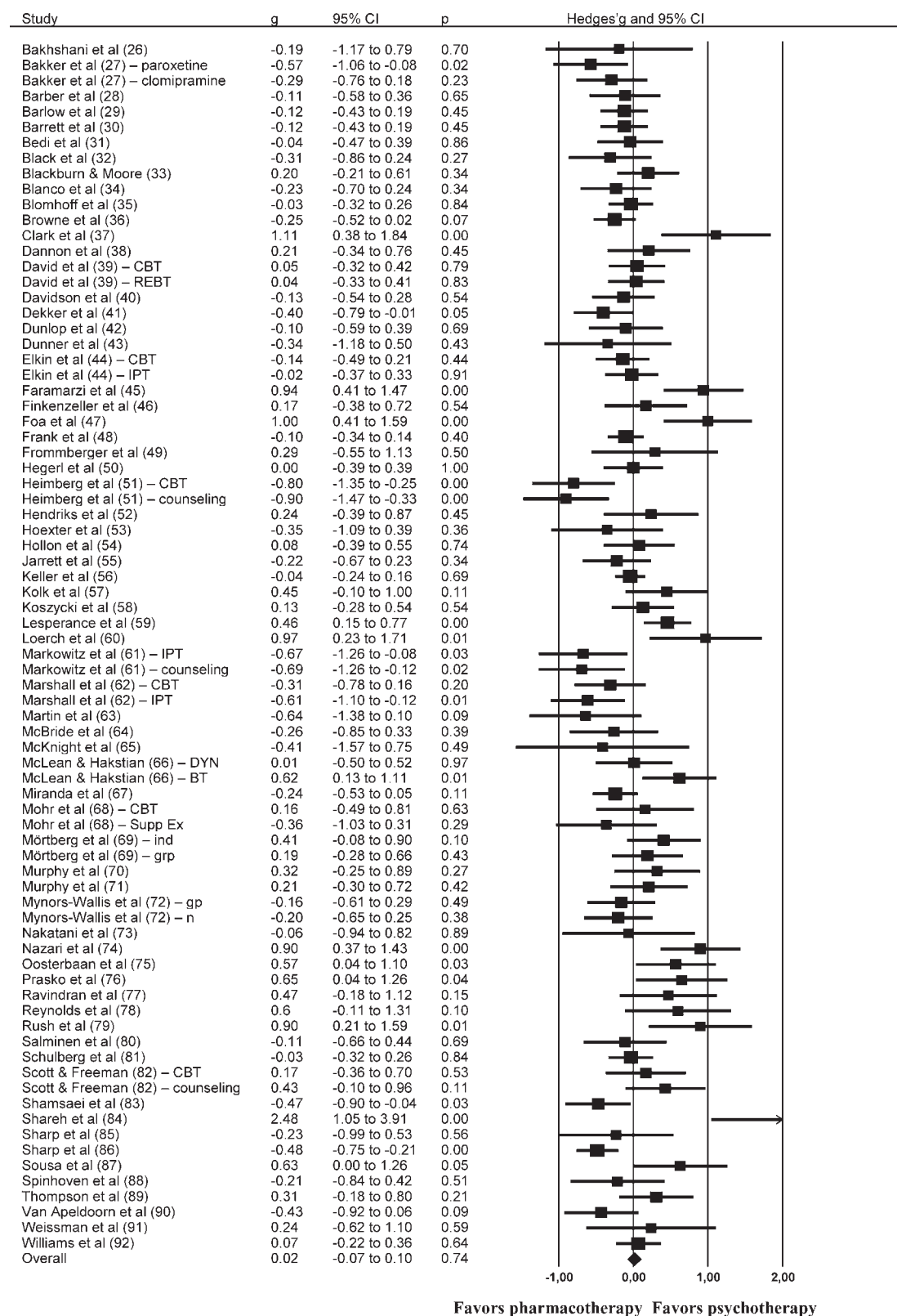
In the 67 studies, a total of 5,993 patients participated (3,142 in the psychotherapy and 2,851 in the pharmacotherapy conditions). Forty studies focused on depressive

Table 2 Comparative effects of psychotherapy and pharmacotherapy: subgroup analyses

		N	g	95% CI	I ²	95% CI	p
All studies		78	0.02	−0.07 to 0.10	62	52 to 70	
Possible outliers removed		68	−0.07	−0.14 to 0.01	41	21 to 56	
One effect size per study (highest)		67	0.06	−0.03 to 0.15	62	51 to 71	
One effect size per study (lowest)		67	0.03	−0.07 to 0.12	62	51 to 71	
Mood disorders							
	Any mood disorder	48	−0.03	−0.14 to 0.08	52	0 to 47	0.01
	Major depression	39	0.02	−0.10 to 0.13	46	22 to 63	
	Dysthymia	5	−0.30	−0.60 to −0.00	55	0 to 83	
	Mixed mood disorders	4	−0.14	−0.45 to 0.17	64	0 to 88	
Anxiety disorders							
	Any anxiety disorder	30	0.10	−0.05 to 0.25	71	59 to 80	
	Panic disorder	12	0.00	−0.28 to 0.28	62	28 to 79	
	SAD	9	−0.03	−0.34 to 0.28	74	50 to 87	
	OCD	6	0.64	0.20 to 1.08	72	36 to 88	
	Other	3	0.24	−0.39 to 0.86	0	0 to 90	
Psychotherapy type							
	Cognitive-behavioral therapy	49	0.09	−0.03 to 0.20	60	46 to 71	0.12
	Interpersonal psychotherapy	11	−0.09	−0.31to 0.14	65	33 to 82	
	Problem-solving therapy	5	−0.04	−0.36 to 0.27	0	0 to 79	
	Counseling	6	−0.33	−0.64 to −0.02	69	27 to 87	
	Other	7	0.07	−0.21 to 0.34	67	27 to 85	
Treatment format							
	Individual	62	0.02	−0.08 to 0.12	61	48 to 70	0.89
	Group	14	0.03	−0.18 to 0.25	71	50 to 83	
Pharmacotherapy							
	SSRI	37	0.01	−0.12 to 0.13	58	40 to 71	0.02
	TCA	20	0.21	0.04 to 0.39	52	19 to 71	
	MAOI	7	−0.05	−0.34 to 0.25	83	65 to 91	
	Mixed/protocol/other	14	−0.19	−0.37 to 0.00	49	5 to 72	
Recruitment							
	Only clinical samples	36	0.07	−0.06 to 0.20	55	34 to 69	0.52
	Also community recruitment	35	−0.03	−0.16 to 0.10	65	50 to 76	
	Other recruitment method	7	−0.04	−0.34 to 0.25	76	49 to 89	
Country							
	USA	31	−0.07	−0.21 to 0.07	52	28 to 68	0.17
	Europe	29	0.03	−0.11 to 0.17	56	34 to 71	
	Other	18	0.15	−0.04 to 0.34	76	62 to 85	
Quality							
	Score 0–1	31	0.10	−0.06 to 0.25	69	56 to 79	0.44
	Score 2–3	23	−0.03	−0.19 to 0.13	65	46 to 78	
	Score 4	24	−0.02	−0.17 to 0.12	38	0 to 62	

All subgroup analyses were conducted with the random effects model; a positive effect size indicates superior effects of psychotherapy; the p values indicate whether the effect sizes in the subgroups differ significantly from each other; significant values are highlighted in bold

SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant, MAOI – monoamine oxidase inhibitor



CBT – cognitive-behavioral therapy, REBT – rationale emotive behavior therapy, IPT – interpersonal psychotherapy, DYN – psychodynamic therapy, BT – behavior therapy, Supp Ex – supportive-expressive therapy, ind – individual format, grp – group format, gp – delivered by a general practitioner, n – delivered by a nurse

Figure 2 Differential effects of psychotherapy and pharmacotherapy (Hedges' g)

Table 3 Standardized regression coefficients of characteristics of psychotherapy and pharmacotherapy studies

		Full model			Parsimonious model		
		Coef.	95% CI	p	Coef.	95% CI	p
Disorder							
	MDD	Ref.					
	Dysthymia	−0.01	−0.46 to 0.43				
	Other mood disorder	0.02	−0.42 to 0.45				
	Panic disorder	−0.10	0.42 to 0.21				
	SAD	0.12	−0.28 to 0.53				
	OCD	0.52	0.01 to 1.03	<0.05	0.76	0.36 to 1.15	<0.001
	Other anxiety disorder	0.32	−0.30 to 0.95				
Recruitment from clinical samples only		0.05	−0.17 to 0.26				
Adults in general vs. specific target group		−0.41	−0.70 to −0.13	<0.01	−0.27	−0.50 to −0.05	<0.05
Psychotherapy							
	CBT	Ref.					
	ITP	−0.16	−0.45 to 0.12				
	Counseling	−0.51	−0.92 to −0.19	<0.05	−0.41	−0.72 to −0.09	<0.05
	Other therapy	−0.03	−0.39 to 0.33				
Pharmacotherapy							
	SSRI	Ref.					
	TCA	0.32	0.06 to 0.58	<0.05	0.31	0.11 to 0.50	<0.01
	MAOI	0.07	−0.34 to 0.48				
	Other	−0.23	−0.51 to 0.05				
Individual psychotherapy format		0.01	−0.27 to 0.28				
Number of psychotherapy sessions		0.01	−0.02 to 0.04				
Quality of study		0.00	−0.07 to 0.08				
Country							
	USA	Ref.					
	Europe	0.26	0.03 to 0.49	<0.05	0.18	0.00 to 0.36	<0.05
	Other	−0.00	−0.31 to 0.31				
Constant		0.31	−0.29 to 0.91		0.09	−0.12 to 0.29	

MDD – major depressive disorder, SAD – social anxiety disorder, OCD – obsessive-compulsive disorder, CBT – cognitive-behavioral therapy, ITP – interpersonal psychotherapy, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant, MAOI – monoamine oxidase inhibitor

disorders (32 on major depressive disorder, four on dysthymia, and four on mixed mood disorders) and 27 on anxiety disorders (11 on panic disorder with or without agoraphobia, six on OCD, seven on SAD, two on PTSD, and one on GAD). Many studies (n=32) recruited patients exclusively from clinical samples, and most (n=56) were aimed at adults in general instead of a more specific population (such as older adults or patients with a comorbid somatic disorder). Most psychotherapies (49 of the 78 that were examined in these studies) were characterized as CBT; 11 studies examined IPT, five problem-solving therapy, six non-directive counseling, four psychodynamic therapies, and the remaining three other therapies. Most therapies (n=62) used an individual treatment format, and the number of treatment sessions ranged from 6 to 20, with most therapies (n=45) having between 12 and 18 sessions. The

antidepressants that were examined in the studies included SSRIs (n=37), TCAs (n=20), SNRIs (n=2), MAOIs (n=7), and treatment protocols with different types of antidepressant medication (n=12). Most studies were conducted in the United States (n=27) or in Europe (n=23).

Quality assessment

The quality of the studies varied. Twenty-seven studies reported an adequate sequence generation, while the other 40 did not. Twenty-four studies reported allocation to conditions by an independent (third) party. Forty-nine studies reported blinding of outcome assessors or used only self-report outcomes, whereas 18 did not report blinding. Forty-two studies conducted intention-to-treat analyses (a post-treatment score was analyzed for every patient even if the last observation

prior to attrition had to be carried forward or that score was estimated from earlier response trajectories). Twenty studies met all four quality criteria, four studies met three criteria, and the remaining 43 studies met two criteria or less.

Comparative effects of psychotherapy and pharmacotherapy

The overall mean effect size indicating the difference between psychotherapy and pharmacotherapy at post-test for all 78 comparisons was 0.02 (95% CI: -0.07 to 0.10; Table 2), in favor of psychotherapy, but not significantly different from zero. Heterogeneity was moderate to high ($I^2=62$; 95% CI: 52 to 70). The results of these overall analyses are presented in Figure 2.

Removing possible outliers (in which the 95% CI of the effect size did not overlap with the 95% CI of the pooled effect size) resulted in a small, non-significant effect size in favor of pharmacotherapy and somewhat lower heterogeneity ($I^2=41$; low to moderate).

In this meta-analysis, we included ten studies in which two psychological treatments were compared with the same pharmacotherapy group, as well as one study in which one psychological treatment was compared with two different types of antidepressant medication. This means that multiple comparisons from these studies, not independent from each other, were included in the same analysis, which may have resulted in an artificial reduction of heterogeneity and may have affected the pooled effect size. We examined the possible effects of this by conducting an analysis in which we included only one effect size per study. First, we included only the comparison with the largest effect size from these studies and then we conducted another analysis in which we included only the smallest effect size. As can be seen from Table 2, the resulting effect sizes as well as the levels of heterogeneity were comparable with the overall analyses.

We found no indications for publication bias. The effect size did not change after adjusting for publication bias according to Duval and Tweedie's trim and fill procedure, and according to this procedure no missing study had to be imputed.

Univariate moderator analyses

We examined whether there were significant differences between psychotherapy and pharmacotherapy in specific subgroups of studies. The results of these subgroup analyses are presented in Table 2. We found that the effect size was significantly associated with the type of disorder ($p<0.01$). More specifically, we found that pharmacotherapy was more efficacious than psychotherapy in dysthymia (differential effect size: $g=-0.30$; 95% CI: -0.60 to -0.00; $I^2=55$; 95% CI: 0 to 83). By contrast, psychotherapy was more efficacious than pharmacotherapy in OCD (differential effect size: $g=0.64$; 95% CI: 0.20 to 1.08; $I^2=72$; 95% CI: 36 to 88).

We also found that type of pharmacotherapy was significantly associated with the differential effect size ($p<0.05$). Treatment with a TCA was significantly less efficacious than psychotherapy ($g=0.21$; 95% CI: 0.04 to 0.39; $I^2=52$; 95% CI: 19 to 71), while there was no significant difference between other types of pharmacotherapy and psychotherapy. Furthermore, we found that treatment with non-directive supportive counseling was less efficacious than pharmacotherapy ($g=-0.33$; 95% CI: -0.64 to -0.02; $I^2=69$; 95% CI: 27 to 87).

We did not find that the effect size was associated with the treatment format in psychotherapy, recruitment method of patients, country where the study was conducted, or the quality of the study.

Multivariate meta-regression analyses

Because we found several important moderators of outcome in the univariate moderator analyses, we decided to conduct a multivariate meta-regression analysis in which we entered the relevant predictors simultaneously. The results of these analyses are presented in Table 3. The effects of psychotherapy were still significantly higher than those of pharmacotherapy in studies on OCD, even after adjusting for other characteristics of the included studies. We also found that non-directive supportive counseling was still significantly less efficacious than pharmacotherapy, and TCAs remained significantly less efficacious than psychotherapy. In dysthymia, psychotherapy and pharmacotherapy did no longer differ significantly from each other.

In the multivariate meta-regression analysis, the effects of two predictors became significant: studies in Europe had a higher pooled effect size (indicating superior effects of psychotherapy) than studies in other parts of the world, and pharmacotherapy was significantly more efficacious in studies among specific target groups (such as older adults and patients who also had a general medical disorder) than in those among adults in general.

We also conducted a (manual) back-step meta-regression analysis. In this analysis, we dropped the least significant variable in each step, until only significant predictors ($p<0.05$) were retained in the model (Table 3). In this parsimonious model, we found that the same predictors were significant as in the full meta-regression model.

DISCUSSION

In this meta-analysis, we found that the differences in effects between psychotherapy and antidepressant medication were small to non-existent for major depression, panic disorder and SAD. We also found evidence that pharmacotherapy was significantly more efficacious in dysthymia, and that psychotherapy was significantly more efficacious in OCD. Furthermore, pharmacotherapy was significantly more efficacious than non-directive counseling,

and psychotherapy was significantly more efficacious than pharmacotherapy with TCAs. These associations remained significant when we controlled for other characteristics of the studies in multivariate meta-regression analysis, except for the differential effects in dysthymia, which were no longer significant. In these multivariate meta-regression analyses, we also found that psychotherapy was more efficacious in studies from Europe compared with those from other countries, and that pharmacotherapy was significantly more efficacious in studies among specific target groups than in those among adults in general.

The present results indicate that different kinds of antidepressants and psychotherapies have varying degrees of efficacy in treating depression and anxiety disorders. TCAs and non-directive counseling seemed to be less efficacious than the other treatments, although we found in an earlier meta-analysis that the lower effects of non-directive counseling may be caused in part by researcher allegiance (93). The finding that psychotherapy is less efficacious than pharmacotherapy in dysthymia is in line with earlier meta-analytic research (94). However, the number of studies is small and the difference was no longer statistically significant after adjusting for quality and other study characteristics. As such, the finding is not very stable and more research is needed to examine this issue.

In OCD, the outcomes are rather straightforward in that psychotherapy is clearly more efficacious than antidepressants, even adjusting for quality and other characteristics of the studies. This is the first meta-analysis to show that psychotherapy is more efficacious than pharmacotherapy. This finding is also important from a clinical perspective, because OCD is often regarded as the most severe anxiety disorder.

One of the strengths of this study is the broad range of disorders and treatments we included. But the study also has some limitations. First, for several disorders insufficient numbers of studies were available. We only had a few studies examining PTSD, GAD and dysthymia. Second, the quality of many of the included studies was not optimal. Third, because of the many differences between the studies, we only examined the differential effects of psychotherapy and pharmacotherapy at post-test, and did not look at the longer-term effects. There are indications that psychotherapy may have sustained effects over the longer-term, while antidepressants do not have strong effects when the patients stop taking them (95). Fourth, we only considered the effects of treatments on the disorders they were designed to address. Finally, while it is well known that pharmacotherapies have several side effects, which are often reported in the studies, the idea that psychotherapies can have negative effects has only recently been recognized (96), and these negative effects are typically not reported in the studies. It was, therefore, not possible to compare psychotherapies and pharmacotherapies in terms of negative effects.

Despite the limitations, we can conclude that pharmacotherapy and psychotherapy have comparable effects in several depressive and anxiety disorders, but this is not true for all disorders, especially not for OCD and possibly dysthymia.

Furthermore, most psychotherapies and pharmacotherapies are equally efficacious, but this again is not true for all treatments, especially for TCAs and non-directive supportive counseling. Finally, while treatments may be equal in effects, they may not be equal in terms of patient preferences and costs, which deserve further investigations across disorders.

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Early childhood sexual abuse increases suicidal intent

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Childhood sexual abuse has been consistently associated with suicidal behavior. We studied suicide attempt features in depressed individuals sexually abused as children. On average, sexual abuse started before age 9. It frequently coexisted with physical abuse. Suicide attempters more often had personality disorders and had endured abuse for longer, but did not differ in terms of other clinical characteristics from non-attempters. Earlier onset of sexual abuse and its duration were associated with more suicide attempts. However, when personality disorders were included in the regression model, only these disorders predicted number of attempts. The severity of sexual abuse and the coexistence of physical abuse were correlated with age at first suicide attempt. However, only severity of sexual abuse was marginally associated with age at first suicide attempt in the regression model. Finally, the earlier the age of onset of sexual abuse, the higher the intent, even after controlling for age, sex and personality disorders. This suggests that the characteristics of childhood sexual abuse, especially age of onset, should be considered when studying the risk for suicidal behavior in abused populations.

Key words: Suicide, suicidal features, early trauma, life events

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Childhood abuse is unfortunately a common problem. In 2008, an estimated 772,000 children in the US were victims of maltreatment, with 120,000 substantiated cases of physical abuse and 70,000 of sexual abuse (1). The lifetime prevalence rate of physical abuse according to the National Comorbidity Survey is estimated at 16.5% (with 62.5% of the reports concerning females) (2), whereas a recent meta-analysis of studies in non-clinical samples has estimated a lifetime prevalence of sexual abuse of 19.2% among females and 7.9% among males (3).

Sexual abuse and, to a lesser extent, physical abuse in childhood have both been consistently associated with suicidal behavior (4–6). Indeed, those reporting any traumatic experience in childhood show a 2 to 5-fold higher risk of being suicide attempters compared to those who do not (5), with the relationship of suicide attempt with childhood physical or sexual abuse being stronger than that with verbal abuse and molestation (7). More physically painful abuse may also relate to a greater number of later suicide attempts than less painful abuse (7). Repeated abuse, compared to single episodes of abuse, or abuse by a member of immediate family may also heighten risk for attempting suicide in later life (8).

Recent work suggests that abuse may be especially damaging when it occurs at a very young age, with high levels of depression being more frequent among children abused in the first five years of life (9). However, to our knowledge, there are no studies examining the relationship between the age at onset of abuse and the risk for suicidal behavior in later life.

We studied the features of suicide attempts in a sample of depressed individuals who had been abused as children. We hypothesized that a greater risk of attempted suicide is associated with childhood sexual abuse rather than

physical abuse, and that measures of severity of the suicidal behavior, such as higher number of suicidal attempts, younger age at first suicide attempt, greater lethality of the attempts and more serious suicidal intent, are related to earlier age at onset of abuse. Given their well-established role in the risk for suicidal behavior (10–12), we controlled for sex, age and personality disorders.

METHODS

Study participants

The initial sample consisted of 288 depressed adult subjects recruited at the inpatient and outpatient units of two university clinics, the Western Psychiatric Institute and Clinic in Pittsburgh (n=188) and the New York Psychiatric Institute (NYSPI, n=100), as part of a larger study (13). To obtain accurate information on the abuse, we selected 222 subjects who had completed the Childhood and Adolescence Review of Experiences (CARE) (14). Because sexual, but not physical, abuse was significantly associated with attempting suicide ($X^2=4.439$; $df=1$; $p=0.035$ and $X^2=0.145$; $df=1$; $p=0.704$, respectively), we further analyzed only individuals who had been sexually abused (n=103). Those with physical abuse, but no sexual abuse, were excluded. All participants gave written informed consent as required by the Institutional Review Board of the University of Pittsburgh, St. Francis Medical Center, and the NYSPI.

The average age in the sample was 40.3 ± 7.9 years (range: 23 to 60 years), and 93.2% of subjects were female (n=96). The mean total number of years of education was 14.0 ± 2.9 (range: 9 to 24 years). Most subjects were either separated/divorced (n=41; 39.8%) or married (n=38; 36.9%).

Regarding ethnicity, 60.2% of subjects were White (n=80), 27.8% were African American (n=37), 0.8% were Asian (n=1), and 3.0% were more than one race (n=4). Race was missing for 11 subjects, most of them being of Hispanic origin (10/11). In total, 9.0% of the subjects were Hispanic (n=12).

Primary lifetime Axis I diagnoses were major depression (86.4%, n=89) and bipolar disorder (13.6%, n=14). Secondary lifetime diagnoses were anxiety disorders excluding post-traumatic stress disorder (PTSD) (54.4%, n=56), PTSD (42.7%, n=44), and dysthymia (12.6%, n=13). Regarding Axis II diagnoses, 38.8% of subjects (n=40) met criteria for a personality disorder, with borderline personality disorder being the most frequently diagnosed (25.2%, n=26). With regard to substance use, 45.6% of subjects (n=47) reported alcohol use, 17.5% (n=18) reported using cocaine, 23.3% (n=24) reported using cannabis, and 58.3% (n=60) reported the use of at least one substance.

Assessment

All subjects were assessed for the presence of lifetime and current DSM-IV psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID-I) (15). Personality disorders were diagnosed using the Axis II Structured Clinical Interview (SCID-II) (16). Depression severity was assessed with the Hamilton Rating Scale for Depression (HAM-17) (17). Suicidal behavior was assessed using the Columbia University Suicide History Form (10), the Medical Damage Lethality Rating Scale (12), and the Beck Suicide Intent Scale (18).

The operational definitions of childhood physical and sexual abuse were based on a previous study by our group (19). Master level clinicians or clinical psychologists carried out the evaluation. MD or PhD level clinicians subsequently confirmed the assessment in consensus meetings. In all subjects, history of childhood physical and sexual abuse was assessed with a series of screening questions in the demographic questionnaire and the CARE. Screening questions asked: a) for any history of physical and/or sexual abuse over lifetime; b) if yes, whether the abuse was physical, sexual, or both; and c) if yes, whether the abuse took place before age 15 years. The CARE is an interview focusing on early childhood adverse experiences. It retrospectively assesses the presence or absence of physical and/or sexual abuse, age at onset, severity, duration, and perpetrator of abuse between the ages of 8 and 18 years. In the assessment of sexual abuse, there was 86.5% agreement between the CARE and the screening questions (192/222; $\kappa=0.73$, 95%CI = 0.63-0.81). Severity of the abuse was the maximal score in any sexual abuse episode according to the CARE scale. Duration of abuse was the maximal length in any episode of sexual abuse according to the data of the CARE. Age at onset of abuse was the earliest age at which the patient endorsed having suffered sexual abuse.

To assess impulsivity/aggression trait measures, participants were administered the Brown-Goodwin Aggression Inventory (20), the Barratt Impulsivity Scale (BIS) (21), and the Buss-Durkee Hostility Inventory (22).

The role of the abuser was categorized in two groups: a) primary caretaker at home (sibling, parent, step-parent, close relative) or non-custodial parent; b) stranger (including acquaintance, babysitter, neighbor and other adult living out of the home). For individuals who suffered abuse from different persons, we considered the person who inflicted the most severe abuse as the main abuser.

Statistical analyses

Chi-square analyses were used to explore the association of ever attempting suicide with reported physical or sexual abuse. In the subsample of sexually abused subjects, attempters versus non-attempters were compared on demographic and diagnostic variables and features of the abuse using chi-square analyses and analyses of variance. Bivariate correlations were conducted within the sample of sexually abused suicide attempters. We used Pearson correlation to examine the association between response variables measuring the severity of the suicidal behavior (number of suicide attempts, lethality of suicide attempt, age at first suicide attempt, and level of suicidal intent) and the characteristics of the abuse (age at onset of the abuse, concurrent physical abuse, role of the abuser, severity of the abuse, duration of the abuse and repetition of abuse episodes).

Linear regression models were developed including the characteristics of abuse that significantly correlated with the response variables. Both main effects and interactions were tested, but no significant interactions were detected. The significance level was set at $\alpha=0.05$ (2-sided). Personality disorders, sex and age were introduced in the regression models as covariates to control for their association with the characteristics of the suicide attempts (age at first attempt was adjusted for personality disorders and sex only). Correlation and regression analyses were repeated including only females (93.2%), but the overall results were similar with and without males, so results are shown only with regards to the total sample.

RESULTS

Description of the sample

Among those who were sexually abused, suicide attempters and non-attempters did not differ in terms of race, age, or other socio-demographic variables (Table 1). Regarding lifetime diagnoses, suicide attempters were more likely to be diagnosed with personality disorders ($X^2=16.32$; $df=1$; $p<0.001$), particularly borderline personality disorder ($X^2=15.4$; $df=1$; $p<0.001$). No differences were found

Table 1 Socio-demographic, clinical and historical variables in sexually abused suicide attempters and non-attempters

	Attempters (n=57)	Non-attempters (N=46)	Test results (df=1)	p
Age (years, mean±SD)	40.1 ± 8.9	40.6 ± 6.7	F=0.92	0.763
Sex (% males)	7.0	6.5	X ² =0.01	0.921
Education (years, mean±SD)	14.0 ± 2.9	14.0 ± 2.8	F=0.001	0.981
Race (% non-Hispanic White)	53.6	65.2	X ² =1.41	0.234
Married (%)	33.3	41.3	X ² =0.69	0.405
Major depression lifetime diagnosis (%)	80.7	93.5	X ² =3.54	0.060
Bipolar disorder lifetime diagnosis (%)	19.3	6.5		
PTSD lifetime diagnosis (%)	47.4	37.0	X ² =1.13	0.288
Personality disorder diagnosis (%)	59.3	18.6	X ² =16.32	0.000
Borderline personality disorder diagnosis (%)	42.6	7.0	X ² =15.48	0.000
Substance use (%)	61.4	54.3	X ² =0.52	0.470
HAM-D score (mean±SD)	13.5 ± 7.0	12.5 ± 7.2	F=0.50	0.480
Impulsivity (BIS, mean±SD)	63.1 ± 19.5	57.2 ± 18.2	F=2.34	0.129
Aggression (Brown-Goodwin, mean±SD)	21.1 ± 5.8	20.2 ± 6.4	F=0.464	0.497
Hostility (Buss-Durkee, mean±SD)	39.4 ± 11.8	36.7 ± 12.5	F=1.18	0.279
Age at onset of abuse (years, mean±SD)	8.00 ± 4.3	8.8 ± 3.7	F=0.91	0.343
Concurrent physical abuse (%)	54.4	54.3	X ² =0.00	0.997
Role of abuser (in home or parent, %)	45.3	32.6	X ² =1.66	0.198
Severity of abuse (CARE, mean±SD)	5.5 ± 6.4	5.9 ± 5.0	F=0.08	0.767
Repeated episodes of abuse (%)	35.1	26.1	X ² =0.96	0.326
Duration of abuse (months, mean±SD)	40.4 ± 47.1	16.7 ± 30.1	F=8.09	0.005

PTSD – post-traumatic stress disorder; HAM-D – Hamilton Rating Scale for Depression; BIS – Buss-Durkee Hostility Inventory; CARE – Childhood and Adolescence Review of Experiences

between attempters and non-attempters with regards to PTSD or substance abuse. The groups did not significantly differ in severity of depression (as assessed by the HAM-17). Similarly, measures of impulsivity, aggression or hostility did not differ between attempters and non-attempters.

On average, sexual abuse occurred before age 9 for both attempters and non-attempters and frequently (54.4%) coexisted with physical abuse. The mean severity was reported between 5 and 6 (5 being “simulated intercourse over clothes” and 6 being “child masturbating abuser or involved in abuser’s masturbation or simulated intercourse under clothes”). With regards to the characteristics of the abuse, suicide attempters suffered sexual abuse for a longer period than non-attempters (40.4 vs. 16.7 months; $F=8.01$; $df=1$; $p=0.005$). No other differences were found between suicide attempters and non-attempters in terms of age at

onset of the abuse, concurrent physical abuse, role of the abuser, severity of the abuse and repetition of abuse episodes (Table 1).

Characteristics of suicide attempts

Within the suicide attempters group, the mean number of attempts was 1.4 ± 0.49 . Earlier onset of the sexual abuse ($r=-.273$; $p=0.048$) and duration of the abuse ($r=.293$; $p=0.004$) were associated with more lifetime suicide attempts. An almost significant correlation was also found between the number of abuse episodes and the number of suicide attempts ($r=.259$; $p=0.052$). The remaining characteristics of the sexual abuse showed no association with the number of suicide attempts (Table 2). We examined other

Table 2 Correlations (r) between severity of suicidal behavior and abuse characteristics

	Age at onset	Maximal duration	Maximal severity	Main abuser	Number of episodes	Physical abuse
Number of attempts	-.273 ($p=0.048$)	.293 ($p=0.004$)	.101 ($p=0.456$)	-.171 ($p=0.222$)	.259 ($p=0.052$)	.187 ($p=0.163$)
Total score (SIS)	-.382 ($p=0.005$)	.183 ($p=0.203$)	-.154 ($p=0.258$)	-.190 ($p=0.178$)	.200 ($p=0.139$)	.141 ($p=0.302$)
Age at first attempt	.135 ($p=0.335$)	-.038 ($p=0.791$)	-.298 ($p=0.024$)	.114 ($p=0.418$)	-.017 ($p=0.901$)	-.323 ($p=0.014$)
Maximal lethality	-.067 ($p=0.631$)	.039 ($p=0.786$)	.005 ($p=0.973$)	.056 ($p=0.689$)	.068 ($p=0.615$)	-.061 ($p=0.651$)

SIS – Suicide Intent Scale

Table 3 Predictors of severity of suicidal behavior

Response variable	Predictor variables	Beta	t	p
Number of suicide attempts	Age	0.09	0.00	0.99
	Sex	0.03	0.66	0.49
	Personality disorders	0.36	0.46	0.000
	Number of abuse episodes	0.14	0.10	0.30
	Duration of abuse	0.151	1.42	0.159
Age at first suicide attempt	Age at onset of abuse	-0.17	-0.05	0.67
	Sex	0.00	-0.00	0.999
	Personality disorders	-0.09	-0.71	0.483
	Severity of sexual abuse	-0.24	-1.70	0.094
Suicidal intent	Physical abuse	-0.24	-1.73	0.090
	Age	-0.25	-1.78	0.083
	Sex	0.06	0.47	0.64
	Personality disorders	-0.06	-0.44	0.66
	Age at onset of abuse	-0.37	-2.67	0.011

demographic and clinical characteristics of the sample, and identified personality disorders as correlated with the number of attempts ($r=.462$; $p<0.001$). After including personality disorders in the regression model, only those disorders, and not age at onset of sexual abuse or the number of episodes of abuse, predicted number of attempts (Table 2). Therefore, we tested the collinearity between age at onset of sexual abuse and personality disorders. Subjects with personality disorder diagnoses tended to report on average an earlier age of onset of the sexual abuse compared with the rest of the sample (7.4 vs 9.1 years respectively; $F=3.87$; $df=1$; $p=0.052$).

The more severe the sexual abuse, the earlier the first suicide attempt occurred ($r=-.298$; $p=0.024$). Similarly, the coexistence of physical abuse was significantly associated with an earlier onset of the suicide attempts ($r=-.323$; $p=0.014$). However, age of onset of the abuse was not associated with age at first suicide attempt. No other significant findings emerged. All significant associations disappeared in the regression model when controlling for personality disorders and sex; only severity of sexual abuse was marginally associated with the age at first suicide attempt (Table 3).

Only one significant correlation was found between the characteristics of the abuse and the level of suicidal intent: the earlier the age of onset of the sexual abuse, the higher the intent ($r=-.382$; $p=0.005$). This finding persisted even after controlling for age, sex and personality disorder diagnoses of the participants in the regression model (Table 3). Subjects younger than 12 years of age at the onset of sexual abuse reported greater suicidal intent than subjects older than 12 years of age ($F=8.35$; $df=1$; $p=0.006$), but no other differences in suicidal features.

The lethality of the most lethal attempt (as assessed by the Medical Damage Lethality Rating Scale) was not

associated with any characteristics of the sexual abuse. Consequently, regression analyses were not performed.

DISCUSSION

Few studies have examined the effects of different characteristics of childhood abuse in relation to later suicide attempts, despite the well-known association between abuse and suicidal behavior (23,24). Yet, severe sexual abuse, such as vaginal or anal penetration in childhood, seems to be associated with higher rates of suicide ideation and attempts than are less severe sexual activities, such as molestation (6). In this study, we examined the effect of age of sexual abuse onset on characteristics of lifetime suicidal behavior. In our sample, only sexual, but not physical, abuse was associated with suicidal behavior. This finding contradicts previous evidence regarding physical abuse and suicide risk in larger samples (25), but is consistent with reports indicating a higher risk of suicide attempts after sexual abuse when compared with physical abuse (5,26). While sexual abuse seems clearly associated with increased risk for suicidal behavior independently of confounding factors, a previous study showed that the association of physical abuse and suicidal behavior could be largely explained by the socio-economic and familial context in which the abuse occurred (6).

As hypothesized, earlier onset of sexual abuse was associated with greater suicidal intent. This finding remained even when other variables, such as personality disorders, age, and sex, were controlled for. However, the age at onset of the abuse was not associated with any other of the selected markers of suicide attempt severity. That personality disorders were associated with both age at onset of abuse and lifetime number of suicide attempts, may explain why age of onset of sexual abuse was not found to be associated with the number of suicide attempts in the adjusted regression model. In agreement with the literature (11,27,28), suicidal behavior was more frequent among individuals with personality disorders. Impulsive aggression traits have been proposed as an intermediate phenotype of suicide (29), and may mediate the association of borderline personality disorder with suicidal behavior (30,31). We did not find greater scores of impulsivity, aggression or hostility among suicide attempters, but differences among the groups were not expected, since sexual abuse correlates with these measures and the whole sample was exposed to this type of abuse (19,32–34).

The mechanisms that link childhood abuse and suicidal behavior remain unknown, but it may be that the effect of childhood abuse on brain development underlies this association at least partly. A large body of developmental research has investigated the consequences of early trauma on cognitive and affective functioning. Individuals who suffered childhood maltreatment have shown decreased intellectual performance, impairments in memory and executive

functions, and deficits in areas of affective functioning, such as reward processing or emotional perception (35). Furthermore, childhood abuse may alter developmental processes related to the strengthening of emotion regulation and associated interpersonal skills (36,37). Difficulties in emotion regulation are thought to confer risk for later mental disorders (38,39), and may mediate the association of childhood trauma with child and adult psychopathology (40–43). There is also evidence that sexual abuse increases the sensitivity to subsequent depressogenic life events (44). The extent to which the psychopathology of abused individuals, which is a major risk factor for suicidal behaviors, mediates the relationship between childhood abuse and suicidal behavior is still to be determined. Cognitive impairments (45) and emotional dysregulation (46) have also been independently associated with increased suicidal behavior.

The timing of physical or sexual childhood trauma may determine the effects of traumatic experiences in the developing brain (38,47). For instance, the impact of stress reactions due to early child abuse might lead these children to be chronically stressed and overly vigilant and with atypical cortisol regulation (41,48). Earlier age at onset of abuse has also been linked with more pronounced over-generalized memory (49), a term that describes a difficulty in retrieving specific autobiographical memories, and to increased risk for PTSD (47). In our sample, the modal onset of abuse was just before age 9. Our finding that the younger the onset of the abuse, the higher the intent of attempts, is consistent with the aforementioned studies. However, more work is needed to elucidate this, as the relation between the age of onset of traumatic experiences and its consequences might not be linear. We also found that sexual abuse starting after age 12 was associated with less suicidal intent in later life. According to developmental research, brain systems undergoing growth spurts may show increased susceptibility to environmental influences (38). Andersen et al (50) reported in a female sample that, during certain periods, sexual abuse was associated with smaller hippocampal volume (at ages 3 to 5) or with dysfunctions in the corpus callosum (at ages 9 to 10) and the prefrontal cortex (at ages 11 to 14) (50). The interaction of early life stress and small hippocampal volume might also increase the risk for depression (51).

Several limitations should be considered in the present study. The relatively small sample size hampers the possibility of finding differences among the study groups, and the analyses are cross-sectional in design. Recall bias might be present, since the mean number of years from childhood abuse onset to the moment of the assessment was 31.7 ± 9.2 . However, most studies in the field have also relied on retrospective records of childhood abuse, even though their use is controversial (52). If personality factors mediate the effects of childhood sexual abuse on later suicidal behaviors, including personality disorders in the model may have led to an underestimation of these effects. Puberty occurs on average between ages 12 and 13 (53), but we did not assess pubertal stage and early puberty has

been associated with sexual abuse (54). Finally, other types of abuse, such as psychological and emotional abuse (55), were not considered and other moderating factors, such as parenting styles (56), may be of importance in the relationship between abuse and suicidal behavior.

In summary, our analyses reveal that, among depressed individuals, the earlier the age at onset of sexual abuse, the greater suicidal intent reported for suicide attempts. This suggests that age of onset of abuse should be considered along with the type and severity of the abuse when studying the risk for suicidal behavior in abused populations.

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Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions

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A systematic electronic PubMed, Medline and Web of Science database search was conducted regarding the prevalence, correlates, and effects of personal stigma (i.e., perceived and experienced stigmatization and self-stigma) in patients with schizophrenia spectrum disorders. Of 54 studies (n=5,871), published from 1994 to 2011, 23 (42.6%) reported on prevalence rates, and 44 (81.5%) reported on correlates and/or consequences of perceived or experienced stigmatization or self-stigma. Only two specific personal stigma intervention studies were found. On average, 64.5% (range: 45.0–80.0%) of patients perceived stigma, 55.9% (range: 22.5–96.0%) actually experienced stigma, and 49.2% (range: 27.9–77.0%) reported alienation (shame) as the most common aspect of self-stigma. While socio-demographic variables were only marginally associated with stigma, psychosocial variables, especially lower quality of life, showed overall significant correlations, and illness-related factors showed heterogeneous associations, except for social anxiety that was unequivocally associated with personal stigma. The prevalence and impact of personal stigma on individual outcomes among schizophrenia spectrum disorder patients are well characterized, yet measures and methods differ significantly. By contrast, research regarding the evolution of personal stigma through the illness course and, particularly, specific intervention studies, which should be conducted utilizing standardized methods and outcomes, are sorely lacking.

Key words: Schizophrenia, psychosis, stigma, self-stigma, personal stigma, perceived stigma, correlates

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Psychiatric stigma research has been, up until recently, primarily focused on public concepts of mental illness and the negative reactions toward mentally ill persons displayed by individuals or societal groups (1–3). Several disease and patient characteristics have been identified as factors influencing stigmatization (4,5), and anti-stigma initiatives have been established to decrease stigmatizing attitudes and discriminating actions in individuals and society as a whole (6,7). In the past decade, however, a better understanding of the stigma process has shifted the attention from public stigma to the subjective experience of stigmatized people. Research has identified *inter*-individual variables that might increase or decrease the impact of stigma on the individual (8), as well as *intra*-individual variables that modify the impact of stigma on health-related outcomes. This new focus of interest was accompanied by a growing body of research regarding therapeutic interventions that address those intra- and inter-individual characteristics in mentally ill people aiming to reduce the prevalence and negative effects of stigma (9–12).

In recent years, the proposed inclusion of the attenuated psychosis syndrome in the DSM-5 has raised concerns about the potential stigmatization of patients being labelled “at-risk” (13–16), particularly considering the high number of false positives (only approximately 30% of patients showing putative initial prodromal symptoms eventually develop psychosis within the following 2.5 years) (17–19). This also raises the question of whether different stages of schizophrenia spectrum disorders – i.e., the clinical high

risk syndrome, first episode and chronic illness – may be differently impacted by stigma and self-stigma.

In order to evaluate stigma research, a precise definition of “stigma” is relevant. In the majority of studies, Goffman’s classical proposal that stigma is an “attribute that is deeply discrediting” and that reduces the person who bears it “from a whole and usual person to a tainted, discounted one” (20) serves as the basic definition that authors expand on. Link and Phelan (21), however, criticize the striking variability of stigma definitions used by members of different disciplines and redefine stigma as the co-occurrence of “labelling, stereotyping, separation, status loss, and discrimination”.

A further important terminological distinction is that between public stigma (i.e., “the general population endorses prejudice and manifests discrimination toward people with mental illness” (22)) and personal stigma (consisting of perceived stigma, experienced stigma and self-stigma). The perception or anticipation of stigma refers to people’s beliefs about attitudes of the general population towards their condition and towards themselves as members of a potentially stigmatized group (23). Experienced stigma refers to discrimination or restrictions actually met by the affected persons. Lastly, the internalization and adoption of stereotypic or stigmatizing views, i.e., of public stigma, by the stigmatized individual is referred to as self-stigma or internalized stigma (12). Self-stigma has also been defined as a type of identity transformation that might lead to the loss of previously held (positive) beliefs about the self, which in turn yields negative

consequences for the person such as diminished self-esteem and self-efficacy (24). In this systematic review, we focused exclusively on publications containing data on any of the above-mentioned three definitions of personal stigma.

Despite the importance of personal stigma, to our knowledge, no systematic review has been published on this topic to date. Therefore, we sought to systematically review the prevalence, correlates and consequences of personal stigma in people suffering from schizophrenia spectrum disorders. Furthermore, we aimed to evaluate whether quantitative or qualitative differences in personal stigma exist depending on the illness phase, hypothesizing that personal stigma would increase with increasing illness duration and experience. We further aimed to assess whether interventions have been tested specifically targeting personal stigma in patients with schizophrenia spectrum disorders. Finally, we sought to evaluate the strengths and deficiencies of the current evidence base in order to identify gaps that need to be addressed by further research.

METHODS

A systematic literature review was conducted to identify studies reporting on the prevalence, correlates and effects of personal stigma in patients with schizophrenia spectrum disorders. We conducted an electronic PubMed, Medline, and Web of Science search for published, peer reviewed articles using the following keywords: “schizophrenia”/“psychosis”/“prodrome”/“ultra high risk”/“clinical high risk” AND “stigma”/“self-stigma”, without time or language restrictions. Additionally, the reference lists of identified articles and of two reviews on stigma scales (25,26) and two narrative reviews on personal stigma (16,27) were screened to identify additional articles. To be included in this review, articles had to meet all of the following inclusion criteria: a) reporting on personal, not public stigma; b) a majority of the sample ($\geq 70\%$) diagnosed with schizophrenia or a schizophrenia spectrum disorder, or results for this diagnostic subgroup being reported separately; c) quantitative or semi-quantitative data available on prevalence, correlates or impact of personal stigma or regarding an intervention addressing personal stigma.

With regard to prevalence data, means and percentages were weighted for the number of cases included in a particular study, whenever possible. To calculate weighted percentages of personal stigma dimensions, only proportions of rating scale scores were used. If a scale measured more than two levels (“yes” vs. “no”), reported proportions of scores greater than the scale’s midpoint were used. Mean scores of scales were not summarized and are not reported here, as there were too few studies using the same scales or subscales.

To categorize results regarding prevalence of anticipated/perceived and experienced stigma, we used the conceptual framework implemented in the Inventory of Stigma Experiences of Psychiatric Patients (28), containing the following four domains: a) interpersonal interaction, b) public image of mentally ill people, c) access to social roles, and d) structural

discrimination. In order to indicate which proportion of patients had anticipated/perceived or experienced stigma *at all* (in at least one of the categories), one overall domain was created using the domain with the highest reported prevalence of stigma per study and sample.

To categorize results regarding self-stigma, we used the subscales alienation, stereotype endorsement (stereotype agreement), self-esteem decrement and stigma resistance of the Internalized Stigma of Mental Illness Scale (ISMI, 25) and the Self-stigma of Mental Illness Scale (SSMIS, 22). The subscale stigma resistance indicates the individual’s ability to defy internalization of stigma and is negatively correlated with all other domains of self-stigma. Since the domains of self-stigma are interrelated and interact hierarchically, no overall category was created.

RESULTS

The search for “schizophrenia” AND “stigma” yielded 377 hits, “psychosis” AND “stigma” 136, “prodrome” AND “stigma” 4, “ultra high risk” AND “stigma” 0, “clinical high risk” AND “stigma” 2, “schizophrenia” AND “self-stigma” 16, and “psychosis” AND “self-stigma” 6 hits, adding up to an overall number of 541 hits. After deleting duplicates, 457 articles were retained, all being in English.

Based on title and abstract, 365 articles were excluded due to lack of relevance. Most of these excluded articles focused on public attitudes and stereotypes toward people with schizophrenia spectrum disorders (public stigma), or the burden on family members and relatives of psychiatric patients, or reported on the need for and the benefit of public anti-stigma initiatives concerning mental illness or schizophrenia. Some discussed the need for “relabeling” schizophrenia in order to decrease stigma (29). Three articles were added after checking additional reference lists. After thoroughly examining 95 studies, 54 articles, published between 1994 and 2011, met our inclusion criteria (Figure 1).

Prevalence of personal stigma

Twenty-three (42.6%) of the 54 included publications reported on the prevalence of anticipated stigma ($n=12$), experienced stigma ($n=17$), or self-stigma ($n=6$). Among these, 15 studies reported primarily on correlates of personal stigma, while assessing prevalence was only secondary. Sample sizes ranged from 31 to 1,229 participants (total $n=5,871$, mean: $n=267$), mean age ranged from 24.5 ($SD=6.3$) to 54.3 ($SD=16.6$) years, and the percentage of male participants ranged between 38 and 71%. Participants were mostly outpatients and without specific focus on or restriction to individual illness stages or severity of disease. While surveys and interviews were implemented in as many as 40 countries, the majority of subjects (71.7%) were assessed in Europe and the USA.

Rates of anticipated/perceived stigma ranged from 33.7% in insurance-related structural discrimination (28) to 80%

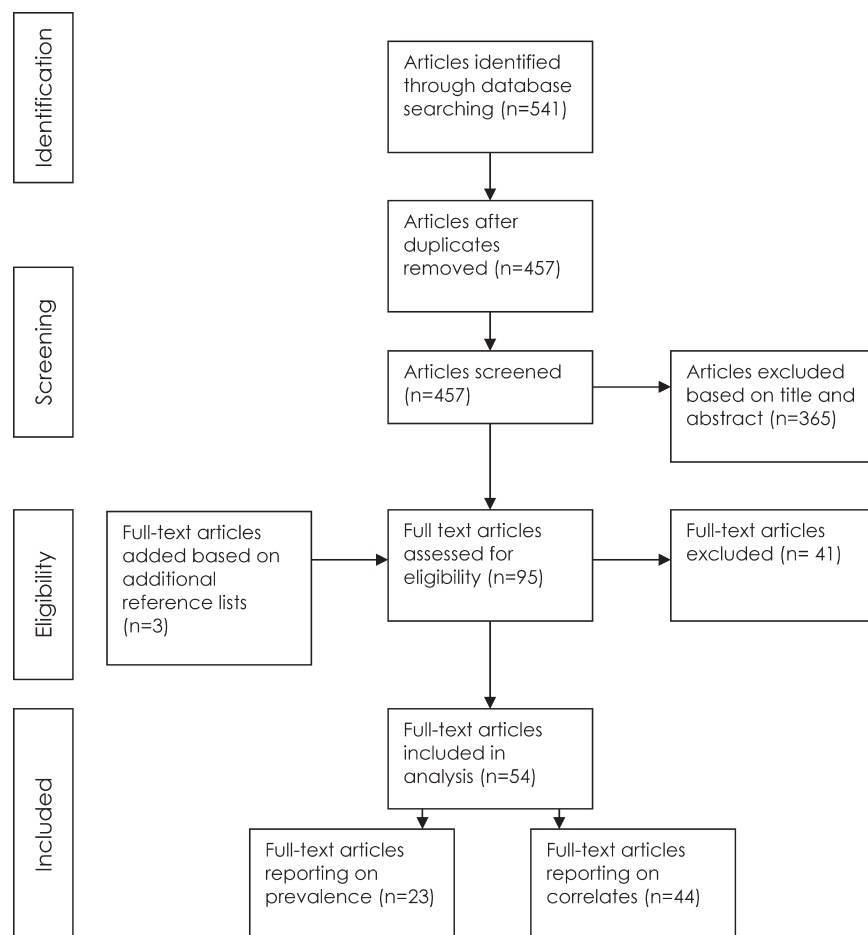


Figure 1 Review process

in interpersonal interactions (30), with a weighted percentage of 64.5% of all patients anticipating/perceiving stigma regarding at least one of the given categories (Table 1).

Concerning experienced stigma, rates ranged from 6% regarding structural stigma (31) to 87% of patients having experienced rejection in interpersonal relations (31), with a weighted proportion of 55.9% of all patients having encountered stigma in at least one of the reported contexts (Table 2).

A weighted percentage of 52.6% of patients reported stigma resistance, 49.2% alienation (shame), 35.2% self-esteem decrement and 26.8% stereotype endorsement/agreement (Table 3).

Correlates and effects of personal stigma

Forty-four studies (81.5%) reported on correlates and/or effects of personal stigma. Among these, 24 examined associations with perceived or experienced stigma and 23 with self-stigma. Included articles were characterized by the heterogeneity of sample characteristics and methods. Sample size ranged from 35 to 1,229 participants (total $n=8,132$, mean $n=185$), mean age ranged from 24.5 ($SD=6.3$) to 64.7 ($SD=8.7$) years, and the percentage of male participants ranged between 39.7% and 100%. In 32 studies, male

participants represented the majority. Most of the studies used a questionnaire design with one measurement date. Participants were recruited from all types of health care facilities, from rural and urban environments, and were in all stages and severity of disease. The majority of studies were carried out in Europe, North America, Australia and Asia, whereas no data reported on South-American or African populations.

In general, variables concerning the psychosocial functioning and general well-being of participants, such as quality of life, empowerment, self-esteem and self-efficacy, were inversely related to personal stigma in the majority of studies. Results showed that, of all the above-mentioned variables, quality of life was most thoroughly examined and was found to be inversely related to perceived/experienced stigma as well as to self-stigma in all studies addressing this relationship. Positive symptoms, depression (only perceived or experienced stigma) and general psychopathology were addressed in several studies and found to be associated with personal stigma in the majority of cases, whereas studies targeting attitudes, beliefs and personality of patients were rare, but produced mostly significant correlations (52,53).

Literacy (i.e., the ability to read and write) was related to perceived/experienced stigma in the only study measuring

Table 1 Prevalence of anticipated/perceived stigmatization

	Study	N	Prevalence (%)
Overall	Angermeyer et al (28)	101	69.0
	Berge & Ranney (30)	31	80.0
	Cechnicki et al (31)	202	58.0
	Dickerson et al (32)	74	70.0
	Ertugrul & Ulug (33)	60	45.0
	Karidi et al (34)	150	66.7
	Kleim et al (35)	127	64.0
	Lai et al (36)	72	51.0
	Lee et al (37)	320	69.7
	McCann et al (38)	81	74.0
	Tarrier et al (39)	35	53.1
	Thornicroft et al (40)	732	64.0
		1985	64.5
Interpersonal interaction			
Rejection	Angermeyer et al (28)	101	64.4
	Cechnicki et al (31)	202	58.0
	Kleim et al (35)	127	64.0
	Lai et al (36)	72	51.0
Avoidance	Angermeyer et al (28)	101	66.3
	Karidi et al (34)	150	67.7
Others	Berge & Ranney (30)	31	80.0
	McCann et al (38)	81	74.0
		865	63.9
Public image of mentally ill people			
Media coverage	Angermeyer et al (28)	101	66.0
Representation in feature films	Angermeyer et al (28)	101	66.0
General	Cechnicki et al (31)	202	41.0
	Dickerson et al (32)	74	70.0
		478	56.3
Access to social roles			
Occupation	Angermeyer et al (28)	101	69.0
	Berge & Ranney (30)	31	51.6
	Cechnicki et al (31)	202	55.0
	McCann et al (38)	81	51.4
	Thornicroft et al (40)	732	64.0
Partnership	Angermeyer et al (28)	101	44.6
	Berge & Ranney (30)	31	74.2
	Cechnicki et al (31)	202	40.0
	Thornicroft et al (40)	732	55.0
Friendship	Berge & Ranney (30)	31	53.3
		2244	56.8

Table 1 Prevalence of anticipated/perceived stigmatization (*continued*)

	Study	N	Prevalence (%)
Structural discrimination			
Insurance	Angermeyer et al (28)	101	33.7
Rehabilitation	Angermeyer et al (28)	101	42.6
General	Cechnicki et al (31)	202	49.0
		404	43.6

For total percentage, mean values were weighted for the number of cases included in a particular study

this relationship (52). Other socio-demographic variables were not associated with perceived/experienced stigma or self-stigma. This also applied to the treatment setting and to most of disease characteristics, including the duration of illness (perceived or experienced stigma only), lifetime number of hospitalizations, negative symptoms (perceived or experienced stigma only) and insight.

Finally, data were equivocal regarding the association of a number of variables with personal stigma. While age was not correlated with perceived/experienced stigma, results were contradictory concerning self-stigma. Karidi et al (34) found higher age to be negatively correlated with self-stigma, whereas other studies reported that higher age was associated with poor stigma resistance (54), more discrimination experience and more stigma-related withdrawal (49). Five of eight studies reported no association between age and self-stigma. Also male sex was found to be related to self-stigma in opposing directions (34,51). Older age of illness onset/first hospitalization was negatively correlated with perceived/experienced stigma in one of two studies (48). Findings regarding self-stigma and age of onset were contradictory, with one study reporting a positive association (34), one reporting a negative association (12) and two studies reporting no association. Furthermore, duration of illness (self-stigma only), negative symptoms (self-stigma only), depression (self-stigma only), treatment compliance (perceived or experienced stigma only) and social functioning (perceived or experienced stigma only) showed ambiguous associations with aspects of personal stigma (Table 4).

Personal stigma as predictor of outcome

15 studies (27.8%) reported regression coefficients of perceived/experienced stigma (6 studies) and self-stigma (12 studies) as predictor variables for patient outcomes. Perceived/experienced stigma was found to predict higher depression, more social anxiety, more secrecy and withdrawal as coping strategies, along with lower quality of life, lower self-efficacy, lower self-esteem, lower social functioning, less support and less mastery. Self-stigma predicted more depression, more social anxiety, lower quality of life, less self-esteem, less social functioning, less hope, less vocational functioning, less recovery, less support and less treatment

Table 2 Prevalence of experienced stigmatization

	Study	N	Prevalence (%)
Overall	Angermeyer et al (28)	101	60.0
	Baldwin & Marcus (41)	86	29.0
	Botha et al (42)	100	65.0
	Brohan et al (43)	904	69.4
	Cechnicki et al (31)	202	87.0
	Chee et al (44)	306	39.0
	Dickerson et al (32)	74	55.0
	Ertugrul & Ulug (33)	60	45.0
	Jenkins & Carpenter-Song (45)	90	96.0
	Karidi et al (34)	150	32.5
	Lai et al (36)	72	73.0
	Lee et al (37)	320	68.0
	Loganathan & Murthy (46)	200	22.5
	Sibitz et al (47)	157	37.6
	Switaj (48)	153	69.0
	Thornicroft et al (40)	732	47.0
	Werner et al (49)	86	27.4
		3793	55.9
Interpersonal interaction			
Rejection	Angermeyer et al (28)	101	60.0
	Cechnicki et al (31)	202	87.0
	Jenkins & Carpenter-Song (45)	90	18.6
	Lee et al (50)	320	48.0
Avoidance	Angermeyer et al (28)	101	51.5
	Karidi et al (34)	150	32.5
	Switaj (48)	153	41.2
Offense	Botha et al (42)	100	58.0
	Dickerson et al (32)	74	55.0
	Loganathan & Murthy (46)	200	22.5
	Switaj (48)	153	69.0
Others	Botha et al (42)	100	39.0
	Cechnicki et al (31)	202	50.0
	Jenkins & Carpenter-Song (45)	90	47.7
	Karidi et al (34)	150	10.0
	Lee et al (37)	320	68.0
	Switaj (48)	153	59.0
		2659	49.9
Public image of mentally ill people			
Media coverage	Angermeyer et al (28)	101	38.0
	Dickerson et al (32)	74	43.0
	Lai et al (36)	72	46.0
	Switaj (48)	153	45.0
	Angermeyer et al (28)	101	40.6

Table 2 Prevalence of experienced stigmatization (*continued*)

	Study	N	Prevalence (%)
Representation in feature films			
Others	Cechnicki et al (31)	202	38.0
	Jenkins & Carpenter-Song (45)	90	24.4
	Switaj (48)	153	63.0
		946	42.8
Access to social roles			
Occupation	Angermeyer et al (28)	101	19.0
	Baldwin & Marcus (41)	86	29.0
	Cechnicki et al (31)	202	31.0
	Jenkins & Carpenter-Song (45)	90	36.0
	Lai et al (36)	72	73.0
	Lee et al (37)	320	46.8
	Thornicroft et al (40)	732	29.0
Partnership	Angermeyer et al (28)	101	21.6
	Cechnicki et al (31)	202	42.0
	Jenkins & Carpenter-Song (45)	90	32.6
	Thornicroft et al (40)	732	27.0
Others	Thornicroft et al (40)	732	47.0
	Thornicroft et al (40)	732	43.0
		4192	36.9
Structural discrimination			
Insurance	Angermeyer et al (28)	101	15.8
	Lai et al (36)	72	40.0
Rehabilitation	Angermeyer et al (28)	101	13.9
	Lee et al (50)	320	44.0
Others	Cechnicki et al (31)	202	6.0
		796	26.6

For total percentage, mean values were weighted for the number of cases included in a particular study

compliance (both attendance and participation subscales) (Table 5).

Additional results

Our literature search did not yield many studies reporting on or comparing data of patients in different stages of disease (i.e., in initial prodrome, first-episode, multi-episode schizophrenia). Only two studies reported explicitly on associations with personal stigma in first-episode psychosis (39,60). As in chronic samples, patients in the first episode showed increased perceived stigma when they had social anxiety (60). This does not differ from the results concerning the relationship of self-stigma and social anxiety in a sample of elderly patients with multiple illness episodes (mean age=64.7, SD=8.7) (66). Likewise, the results of the second sample of

Table 3 Prevalence of self-stigma/internalized stigma

	Study	N	Prevalence (%)
General self-stigma	Brohan et al (43)	904	41.7
Alienation shame	Botha et al (42)	100	77.0
	Lai et al (36)	72	47.0
	Sibitz et al (47)	157	43.9
	Werner et al (49)	86	27.9
		415	49.2
Stereotype endorsement/ agreement	Botha et al (42)	100	42.0
	Sibitz et al (47)	157	15.2
	Werner et al (49)	86	30.0
		343	26.8
Self-decrement, self-esteem decrement	Jenkins & Carpenter-Song (51)	90	20.9
	Lai et al (36)	72	53.0
		162	35.2
Stigma resistance	Botha et al (42)	100	84.0
	Brohan et al (43)	904	49.2
	Sibitz et al (47)	157	63.3
	Werner et al (49)	86	32.5
		1247	52.6

For total percentage, mean values were weighted for the number of cases included in a particular study

patients with first-episode psychosis concerned prevalence rates and the relationship between positive symptoms and perceived stigma (39), and they did not differ from results regarding patients in later disease stages (5,48,53).

Concerning interventions targeting personal stigma in particular, the search only yielded two trials. The first study found no effect on perceived discrimination of a 6-week group cognitive-behavioral therapy in 21 patients with schizophrenia followed for 18 weeks, but significant improvement of self-esteem (78). No control group was included. The second study, a randomized controlled trial, examined the effect of a 10-week culturally sensitive psychoeducational group program on the perception of stigma in 48 patients with schizophrenia and found a significant decrease in the perceived discrimination score and greater coping skills in the experimental group (79).

DISCUSSION

Results from this systematic review indicate that perceived and experienced stigma as well as self-stigma are phenomena concerning a high percentage of patients with schizophrenia spectrum disorders. An average of 64.5% of patients had perceived stigma, 55.9% actually had experienced stigma and 49.2% reported alienation (shame) as the most common aspect of self-stigma.

Socio-demographic variables are only marginally associated with personal stigma, although some evidence was

found for a significant association with literacy. In contrast, it is rather evident that psychosocial factors such as quality of life are inversely associated with personal stigma. The picture concerning illness-related variables is rather equivocal. On the one hand, age of onset, duration of illness and lifetime number of hospitalizations showed few significant or contradictory associations with personal stigma and need to be examined further. On the other hand, positive symptoms, depression and general psychopathology were mostly found to correlate significantly with personal stigma. However, no illness-related variable was unequivocally correlated with personal stigma, except for social anxiety, which was only assessed in two studies, one on perceived stigma (60) and one on self-stigma (66). These results are in line with another study that was excluded from our review due to the heterogeneity of its sample (80). However, the association of depression and social anxiety with personal stigma may be an artifact in the sense that depressed people tend to perceive the reactions of their social environment in a negative way. In this case, the perception of stigmatization would be a symptom of the underlying pathology rather than an independent variable.

We were not able to identify a single study addressing differences concerning the impact of personal stigma on patients in different stages of the illness. The only two studies (39,60) explicitly examining samples of first-episode patients reported results that were similar to those in chronically ill cohorts. However, these observations cannot replace quantitative group comparisons. Thus, the evolution and effects of personal stigma in early illness phases remain an important open research question, particularly given the current focus on early identification and prevention of schizophrenia spectrum disorders and the concerns regarding the public and, especially, personal stigmatization of adolescents and young adults who may be given the label of a disorder they might never develop. Such research is especially pressing, given the introduction of the attenuated psychosis syndrome in Section 3 of DSM-5 (81).

The literature search identified only two studies focusing on the development or evaluation of interventions aimed at reducing personal stigma in patients with schizophrenia spectrum disorders. On the one hand, this is surprising, given the large amount of research on intra- and interpersonal variables modifying personal stigma and on its adverse effects, which could guide the development of such interventions. In fact, many studies included in this review discussed the implications of their findings for the development of therapeutic interventions (30). This is in contrast to numerous interventions aimed at reducing public stigma (6,7). On the other hand, our focus on samples with schizophrenia spectrum disorders may have excluded studies conducted in more general samples of mentally ill people. In addition, we may have missed studies that targeted stigma indirectly without explicitly mentioning it. Nevertheless, the lack of interventions targeting personal stigma is striking. Hence, although psychosocial interventions frequently include the general topic of public and personal stigma in psychoeducational and other

Table 4 Level of the evidence of associations of specific variables with personal stigma

	Correlates of perceived/experienced stigmatization	Correlates of self-stigma
Existing association		
Risk factors (positive association)	Literacy (52) Relatives' perceived stigma (52) and evaluation of patient's stigma (52) Belief that illness is a disease (52), due to karma (52) or evil spirit (52) Number of any (52) and of non-medical causal beliefs (52) Schizophrenia diagnosis (28,55) Positive symptoms (5,32,33,35,39,48,52,56,57) General psychopathology (33,35,48,56,57) Depression (32,35,48,57–59) or guilt (62) Social anxiety (60) Disability (33) Coping strategy: withdrawal (35,57) or secrecy (35,57) Discrimination experience (62)	Harm avoidance (53) Positive symptoms (12,64,65) General psychopathology (34) Social anxiety (66) Social avoidance (12) Withdrawal as coping strategy (12) Insight in effect of medication (67) Discrimination experience (62) Emotional discomfort (64)
Protective factors (negative association)	Social integration (32,58,61) Quality of life (32,48,55,58,59,61,63) Empowerment (57,58) Self-esteem (30,47,59) and self-efficacy (35,57) Satisfaction with finances (32) Support (63) Mastery (63)	Self-directedness (53) and persistence (53) Social integration (64) and support (72) Treatment compliance (67–70) Hope (65,71) and empowerment (58) Quality of life (58,65,72,73) Self-esteem (12,54,47,49) Social (43,62) and vocational functioning (73) Recovery (62,74)
Lack of association	Being married (33,48,58) Living alone (48,58) Education (32,33,40,48) Age (33,35,48,52,56,58) Male gender (5,32,33,35,40,48,52,58) Ethnicity (5) Residency (52) Employment (33,35,40,48,52) and income (32,41,52) No. of systems of therapy used (52) Hospital type (40,48) Belief that illness is due to punishment by god (52), black magic (52) Belief that illness should be treated by a doctor/hospital (52), traditional healer (52), mantravadi/shaman (52), be cured by going to a temple/place of worship (52) Number of treatment beliefs (52) or non-medical treatment beliefs (52) Duration of illness (48,58) Lifetime number of hospitalization (48,58) Negative symptoms (5,32,33,35,48,52,56) Insight (32,35,40,74)	Being married (58) Living alone (58) Education (10,54,64,65,75) Lifetime number of hospitalizations (34,58,64,65) Diagnosis of schizophrenia (64) Insight (12) Medication compliance (76)
Mixed/unclear results	Age at onset/first hospitalization (48,58) Treatment compliance (38,59) Social functioning (5,32,58,62)	Age (10,34,49,54,58,64,65,75) Male gender (10,34,45,58) Age at onset/first hospitalization (12,34,58,65) Duration of illness (34,58) Depression (12,58) Negative symptoms (64,65)

Table 5 Personal stigma as predictor of outcome

Perceived/ experienced stigma	Self-stigma
Depression (58)	Depression (58)
Social anxiety (60)	Social anxiety (66)
Withdrawal (35)	Quality of life (72)
Secrecy (35)	Self-esteem (12)
Quality of life (63)	Social functioning (43,62)
Social functioning (62)	Hope (71)
Self-efficacy (35)	Vocational functioning (73)
Self-esteem (77)	Recovery (75)
Support (63)	Support (72)
Mastery (63)	Treatment compliance: attendance (67)
	Treatment compliance: participation (69)

intervention techniques, the results of this review emphasize the need for interventions more specifically targeting stigma acceptance and incorporation by patients and the increase of stigma resistance among patients. This is especially relevant since the success of anti-stigma initiatives aimed to reduce public stigma has been quite limited (82,83). By contrast, one pilot study in individuals at clinically elevated risk for psychosis suggested that general psychoeducation can help reduce self-stigma, which in that study was not a primary focus (84).

The findings of this review have to be interpreted within its limitations. These include the small sample sizes in a number of the included studies, the use of diverse designs and rating scales, and the selection of often highly heterogeneous outcome and predictor variables. Moreover, comparison groups were generally not available, precluding an assessment of the specificity or quantitative differences of the findings in patients with schizophrenia spectrum disorders compared to other mental disorders.

In summary, perceived and experienced stigma, as well as self-stigma, are frequent in patients with schizophrenia spectrum disorders. Ten years after Link and Phelan called for the development of “multifaceted multilevel interventions” to produce “real change” (21) in stigma-related processes, the requested descriptive research on underlying factors and characteristics to inform the development of such interventions has been done. The practical implementation of these interventions, however, is the next important step, seeking to optimize outcomes through better social integration and functioning. It is hoped that the next decade will see major strides in this direction.

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Priorities for mental health research in Europe: a survey among national stakeholders' associations within the ROAMER project

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Within the ROAMER project, funded by the European Commission, a survey was conducted with national associations/organizations of psychiatrists, other mental health professionals, users and/or carers, and psychiatric trainees in the 27 countries of the European Union, aiming to explore their views about priorities for mental health research in Europe. One hundred and eight associations/organizations returned the questionnaire. The five most frequently selected research priorities were early detection and management of mental disorders, quality of mental health services, prevention of mental disorders, rehabilitation and social inclusion, and new medications for mental disorders. All these areas, except the last one, were among the top ten research priorities according to all categories of stakeholders, along with stigma and discrimination. These results seem to support the recent argument that some rebalancing in favor of psychosocial and health service studies may be needed in psychiatric research.

Key words: Mental health research, stakeholders, Europe, ROAMER project

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A general principle repeatedly affirmed in recent years in the health care field (e.g., 1,2) is that research agendas should reflect the needs and values of the people who use and pay for health services as well as those of the professionals who work in those services. This is unlikely to be achieved without directly involving representatives of both categories of stakeholders in the development of those agendas.

This general principle seems to be particularly relevant in the field of mental health, where different views of the various groups of interest have been reported concerning several issues, such as the target of mental health services (in particular, thresholds for diagnosis and intervention), the expected outcomes of the interventions, and the research priorities to be pursued (e.g., 3,4).

Within the frame of ROAMER (“A Roadmap for Mental Health Research in Europe”) (5) – a project funded by the European Commission and designed to develop a comprehensive, consensus-based roadmap to promote and integrate mental health research in Europe – a workpackage has been established to “implement a formal consultation process of various categories of stakeholders about priority areas for mental health research at the national and European level, and about the most appropriate modalities for their involvement in that research”.

The first initiative within this workpackage has been to conduct a survey with national associations/organizations of psychiatrists, other mental health professionals, users and/or carers, and psychiatric trainees in the 27 countries of the European Union, aiming to explore their views about priorities for mental health research in Europe, and the importance and the level of development in their country of various mental health research areas.

METHODS

A list of national associations/organizations of psychiatrists, other mental health professionals, users and/or carers, and psychiatric trainees active in the countries of the European Union was built up with the participation of the leaders of the ROAMER project. The associations/organizations whose e-mail address was not available, or which could not be contacted because messages bounced back, were deleted from the list. A total of 154 associations/organizations were contacted.

The survey was conducted by e-mail using a very simple questionnaire, developed with the participation of ROAMER leaders and made available in 14 languages (English, Czech, Dutch, French, German, Greek, Hungarian, Italian, Polish, Portuguese, Romanian, Slovenian, Spanish and Swedish). The questionnaire asked participants to identify the five priorities for mental health research in Europe from a list of research areas, and to rate on a six-point scale the importance and the level of development in their country of each research area. Respondents were allowed to suggest other priorities not included in the list. Each association/organization was asked to provide its collective feedback, rather than that of any individual officer or member.

One hundred and eight associations/organizations (listed in Annex 1) returned the questionnaire. These included 31 associations of psychiatrists out of 34 contacted (91.2%), 32 associations of other mental health professionals out of 52 contacted (61.5%), 23 organizations of users and/or carers out of 44 contacted (52.3%), and 22 associations of psychiatric trainees out of 24 contacted (91.7%). Organizations representing only users, only carers, and both users and carers were included in the same category, due to the small sample size.

Table 1 Priorities for mental health research in Europe according to national associations/organizations of stakeholders

Research areas	Total sample (N=104) ^a , %	Psychiatrists (N=31), %	Other mental health professionals (N=30), %	Users/carers (N=23), %	Trainees (N=20), %
Early detection and management of mental disorders	52.4	53.3	60.0	34.8	60.0
Quality of mental health services	43.7	53.3	43.3	43.5	30.0
Prevention of mental disorders	40.8	36.7	53.3	30.4	45.0
New medications for mental disorders**	32.0	46.7	10.0	26.1	50.0
Rehabilitation and social inclusion	32.0	23.3	33.3	39.1	35.0
Stigma and discrimination	29.1	26.7	20.0	39.1	35.0
Increasing access to available treatments	26.2	40.0	30.0	17.4	10.0
New psychological interventions for mental disorders*	23.3	10.0	30.0	39.1	15.0
Relationships between mental and physical health	18.4	20.0	16.7	21.7	15.0
Suicide prevention	18.4	20.0	16.7	17.4	20.0
Environmental risk/protective factors for mental disorders	17.5	16.7	26.7	4.3	20.0
Social and economic impact of mental disorders	16.5	20.0	23.3	8.7	10.0
Mental health and well-being in the general population	15.5	6.7	30.0	13.0	10.0
Users' perception of illness and treatment impact*	15.5	6.7	10.0	34.8	15.0
Health and well-being of carers**	14.6	6.7	10.0	39.1	5.0
Epidemiology of mental disorders	12.6	13.3	10.0	17.4	10.0
Improving adherence to available treatments	11.7	23.3	3.3	13.0	5.0
Resilience and mental health	10.7	10.0	16.7	13.0	0
Neuroimaging of mental disorders***	9.7	3.3	3.3	0	40.0
Molecular bases of mental disorders	9.7	13.3	6.7	0	20.0
Clinical characterization of mental disorders*	8.7	20.0	0	4.3	10.0
Genetic risk/protective factors for mental disorders	7.8	13.3	3.3	4.3	10.0
Cognitive dysfunction in mental disorders and its neural bases*	6.8	0	10.0	0	20.0
Mental health consequences of trauma	1.9	3.3	3.3	0	0
Culture and mental health	1.9	0	6.7	0	0
Animal models of mental disorders	1.0	3.3	0	0	0

^aFour associations/organizations did not compile the relevant section of the questionnaire

Bold prints identify the top 10 priorities for each group

Significant differences among groups: *p<0.05; **p<0.01; ***p<0.0001

Data were analyzed by descriptive statistics. Differences among the four categories of stakeholders were tested using χ^2 and analysis of variance (ANOVA), as appropriate.

RESULTS

The priorities for mental health research in Europe identified by the associations/organizations are reported in Table 1. Considering the whole sample, the five most frequently selected research priorities were early detection and management of mental disorders, quality of mental health services, prevention of mental disorders, rehabilitation and social inclusion, and new medications for mental disorders. All these areas, except the last one, were among the top ten research priorities according to all categories of stakeholders, along with stigma and discrimination.

Only organizations of psychiatric trainees identified some biological research areas (i.e., neuroimaging of mental disorders, molecular bases of mental disorders, and cognitive dysfunction in mental disorders and its neural bases) among the top ten research priorities. Research on new psychological interventions for mental disorders was selected among the top ten priorities by non-psychiatrist mental health professionals and users/carers, but not by psychiatrists and psychiatric trainees. Only non-psychiatrist mental health professionals regarded research on mental health and well-being in the general population as a top ten priority. Users' perception of illness and treatment impact, and health and well-being of carers were among the top ten research priorities only for users/carers, whereas improving adherence to available treatments was prioritized only by psychiatrists.

Table 2 Importance of the research areas according to national associations/organizations of stakeholders

Research areas	Other mental health professionals				
	Total sample (N=107) ^a , m (SD)	Psychiatrists (N=30), m (SD)	Other mental health professionals (N=32), m (SD)	Users/carers (N=23), m (SD)	Trainees (N=22), m (SD)
Quality of mental health services*	4.5 (0.7)	4.6 (0.7)	4.5 (0.6)	4.8 (0.4)	4.1 (0.9)
Suicide prevention	4.5 (0.8)	4.6 (0.7)	4.4 (0.7)	4.4 (1.2)	4.5 (0.7)
Early detection and management of mental disorders	4.4 (1.0)	4.5 (0.6)	4.4 (0.7)	4.0 (1.6)	4.5 (0.7)
Rehabilitation and social inclusion	4.4 (0.9)	4.3 (0.8)	4.3 (0.9)	4.6 (1.1)	4.3 (0.9)
Prevention of mental disorders	4.3 (1.0)	4.5 (0.7)	4.4 (0.8)	4.1 (1.5)	4.2 (0.9)
Increasing access to available treatments*	4.2 (0.9)	4.5 (0.7)	4.3 (0.8)	4.1 (1.1)	3.9 (0.9)
Stigma and discrimination	4.2 (0.9)	4.2 (1.0)	4.0 (0.8)	4.5 (0.9)	4.2 (0.8)
Social and economic impact of mental disorders	4.2 (0.9)	4.1 (1.0)	4.2 (0.8)	4.5 (1.0)	3.9 (0.8)
Relationships between mental and physical health	4.2 (0.8)	4.4 (0.7)	4.1 (0.9)	4.5 (0.7)	4.0 (1.0)
Users' perception of illness and treatment impact*	4.1 (1.0)	4.0 (0.9)	4.1 (0.9)	4.5 (1.2)	3.9 (0.9)
New psychological interventions for mental disorders**	4.1 (0.9)	3.8 (0.8)	4.2 (0.8)	4.6 (0.7)	3.8 (1.1)
Mental health and well-being in the general population	4.0 (1.2)	4.1 (0.9)	4.3 (1.1)	4.0 (1.5)	3.6 (1.1)
Environmental risk/protective factors for mental disorders	4.0 (1.0)	4.0 (1.0)	4.1 (0.8)	4.1 (1.0)	3.7 (1.0)
Health and well-being of carers***	4.0 (1.0)	3.8 (1.1)	4.1 (0.9)	4.6 (0.8)	3.4 (1.1)
New medications for mental disorders	3.9 (1.2)	4.3 (1.0)	3.5 (1.3)	3.8 (1.3)	3.9 (0.9)
Improving adherence to available treatments	3.9 (1.0)	4.2 (0.9)	3.7 (0.8)	3.6 (1.3)	4.0 (0.8)
Epidemiology of mental disorders	3.8 (1.0)	3.9 (0.8)	3.8 (1.1)	3.8 (1.1)	3.6 (0.8)
Clinical characterization of mental disorders****	3.7 (1.2)	4.3 (0.8)	3.4 (1.0)	3.1 (1.7)	4.1 (0.7)
Cognitive dysfunction in mental disorders and its neural bases	3.7 (1.1)	3.7 (0.9)	3.6 (1.1)	3.6 (1.4)	3.9 (1.0)
Resilience and mental health	3.6 (1.1)	3.7 (1.0)	3.8 (1.0)	3.8 (1.4)	3.1 (1.1)
Mental health consequences of trauma	3.6 (1.0)	3.7 (0.9)	3.7 (0.7)	3.4 (1.5)	3.6 (0.8)
Culture and mental health	3.5 (1.0)	3.4 (0.9)	3.5 (1.0)	3.9 (1.2)	3.2 (1.1)
Genetic risk/protective factors for mental disorders	3.4 (1.1)	3.6 (1.1)	3.3 (1.0)	3.3 (1.3)	3.1 (0.9)
Neuroimaging of mental disorders	3.3 (1.2)	3.5 (1.1)	3.1 (1.1)	2.9 (1.5)	3.8 (1.1)
Molecular bases of mental disorders	3.2 (1.2)	3.5 (1.1)	3.0 (1.2)	2.9 (1.5)	3.7 (0.9)
Animal models of mental disorders	2.6 (1.4)	2.8 (1.4)	2.3 (1.3)	2.3 (1.7)	2.9 (1.1)

^aOne association did not compile the relevant section of the questionnaire. The importance of research areas was rated on a six-point scale (from 0 – not important at all, to 5 – very important)

Significant differences among groups: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

The importance of the research areas as rated by the associations/organizations is reported in Table 2. The top five in terms of perceived importance were quality of mental health services, suicide prevention, early detection and management of mental disorders, rehabilitation and social inclusion, and prevention of mental disorders.

The level of development of research areas in the respective countries according to the opinion of the participating associations/organizations is reported in Table 3. The fields identified as the most developed were clinical characterization of mental disorders, suicide prevention, new medications for mental disorders, increasing access to available treatments, early detection and management of mental disorders,

quality of mental health services, and relationships between mental and physical health. On the other hand, molecular bases of mental disorders, environmental risk/protective factors for mental disorders, resilience and mental health, prevention of mental disorders, health and well-being of carers, culture and mental health, and animal models of mental disorders were reported as the least developed.

DISCUSSION

These results seem to support the recent argument (6) that some rebalancing in favour of psychosocial and health

Table 3 Level of development of the research areas in their countries according to national associations/organizations of stakeholders

Research areas	Total sample (N=106) ^a , m (SD)	Psychiatrists (N=31), m (SD)	Other mental health professionals (N=32), m (SD)	Users/carers (N=21), m (SD)	Trainees (N=22), m (SD)
Clinical characterization of mental disorders	3.3 (1.0)	3.3 (1.1)	3.2 (1.1)	3.3 (1.3)	3.4 (0.9)
Suicide prevention	3.0 (1.3)	3.2 (1.1)	3.0 (1.2)	2.2 (1.4)	3.4 (1.2)
New medications for mental disorders	3.0 (1.2)	2.7 (1.2)	3.4 (1.1)	2.8 (1.4)	3.1 (1.1)
Increasing access to available treatments	2.8 (1.1)	2.8 (1.2)	2.6 (1.1)	2.8 (1.1)	3.0 (0.8)
Early detection and management of mental disorders	2.8 (1.1)	2.9 (1.1)	2.6 (0.9)	2.6 (1.3)	3.1 (1.1)
Quality of mental health services	2.8 (1.0)	3.0 (1.1)	2.7 (0.9)	2.4 (1.0)	3.1 (0.9)
Relationships between mental and physical health	2.8 (1.0)	2.8 (1.0)	2.9 (0.9)	2.5 (1.1)	2.6 (1.0)
Epidemiology of mental disorders	2.7 (1.4)	2.5 (1.5)	2.2 (1.4)	2.5 (1.6)	2.9 (1.0)
New psychological interventions for mental disorders	2.7 (1.2)	2.9 (1.1)	2.9 (1.2)	2.2 (1.3)	2.4 (1.1)
Cognitive dysfunction in mental disorders and its neural bases	2.7 (1.1)	2.7 (1.1)	2.9 (1.0)	2.2 (1.3)	2.9 (1.1)
Improving adherence to available treatments	2.7 (0.9)	2.7 (1.1)	2.6 (1.0)	2.6 (0.7)	2.6 (0.8)
Neuroimaging of mental disorders	2.6 (1.4)	2.5 (1.4)	2.8 (1.4)	1.9 (1.2)	2.9 (1.4)
Stigma and discrimination	2.6 (1.1)	2.5 (1.2)	2.6 (1.0)	2.6 (1.1)	2.9 (0.9)
Rehabilitation and social inclusion	2.6 (1.1)	2.7 (1.1)	2.7 (0.9)	2.2 (1.3)	2.9 (0.9)
Genetic risk/protective factors for mental disorders	2.5 (1.3)	2.5 (1.3)	2.8 (1.2)	2.2 (1.2)	2.2 (1.3)
Mental health and well-being in the general population	2.5 (1.1)	2.5 (1.1)	2.8 (1.0)	2.0 (1.3)	2.4 (1.1)
Mental health consequences of trauma	2.5 (1.1)	2.3 (1.1)	2.7 (1.2)	2.1 (1.1)	2.7 (1.0)
Users' perception of illness and treatment impact	2.5 (1.0)	2.6 (1.1)	2.4 (1.2)	2.2 (1.0)	2.7 (0.7)
Social and economic impact of mental disorders	2.4 (1.1)	2.4 (1.3)	2.5 (1.0)	2.2 (1.1)	2.3 (1.1)
Molecular bases of mental disorders	2.3 (1.3)	2.0 (1.2)	2.6 (1.5)	1.7 (1.1)	2.6 (1.1)
Environmental risk/protective factors for mental disorders	2.3 (1.2)	2.6 (1.2)	2.5 (1.1)	1.8 (1.1)	2.2 (1.2)
Resilience and mental health	2.3 (1.1)	2.4 (1.2)	2.5 (0.9)	1.7 (1.1)	2.2 (1.0)
Prevention of mental disorders	2.3 (1.1)	2.4 (1.1)	2.5 (1.1)	1.7 (1.2)	2.4 (0.9)
Health and well-being of carers	2.2 (1.0)	2.3 (1.1)	2.2 (1.0)	2.0 (1.0)	2.1 (1.1)
Culture and mental health	2.0 (1.2)	2.1 (1.4)	1.8 (0.9)	2.1 (1.0)	1.9 (1.3)
Animal models of mental disorders	1.8 (1.4)	2.0 (1.4)	1.9 (1.5)	0.7 (0.8)	2.1 (1.3)

^aTwo organizations did not compile the relevant section of the questionnaire. The level of development of research areas was rated on a six-point scale (from 0 – not developed at all, to 5 – very well developed)

service studies may be needed in psychiatric research. In fact, the only research areas included in the top ten priorities by all categories of stakeholders were early detection and management of mental disorders, quality of mental health services, prevention of mental disorders, rehabilitation and social inclusion, and stigma and discrimination. Among the several biological research areas proposed by the questionnaire, only three (i.e., neuroimaging of mental disorders, molecular bases of mental disorders, and cognitive dysfunction in mental disorders and its neural bases) were prioritized, and only by psychiatric trainees. No biological research area was endorsed as a priority by users/carers.

Clinical characterization of mental disorders was rated as the first or second most developed research area in their countries by all categories of stakeholders, while it was regarded as a

top ten research priority only by psychiatrists. This may reflect a general perception that this area has been already pursued sufficiently and does not represent anymore a priority, a perception not shared by most psychiatrists, who are aware and concerned about the limitations of current diagnostic systems and their implications for ordinary clinical practice (see 7).

There was a divide among stakeholders concerning the priority ascribed to research on various mental health interventions. In fact, research on new psychological interventions for mental disorders was selected among the top ten priorities by non-psychiatrist mental health professionals and users/carers, but not by psychiatrists and psychiatric trainees, while research on new medications for mental disorders was prioritized by psychiatrists, users/carers and psychiatric trainees, but not by non-psychiatrist mental health professionals.

Apparently, while users/carers welcome new developments in both psychological and pharmacological interventions, professionals' views diverge in this respect, possibly reflecting different perceptions (or assumptions) about the role and the potential of currently available treatments.

This survey has some methodological limitations, which have to be acknowledged. The associations/organizations were invited to participate upon selection by ROAMER leaders. Although we tried to reach all major national associations/organizations active in the mental health field in the various countries of the European Union, we may have missed some of them. Moreover, we deleted from the list those associations/organizations for which an e-mail address was not available and those that could not be reached because messages bounced back. While this was unavoidable, we may have excluded some active associations/organizations through this procedure. Nevertheless, the survey involved more than one hundred national associations/organizations, with a high response rate, and may be regarded as a first step in the attempt to explore the views of the various categories of stakeholders active in Europe about priorities for mental health research in the continent.

Of course, this is work in progress. The results of this survey are being discussed in several meetings within the ROAMER project, and the views expressed by the various categories of stakeholders are going to be integrated with those of European scientists active in the mental health field, with the aim of building common views and a consensus when possible.

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Annex 1 – Professional associations/organizations participating in the ROAMER stakeholders' survey

Austrian Association for Psychiatry and Psychotherapy, Austrian Psychological Society, Pro Mente Oesterreich - Austrian Federation for Mental Health, Hilfe für Angehörige und Freunde psychisch Erkrankter, Psychiatric Trainees' Section of the Austrian Association of Psychiatry and Psychotherapy (**Austria**); Society of Flemish Neurologists and Psychiatrists, Belgian Association for Psychological Sciences, Flemish Mental Health Association (VVG), Vlaamse Vereniging Assistenten Psychiatrie (**Belgium**); Bulgarian Psychiatric Association (**Bulgaria**); Cyprus Psychiatric Association, Cyprus Advocacy Group for the Mentally Ill (KIPRO.DI.PS.A) (**Cyprus**); Czech Psychiatric Association, Czech-Moravian Psychological Society, Union of Psychologists Associations in the Czech Republic, KOLUMBUS, Section of Young Psychiatrists of the Czech Psychiatric Association (**Czech Republic**); Danish Psychiatric Association, Danish Psychological Association (**Denmark**); Estonian Psychiatric Association, Estonian Psychologists' Association, Estonian Patient Advocacy Association (EPAA), Young Psychiatrists' Section of the Estonian Psychiatric Association (**Estonia**); Finnish Psychiatric Association, Finnish Psychological Society, Finnish Psychological Association, Finnish Association for Mental Health, National Family Association Promoting Mental Health in Finland (FINFAMI), Young Psychiatrists' Section of the Finnish Psychiatric Association (**Finland**); French Association of Psychiatry, French Psychiatric Information Society, French Association of Psychiatrists in Private Practice, Medical Psychological Society, Ligue Française pour la Santé Mentale, Advocacy France, Association Française Federative des Etudiants en Psychiatrie (**France**); German Association for Psychiatry and Psychotherapy, German Psychological Association, Bundespsychotherapeutenkammer, Wissenschaftlicher Beirat Psychotherapie, Young Psychiatrists' Section of the German Association for Psychiatry and Psychotherapy (**Germany**); Hellenic Psychiatric Association, Hellenic Society of Neurology and Psychiatry, Hellenic Psychological Society, Pan-Hellenic Association of Families for Mental Health, Society for the Rights and Responsibilities of Psychiatric Patients, Hellenic Association of Psychiatric Trainees (**Greece**); Hungarian Psychiatric Association, Hungarian Psychological Association, Pszichiatriai Erdekvedelmi Forum, Young Psychiatrists' Section of the Hungarian

Psychiatric Association (**Hungary**); Psychological Society of Ireland, SHINE – Supporting people affected by mental ill health, Impero (Irish Mental Patients' Educational and Representative Organization), Trainee Committee of the College of Psychiatry of Ireland (**Ireland**); Italian Psychiatric Association, Italian Psychological Society, Italian Society of Psychopathology, UNASAM, IDEA, Early Career Psychiatrists' Committee of the Italian Psychiatric Association (**Italy**); Latvian Psychiatric Association, SKALBES, Young Psychiatrists' Section of the Latvian Psychiatric Association (**Latvia**); Lithuanian Psychiatric Association, Lithuanian Psychological Association, Club13&Co, Young Psychiatrists' Section of the Lithuanian Psychiatric Association (**Lithuania**); Luxembourgish Society of Psychiatry, Neurology and Psychotherapy (**Luxembourg**); Maltese Association of Specialists in Psychiatry, Maltese Psychological Association, Malta Mental Health Association, ANTIDE, Young Psychiatrists' Section of the Maltese Psychiatric Association (**Malta**); Netherlands Psychiatric Association, ANOIKSIS, Netherlands Psychiatric Trainees Association (**The Netherlands**); Polish Psychiatric Association, Coalition for Mental Health of Poland, INTEGRATION, Division of Psychiatric

Training of the Polish Psychiatric Association (**Poland**); Portuguese Society of Psychiatry and Mental Health, Portuguese Association for Mental Health, Associação Portuguesa de Internos de Psiquiatria (**Portugal**); Romanian Association of Psychiatry and Psychotherapy, Romanian Association of Community Psychiatry, Romanian League for Mental Health, ALIAT ONG, Romanian Association of Residents in Psychiatry (**Romania**); Slovak Psychiatric Association, Slovak League for Mental Health (**Slovak Republic**); Psychiatric Association of Slovenia, Slovenian Psychological Association, Slovenian Association for Mental Health, HUMANA, Psychiatric Trainees of the Psychiatric Association of Slovenia (**Slovenia**); Spanish Society of Psychiatry, Spanish Association of Neuropsychiatry, Young Psychiatrists' Section of the Spanish Psychiatric Association (**Spain**); Swedish Psychiatric Association, National Coalition for Mental Health (NSPH), Swedish Association of Psychiatric Trainees (**Sweden**); Royal College of Psychiatrists, British Psychological Society, RETHINK, Hafal, PENUMBRA, Trainees' Section of the Royal College of Psychiatrists (**UK**).

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DSM-5 grief scorecard: assessment and outcomes of proposals to pathologize grief

Where does grief stand diagnostically, now that the dust has settled and the DSM-5 has been approved? The DSM-5 Task Force considered an unprecedented series of proposals to identify grief-related mental disorders where now there are assumed to be normal variations. The proposals taken together had the potential to transform psychiatry's conceptualization of grief and the clinician's response to bereaved patients. Targets for pathologization included both depressive symptoms during grief and grief itself – the yearning, disbelief, and other experiences distinctive of grief.

Four grief-related proposals made it to the final leg of the DSM-5 revision process, a major event in itself. Here I review the proposals, assess their validity, and present the Task Force's final decisions, providing an overview of the status of grief post-DSM-5.

PROPOSAL TO ELIMINATE THE MAJOR DEPRESSION BEREAVEMENT EXCLUSION

This was perhaps the most controversial diagnostic proposal since depathologization of homosexuality. Grief sometimes triggers a major depressive disorder (MDD). However, some depressive symptoms, such as depressed mood, insomnia, decreased interest, decreased appetite, and lack of concentration, are general-distress symptoms that frequently occur in normal grief (1). Thus, normal grief can satisfy the DSM's 5-symptoms-for-2-weeks criterion for MDD, yielding a mistaken "false positive" MDD diagnosis. The bereavement exclusion (BE) rectified this situation by distinguishing as normal those "uncomplicated" grief-related depressive episodes that included only general distress symptoms and remitted quickly. "Complicated" episodes were classified as MDD, despite the recent loss, if they included pathosuggestive symptoms such as psychomotor retardation, suicidal ideation, sense of worthlessness, or lengthy duration. The BE's elimination means that two weeks of general-distress depressive symptoms after death of a loved one falls under MDD.

The main argument for the BE's elimination was that excluded cases are just like other MDD on pathology validators (2). However, when reviewed, claims that research evidence supports such similarity were shown to be unfounded (3). Several new studies falsified the similarity claim, showing, for example, that depression recurrence and development of anxiety disorders, which occur at high rates after MDD, occur no more frequently in BE-excluded episodes than in populations who have never had MDD, demonstrating the BE's strong predictive validity (4–6). Warnings that excluded depressive episodes would contain elevated rates of suicidal cases turned out to be groundless (7). Two studies

demonstrated that uncomplicated grief-related depression is similar to uncomplicated reactions to other stressors, raising the question of whether the BE should be eliminated or expanded to other stressors (8,9). Recent studies answer that a broadened exclusion applied to uncomplicated reactions to all major stressors has both concurrent and predictive validity, with recurrence and other predictive validators not different from background population levels, unlike other MDD (10,11).

Assessment: This is an invalid and empirically unsupported proposal. The BE's rules have been demonstrated to be both concurrently and predictively valid with ample, replicated, high-quality evidence. Speculative claims supporting elimination have been empirically falsified.

Outcome: The proposal to eliminate the BE was accepted by the DSM-5 Task Force. The BE has been eliminated in DSM-5. It has been replaced by a vague note stating that normal grief and reactions to other stressors can have depressive symptoms, and the clinician must judge the diagnosis, but with no guiding criteria, making research virtually impossible and the note likely to be ignored.

PROPOSAL FOR A NEW CATEGORY OF "PERSISTENT COMPLEX BEREAVEMENT-RELATED DISORDER"

Until DSM-5, non-depressive grief feelings were not targeted by any category of disorder. However, two grief research groups have been working to validate intense, lengthy grief as pathology, called "prolonged" or "complicated" grief disorder (12,13). Validation rested either on risk of future harms such as disorders, thus potentially confusing risk of disorder with disorder, or on the claim that grief in the identified group is "derailed" or "frozen" in "interminable" grief, a claim unsubstantiated by longitudinal evidence.

The two research groups proposed different diagnostic criteria for the proposed category, both claiming empirical support. The DSM-5 resolved this conflict by creating diagnostic criteria combining elements from both proposals along with some new elements, and recommending placement in section 3 for further study. Moreover, the grief researchers' criteria do not require that symptoms have been continuous since the acute grief stage, whereas the DSM-5 requires the symptoms to be present more days than not since the death. Finally, DSM-5 increased the post-loss duration threshold from the grief researchers' 6 months to 12 months, a much more defensible cut-point, though likely still too short given evidence that many individuals are still on a healing trajectory and are not "derailed" or "frozen" in their grief at that point (14).

Symptom criteria for the DSM-5 grief disorder require at least one out of four "separation distress" symptoms

(yearning/longing, intense sorrow, preoccupation with the deceased, preoccupation with the death's circumstances) and at least six out of 12 additional symptoms including difficulty accepting, shocked/stunned/numb, difficulty positively reminiscing, bitterness/anger, self-blame, avoidance of reminders, difficulty trusting, wanting to join the deceased, loneliness/detachment, meaninglessness/emptiness, role confusion or feeling part of oneself died, and difficulty pursuing interests or plans. Note that all of these phenomena can occur normally during acute grief, so it is the prolonged intensity rather than a trajectory of resolution that suggests pathology.

Assessment: In principle, adding a suitably formulated category for enduring intense grief without a normal trajectory of adaptation makes sense. The DSM-5 criteria improved grief researchers' proposals in terms of face validity and greater consistency with durational evidence. However, the original proposals each had an empirical track record, whereas the DSM-5 compromise proposal has no research history. Moreover, many case examples suggest that grief at durations suggested in these criteria sets may represent a plateau along a normal but slower healing trajectory, especially when the loss or its interaction with personality or contextual variables is particularly difficult. Grief researchers' proposals seem to err on the side of caseness, whereas caution is warranted because this category has high potential for abuse, especially if grief becomes targeted for medication development.

Outcome: Persistent complex bereavement-related disorder was accepted for inclusion in DSM-5's section 3, for further study. This allows immediate diagnosis under "other specified" categories.

PROPOSAL TO ELIMINATE THE ADJUSTMENT DISORDER BEREAVEMENT EXCLUSION

The DSM-IV also contained a bereavement exclusion for adjustment disorder (AD): "the symptoms do not represent bereavement". Because of the anticipated demise of the major depression BE, it was proposed that the AD exclusion also be eliminated.

However, AD and MDD are not analogous in this regard. AD diagnosis includes the specifier "with depressed mood" ("when the predominant manifestations are symptoms such as depressed mood, tearfulness, or feelings of hopelessness"), but unlike major depression, there are no duration or symptom thresholds. Consequently, eliminating the AD bereavement exclusion would mean that any transient subsyndromal depressive symptoms such as sadness and insomnia within the first weeks or months post-loss would qualify for AD diagnosis. Such symptoms are almost universal in early normal bereavement (1). No research has examined the AD bereavement exclusion (15).

Assessment: This is an invalid and empirically unsupported proposal.

Outcome: This proposal was rejected by the DSM-5 Task Force. The DSM-5 AD criteria include the bereavement exclusion.

PROPOSAL FOR A NEW CATEGORY OF "ADJUSTMENT DISORDER RELATED TO BEREAVEMENT"

Anticipating elimination of the AD bereavement exclusion, thus the perceived need to include grief symptoms among AD symptoms, a new category of "AD related to bereavement" was proposed to diagnose persistent non-depressive grief symptoms. This proposal offered a back-door way to introduce complicated/prolonged grief into the manual.

The proposed symptom criteria required that "for at least 12 months following the death of a close relative or friend, the individual experiences on more days than not intense yearning/longing for the deceased, intense sorrow and emotional pain, or preoccupation with the deceased or the circumstances of the death. The person may also display difficulty accepting the death, intense anger over the loss, a diminished sense of self, a feeling that life is empty, or difficulty planning for the future or engaging in activities or relationships".

This definition requires only one symptom, either yearning, sorrow, "or" preoccupation; the others "may also" be present. Whether one or a few symptoms are required, there is no research on such a category, and existing evidence strongly suggests invalidity, with many or most griever's qualifying for diagnosis in multiple studies (16–20). For example, Prigerson et al (16) found that the average yearning frequency for all griever's at 1 year post-loss is about every other day, not distant from the DSM's proposed pathological AD threshold of yearning "more days than not".

Assessment: This is an invalid and empirically unsupported proposal.

Outcome: This proposal was rejected by the DSM-5 Task Force. No bereavement-related AD category appears in DSM-5.

CONCLUSIONS

Of the four proposals, the two that would have pathologized virtually all grief as adjustment disorder were rightly rejected. The bereavement exclusion to major depression was eliminated despite excellent evidence supporting its validity, a triumph of DSM politics over science. Finally, the new category of persistent complex bereavement-related disorder, in principle a needed category if properly formulated, was incorporated into section 3 of the manual for further study, with adjusted criteria that are more rigorous than the original proposals but still lack adequately demonstrated specificity.

In all, the Task Force made three reasonably wise decisions, and one major error with the BE that should be rectified as soon as possible. Post-DSM-5, normal grief remains safe from diagnosis when it includes few depressive symptoms. However, normal grief reactions that include several general-distress depressive symptoms have been mistakenly pathologized. Given how common such depressive feelings

are as part of normal grief, this puts a sizable percentage of grieverers at risk for false positive diagnosis.

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Understanding Breivik and Sandy Hook: sin and sickness?

In a recent issue of *World Psychiatry* (1), I. Melle attempted to make sense of the case of Anders Breivik, the Norwegian convicted of killing 77 people in 2012. Sadly, in the same year, Adam Lanza stormed Sandy Hook elementary school in Connecticut and killed 26 people, including 20 children.

Heinous crimes like these beg for answers and demand action: why might people do these horrors and how can they be stopped in the future? In earlier times such events were attributed to sin, but in a more scientifically enlightened age we focus on psychiatric sickness, leading to calls for action “to better treat mental illness”. Focusing solely on mental health, however, offers an incomplete picture that distorts our understanding of these tragedies. This kind of misunderstanding generates flawed policy that further chips away at rights of citizens labeled mentally ill. We propose a conceptual unpacking to better understand these crimes, so that service providers respond to questions from reporters and government officials in ways that do not perpetrate further harm.

Social psychologists theorize that humans have an intrinsic need to understand events, especially those involving life and death; attribution theory, for example, attempts to make sense of killer actions by framing them in terms of personal responsibility (2). People committing heinous crimes cannot possibly be responsible for this kind of behavior (“How else to explain the inexplicable!”) and hence must be mentally ill. Conversely, attribution theory implies that shooters in control are sinners with significant moral flaws. Psychology’s focus on attributions of control parallels legal questions on criminal intent. According to the law, a crime is senseless (and hence based on mental illness) when its intent fails to reflect normative motivators of crime (e.g., greed, retribution, economic need, peer group pressure, and passion) (3). Normal motives are not obviously present with Breivik or Lanza, so mental illness is presumed. However, Western jurisprudence recognizes that not all instances of inexplicable crime represent mental illness. Absence of insanity leads to attribution of some kind of moral failing: sin.

Sin, as an explanation of behavior, is mostly absent from modern psychiatry and psychology, rejected by proponents of psychological determinism such as S. Freud and B.F. Skinner. However, proxies of mental illness and general human behavior are modestly associated with aggression at best (4). These small effect sizes make sense phenomenologically to mental health providers and researchers, who know the vast majority of people with

mental illnesses are unlikely to be violent. Might not some proxy of sin help to better explain the behavior of these vicious killers?

Of course, here’s the rub: how can behavioral science, mostly divorced from moral thought, develop a meaningful measure of sin? I do not propose a conceptual *rap-prochement* between sin and sickness, some translational bridge that might be used to answer questions about these tragedies. I, like most mental health providers, lack the skills and credentials to do so. Hence, we need to tell news reporters seeking answers: “I, as a mental health scholar, am not expert in this arena”. Or, if motivated to become proficient, then partner with those who might complement the mental health answer – social ethicists, legal scholars, or theologians – groups, by the way, that are assuming greater prominence in the practice of modern medicine.

Some might question the harm of a mental health focus on violent crime, arguing that this is an opportunity to advance resources for mental health (e.g., 5). I believe this “ends justifies the means” approach is problematic, because it further harms people labeled mentally ill as well as the community violated by this crime. First, research shows that public education programs stressing the connection between violence and mental illness fail to improve public endorsement of greater funds for mental health (6). On the contrary, media messages that link violence and mental illness significantly increase discriminatory calls for social avoidance, institutional segregation, and coercive treatment. Second, any predictive tool of violence yields massive false positives, leading to egregious civil rights violations (4). Third, fear of being labeled violent is likely to drive people away from needed services rather than drawing them in. Lastly, even if these civil rights threats are somehow justified, the police burden that results would be untenable. The number of people that would need to be monitored to avoid another Sandy Hook would easily overload any combined mental health/police effort.

So, let’s be clear on what to do next time a tragic crime occurs and news reporters come calling. Almost all of us are unable to answer questions like these. Instead, let’s direct them to the hand full of researchers who have tried to span the sin and sickness chasm. And let’s support scholarship attempting to make sense of this split.

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Community mental health care in South Asia

This report is part of a series describing the development of community mental health care in regions around the world (see 1–6), produced by a Task Force appointed by the WPA as part of its Action Plan 2008–2011 (7,8). The WPA Guidance on Steps, Obstacles and Mistakes to Avoid in the Implementation of Community Mental Health Care, developed by the Task Force, has been previously published in this journal (9). Here we describe these issues in relation to South Asia.

South Asia, home to 23% of the world's population and with 40% of the poorest people, has approximately 150–200 million mentally ill. For centuries, the mentally ill were managed by the community in several ways, ranging from physical restraint by using chains to treatment by ancient systems of medicine such as Ayurveda. Asylums or mental hospitals came with the British rule in India and colonization in other South Asian countries. While providing treatment and some relief for the mentally ill, they also were edifices of neglect, abuse and violation of human rights. While many such hospitals in Asia have undergone changes for the better, some of them still retain the old character and are largely custodial in their function. In India, the 42 mental hospitals catered to a mere 20% of the population, all in urban areas, with no services being available for the vast rural areas.

Current policies in the region include the development of community mental health care, the incorporation of mental health in primary care, ensuring availability of medication, involvement of users and families and a focus on human rights and equity of access to mental health care across different groups. Amongst the nations, Bangladesh, Bhutan, Pakistan, India and Sri Lanka have made some progress in the implementation of these components. Nepal focuses on providing minimal mental health care and basic medication, protecting human rights and creating awareness. Maldives has no policy, legislation or plan. Several studies in the region have highlighted the large number of untreated patients in the community. Even the existing services are under-utilized, because of varied explanatory models held by patients and families (9), which result in their seeking help from religious and traditional healing sites.

In the last 30–40 years, some attempts have been made to establish community based care in many countries of the region. In India, general hospital psychiatry units were started in the 1960s, followed by the drafting of the national mental health programme in 1982. The programme envisaged deinstitutionalization and the integration of mental health care with primary care.

The World Health Organization (WHO)'s technical report in 1990 (10) also provided an impetus for community care programmes. A series of other initiatives, such as initiation of community or satellite clinics, domiciliary care programmes, training of school teachers, volunteers and village leaders in

early identification of mental disorders, also helped galvanize the community programmes.

Non-governmental organizations (NGOs) have also played a role in the growth of community care. Mental health NGOs in India, Maldives, Nepal and Sri Lanka deal with numerous mental health problems in the community. Common NGO activities include advocacy, mental health promotion, prevention of mental disorders, rehabilitation, and direct service provision (11). Some NGOs have their own community based programmes and cater to a variety of conditions. In Maldives, six NGOs are actively involved in mental health-related work, including rehabilitation, outreach, life skills training, provision of psychosocial support, and resilience building around social issues. In Nepal, the Centre for Mental Health and Counselling, a national NGO, works on various levels with preventive, promotional and curative aspects of mental health in the community. It is also supporting other organizations in their psychosocial programmes (12). It is a pity that NGOs work in isolation and are not being utilized by the governments for private-public partnerships.

Mental health is not a priority area for many governments in this region and hence the funds allocated are quite meagre. National and international funding does not come easily for community projects. This situation is however changing, at least in India. The new 5-year plan of the Indian government has increased the allocation of funds to mental health. Although a bulk of it will be spent on improving the conditions of mental hospitals, a portion has also been allocated to district mental health programmes in various states.

A huge brain drain has left some of the countries of the region with much fewer psychiatrists. There is also a lack of other mental health professionals, such as clinical psychologists, social workers and more specifically psychiatric nurses. This gives rise to a need to involve community level health workers, teachers, volunteers, key persons in the local community and family members, in the process of identifying persons with mental disorders, making appropriate referrals and providing care and simple psychosocial interventions. This has been successfully done in Sri Lanka, where community support officers, a new cadre of mental health workers, was established in the wake of the tsunami, after it was evident that in most districts the basic primary care services were overwhelmed and could not take on any additional activities (13).

Training and capacity building are critical pieces of the puzzle and should form an integral part of all community oriented activities. This would necessitate use of simple information technologies, periodic reinforcer sessions and a component of evaluation. There is a need for a new set of competencies which would focus on recovery and rehabilitation, and for training of a wider range of workers, including informal

community care workers, within the context of the practical needs of a country (14). Several countries in South Asia have developed training programmes for various groups like lay community workers, school teachers, and primary health care personnel.

Existing primary care physicians in the community are often not ready or inclined to treat the mentally ill. While training enhances their skills, they should be sufficiently motivated to take on the additional responsibility of caring for people with mental disorders. Innovations to address the challenge of inadequate personnel include the use of telepsychiatry, which is being successfully used in Tamil Nadu, a Southern Indian state, by the NGO Schizophrenia Research Foundation (15,16).

Reallocation of the mental health budget in many countries is called for, as a large part of the budget is spent on mental hospitals with long-stay patients with minimal turnover. There needs to be an increased allocation for community based care and helping families cope with the problem.

One of the pitfalls of community based programmes is the lack of access to services. Unless the community systems of care are strengthened, many patients will continue to be untreated. Priority should be given to rural areas, since most of the populations in these countries live in villages.

Community care requires a right mix of clinical skills and practical knowledge of working in and with communities. Continuing professional development and equipping professionals with skills based on evidence is critical. In many areas in this region, this translates into a greater emphasis on mental health at the undergraduate level.

In the absence of qualified mental health professionals, many countries have trained lay community workers, as in the case of community support officers in Sri Lanka. These officers have significantly enhanced both the overall access and coverage of mental health services to communities across all four districts, especially in areas where there was previously limited or no local access to psychiatric care (either due to protracted civil conflict or lack of mental health service structures) (17). For training community liaison workers, several organizations have developed tool kits and manuals in local languages, but these also should be disseminated widely and put to use.

Special programmes are needed during and after disasters and for the socially and economically marginalized, such as poor women and children, especially in rural areas. Some countries like India have drawn up clinical and practice guidelines in this respect, which need to be disseminated widely to provide uniformity in care.

Awareness programmes should be developed using local media – print, audio (community radio) and visual (local TV channels) – and organizing classes in schools, colleges and other educational institutions. There is a need for promotional and preventive components, for example referring to

suicide prevention, workplace stress management, school and college counseling services. Mental health programmes should be integrated with other health programmes, such as those for women and children, or rural development. Finally, for the system to be culturally relevant, it is important to understand people's perception of mental health needs.

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Management of the psychosocial effects of economic crises

The actions to alleviate the mental health impact of the economic crisis proposed by Wahlbeck and McDaid in the October 2012 issue of *World Psychiatry* (1) are indeed thoughtful and realistic. It is important, however, to draw attention to the fact that some of these proposed actions do not have a universal application potential.

For example, while it is true that alcohol-related deaths are linked to economic crises in certain countries, in others, notably Greece, the crisis has had an opposite effect, i.e. reduction in alcohol consumption as well as drunk driving (2). In these cases, alcohol pricing and restrictions in alcohol availability would serve no purpose – they might even produce increased demand for alcoholic drinks for reasons similar to those observed between 1920 and 1933 during the prohibition of alcohol in the USA.

Depression is one of the main consequences of economic crises. It should be taken into account, however, that clinical depression is different from normal sadness. Sadness is a normal adaptive response to adverse circumstances. It is the opposite, i.e. the lack of a response (apathy) that under adverse circumstances could be considered to be abnormal, and sometimes even a sign of underlying psychopathology (schizophrenia, personality problems or hysterical negation of reality) (3).

Although the differentiation between depression and normal sadness is sometimes difficult (4), it is important to keep it in mind. During periods of crisis (like the one presently occurring in Southern Europe) the mass media are very quick in claiming that society as a whole has become depressed (“a depressed society”, “a depressed nation” and the like). Obviously what is happening is an adaptive and fully understandable phenomenon, not requiring treatment but measures to combat the causes that produce it. Not so much on a behavioral medicine basis but rather on a political and economic basis.

While overdiagnosing depression is an issue, underdiagnosing it is an equally important issue. The polymorphic and atypical clinical expression of depression is a major source of diagnostic difficulty. Depression can hide behind a great number of conditions, ranging from alcoholism, substance misuse and burn-out to accident proneness, sexual dysfunction and a great variety of somatizations, and even antithetical symptoms (“smiling depression”) (3).

It appears that a great proportion of suicides occurring during periods of economic crisis are committed by people who suffer from either atypical or typical depression.

In view of this, it is important to carefully screen for depression. This is important anyway, but during periods of economic crisis it becomes an absolute necessity.

Policies aimed at strengthening social capital need to focus on culture-specific social resilience factors. For instance, in Southern European countries, family (and the local community) has traditionally fulfilled a substantial role in social welfare. Supporting local communities and the family institution in these countries at times of crisis is therefore a priority.

Vulnerable persons in the community and psychiatric patients are among the persons most likely to suffer during periods of economic recession. Paradoxically, it is the services for these very groups (that are at risk and hence in greater need of protection) that are curtailed during economic crises. This obviously calls for evidence-based advocacy interventions. It is important to speak to decision-makers not so much on humanistic grounds but rather in a language they understand, i.e., in terms of cost-effectiveness (5,6). Further research on cost-effectiveness is of course necessary to reinforce the existing data.

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Mental health and psychosocial support interventions for survivors of sexual and gender-based violence during armed conflict: a systematic review

Sexual violence has been defined as “any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic, or otherwise directed, against a person’s sexuality using coercion, by any person regardless of their relationship to the victim, in any setting, including but not limited to home and work” (1). Gender-based violence is a broader umbrella term referring to any harmful act that is perpetrated against a person based on socially ascribed (gender) differences between males and females.

Rates of sexual and other forms of gender-based violence are typically higher in areas of armed conflict than in non-conflict settings (2). Sexual and gender-based violence during conflict is not restricted to rape, nor does conflict-related violence end when conflicts do. Furthermore, the prevalence of sexual violence by intimate partners is usually higher than that of sexual violence by strangers (3).

Sexual and gender-based violence has been associated with a high prevalence of social problems (such as social exclusion), psychological distress and mental disorders, including anxiety disorders (such as post-traumatic stress disorder), mood disorders, and substance use disorders (4).

International consensus guidelines for prevention and response to sexual and gender-based violence and for mental health and psychosocial support in emergency settings exist (5,6). However, despite the increasing implementation of these interventions, there is a wide gap between popular practices and knowledge on effectiveness of interventions (7).

We conducted a systematic review on the impact of mental health and psychosocial support interventions for survivors of sexual and gender-based violence during armed conflict. Grey (i.e., evaluations published on websites, humanitarian reports, etc.) and academic literature were searched between May 13 and August 30, 2011.

With regard to grey literature, we searched the Internet (Google) using identified territories where armed conflicts were recorded between 2001 and 2009 as keywords, in combination with Boolean phrases (available upon request) to narrow the search to: sexual and gender-based violence, mental health and psychosocial well-being outcomes, and a broad range of interventions. In addition, we searched 14 websites of key agencies and initiatives in this field for relevant reports.

For the academic literature we searched the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, PubMed/Medline, PsycINFO, and PILOTS.

We examined reference lists of a number of relevant reviews and of included evaluation studies. We contacted key authors in the field to find out whether they were aware of further studies that would meet inclusion criteria. Studies were included if they were conducted with survivors of sexual or gender-based violence in areas of armed conflict, described a mental health or psychosocial support intervention, and reported evaluation methodology.

We searched without date limitations and limited our search to reports in English. Quality of papers was assessed using the Downs & Black’s checklist for the assessment of the methodological quality of studies of health care interventions (8).

Out of 5,684 returned records, 189 full text papers were assessed for eligibility and seven studies met inclusion criteria (9-15). One was a non-randomized controlled study; three applied non-controlled pre-posttest designs; one was a retrospective cohort study with a comparison group; and two were single case studies. Four studies were conducted in West and Central Africa, two were conducted with refugees in the USA, and one was conducted in Albania.

Studies included women exclusively and evaluated more generic multidisciplinary interventions (e.g., group counseling or support groups, combined psychosocial and economic interventions, medical care and psychological support) or specialized psychotherapeutic interventions (such as cognitive behavioral therapy). The quality of studies ranged from 12 to 16 out of 27 items on the Downs & Black’s checklist (8), indicating substantial limitations in study design and reporting.

An obvious conclusion from this systematic review is that the number and quality of conducted studies does not match the significance of the problem. The extent to which knowledge from other types of populations, for example those affected by disasters (7), is generalizable is not known. No studies were found with children below 14 years of age, male participants, and survivors of intimate partner/domestic violence in conflict-affected areas, despite this being a more common form of violence than rape by armed groups. In addition to their relative scarcity, it is difficult to draw any robust conclusions from the identified evaluation studies because of serious methodological limitations.

Nonetheless, the seven studies together point to potential beneficial effects of intervention, and no harmful effects of treatment were reported. Despite their limitations, the studies suggest that evaluations of popular interventions can be conducted in challenging situations through partnerships between academia and implementing organizations. Such

efforts are crucial to strengthen evidence of effectiveness or potential harm and provide accountability to stakeholders in real-world settings. More focused research efforts are urgently needed to isolate the effects of specific strategies that improve well-being and prevent or manage mental disorders and psychosocial problems in people who have survived sexual and gender-based violence in conflict settings (16).

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The International Study on Career Choice in Psychiatry: a preliminary report

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As part of the WPA Action Plan 2008–2011 (1), it was agreed to explore reasons which put medical students off psychiatry. Indeed, over the past three decades, concerns have been raised about difficulties in recruiting medical students into psychiatry (2). It has been shown that poor recruitment is influenced by a number of factors which can be addressed readily (3).

Potential psychiatrists fall into three major groups: a) those who choose psychiatry as a speciality prior to joining medical school and stick with this choice (some would have gone into medicine to do psychiatry; this may be linked with direct or indirect exposure to mental illness or to mental health professionals); b) those who decide during medical school, who are likely to be influenced by teachers and quality of clinical attachment and experience; c) those who decide after qualification or change their minds after exposure to other specialities out of interest, for career prospects or work-life balance.

We explored these three sets of factors among final year medical students in 20 countries through selected medi-

cal schools. Questionnaires were used (in e-mail or paper versions according to the respondents' preferred method of contact) to assess attitudes towards psychiatry (Attitudes Toward Psychiatry - 18 items, ATP-18) and personality traits (International English Mini-Markers), along with questions on teaching methods and exposure to the subject.

A total of 2198 students responded. 4.5% of the sample planned to become psychiatrists, with a further 15% considering it as a possible career. Women were more likely to consider psychiatry than men. Key factors associated with choosing psychiatry were personal or family exposure to physical or mental illness. 2.7% of the sample had decided to be a psychiatrist before admission to medical school and three quarters maintained this choice by their final year.

The quality and quantity of teaching received was positively correlated with attitudes towards psychiatry. Special study courses, electives, research opportunities and exposure in psychiatry, and university psychiatry clubs were all significantly associated with choice of psychiatry. Clinical experience of seeing and participating in managing acute patients contributed positively too.

Career pathways need to be flexible, to encourage especially those who want a better work-life balance to choose psychiatry as a speciality. It is important that the WPA, in conjunction with national

associations, set up and maintain an international electives network to expose interested students to clinical, research and policy options, and support student psychiatric clubs and associations. National associations and medical schools should work together to offer medical students attachments to work with researchers and clinicians. The WPA needs to set up an online resource centre to bring stakeholders in recruitment together.

Further work is required to explore differences within the same country across the various medical schools and to understand what influences decision making. It would be useful to repeat the study in a few years' time to explore if interventions put in place have borne fruit.

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WPA educational activities

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The WPA is promoting a comprehensive and interdisciplinary program combining research and education, self-learning and teamwork. The foundation is the development of a professional vision, an active, creative,

critical and ethical attitude consistent with the strategies of the triennial plan of the Association.

The main focus is being the development of regional training activities, particularly in Latin America, Asia, Africa, and Eastern Europe, and the adaptation of these activities to local circumstances, working hand in hand

with the presidents of the societies and institutions in the regions. We are trying to identify subject areas and issues of great relevance to the profession and the communities. Moreover, the model emphasizes the development of educational networks with the participation of experts in different areas of psychiatry.

Among the main recent activities are the educational seminar on bipolar disorder held in Lima, Peru in May 2012 (attended by about 90 psychiatrists from almost all Latin American countries); the educational programme on response to emergencies held in Bali, Indonesia in September 2012; the educational programme on preventive psychiatry held in Bilbao, Spain in September 2012; the educational symposium taking place in Prague, Czech Republic in October 2012, focusing on early career psychiatrists; the educational symposium held in Natal, Brazil in November 2012, on education and training in medical practice; the educational forum held in Buenos Aires, Argentina, in November 2012 on the identity of Latin America psychiatry; the educational seminar held in Athens, Greece in November 2012 on the multidisciplinary facets of psychiatry; the educational symposium taking place in La Asuncion, Paraguay in January 2013, on Latin American perspectives about addressing mental needs; the educational seminar on schizophrenia held in Cairo, Egypt in January 2013; and the educational symposium on fighting stigma and discrimination taking place in Guayaquil, Ecuador in February 2013.

The educational materials available on the WPA website (www.wpanet.org) include: the WPA e-learning programme, covering videos and slide sets of prominent scientific lectures from WPA meetings (1); the three sets

of slides based on the WPA books dealing with the comorbidity of depression with diabetes, heart disease and cancer (2–4); the educational module on physical illness in patients with severe mental disorders (5,6); the WPA guidance papers on implementation of community mental health care (7), how to combat stigmatization of psychiatry and psychiatrists (8), mental health care in migrants (9), and promotion of mental health in children of persons with severe mental disorders (10); the WPA template for undergraduate and postgraduate education in psychiatry and mental health; the recommendations for relationships of psychiatrists and psychiatric organizations with the pharmaceutical industry (11); the recommendations on best practices in working with service users and carers (12); the WPA/PTD educational programme on depressive disorders, and the WPA/ISSPD educational programme on personality disorders.

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WPA scientific meetings

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Since my election as WPA Secretary for Meetings during the 14th World Congress of Psychiatry in September 2008, I have had the opportunity to work during the triennium 2008–2011 under the leadership of Prof. Mario Maj. During the triennium 2008–2011,

the WPA scientific meetings were held in all the WPA four regions and in all the WPA 18 zones ((1)). The WPA held a total of 138 scientific meetings. Out of those meetings, 11 were WPA sponsored meetings (so called when the organizing committee takes responsibility for hosting a meeting of the WPA Executive Committee) and 127 were WPA co-sponsored meetings (so called when they are organized by

WPA Member Societies and other organizations or institutions whose goals are harmonious with those of the WPA) ((2,3)). A major scientific impact was the number of mental health professionals (psychiatrists, psychologists, nurses, primary care physicians) reached by the WPA scientific meetings, making a total of 127,417. The triennium ended with the 15th World Congress of Psychiatry, which was

held in Buenos Aires, Argentina and had a record attendance of more than 14,000 delegates (the most attended psychiatric congress in 2011 and the most attended World Congress in the history of the WPA), as well as an outstanding scientific program.

In the current triennium 2011–2014, under the leadership of Prof. Pedro Ruiz, the WPA Operational Committee on Scientific Meetings, which I am honoured to chair, includes Wolfgang Gaebele as co-chair; Sue Bailey, Edmond Pi, and Rodrigo Cordoba as members. The committee has arranged for three International Congresses (one was held in Prague, Czech Republic in 2012, and two will take place in Istanbul, Turkey in June 2013 and in Vienna, Austria in October 2013). We also have seven Regional Congresses and Meetings (in Kaohsiung, Taiwan, 2011; in Bali, Indonesia, 2012; in Asuncion, Paraguay, 2013; in Bucharest, Romania, 2013; in Guadalajara, Mexico, September 2013; in Kampala, Uganda, February 2014; and in Ljubljana, Slovenia, April 2014). We also have six Thematic Conferences (in Granada, Spain, 2012; in Tarragona, Spain, 2012; in Athens, Greece, 2012; in Yerevan, Armenia, August 2013; in

Melbourne, Australia, September 2013; and in Warsaw, Poland, June 2013), and last but not least the 16th World Congress of Psychiatry, to be held in Madrid, Spain from 14 to 18 September, 2014.

We have already had more than 100 co-sponsored WPA Meetings, co-organized with WPA Member Societies or Affiliated Associations as well as other associations whose goals and objectives are in harmony with the WPA.

The Committee also decided to implement and improve the tasks and functions of the WPA related to sponsored and co-sponsored meetings, by: a) reviewing and improving the scientific quality of WPA scientific meetings; b) working with the WPA Secretary for Education and Secretary General to provide educational credits; c) working with the WPA Secretary for Finances to improve the financial income and stability of the WPA through sponsored meetings and setting up a financial code for WPA sponsored meetings; d) working hard to ensure that WPA meetings are present across the four regions and 18 zones of the WPA, with special emphasis on middle and low income countries.

With the strong interest of the WPA Member Societies and Affiliated Associations to hold WPA sponsored and co-sponsored meetings, it seems that we will not only have the same success with WPA meetings as in the last triennium, but we may surpass that level. If these expectations and efforts are properly met, the WPA will have a major role in contributing to the quality of scientific knowledge and psychiatric care offered across the world, in particular to middle and low income countries. The number of WPA co-sponsored meetings is increasing at a steady rate and we hope to set a new record for WPA meetings at the end of this triennium.

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WPA contribution to the development of the chapter on mental disorders of the ICD-11: an update

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The WPA is partnering with the World Health Organization (WHO) in the development of the chapter on mental disorders of the 11th edition of the International Classification of Diseases (ICD), whose publication is expected in the year 2015.

WPA Member Societies participated in the WPA-WHO Global Survey on Psychiatrists' Attitudes Towards Mental Disorders Classification (1), which will guide the WHO in improving the clinical utility of the ICD classification of

mental disorders. Almost 5,000 psychiatrists worldwide provided their feedback about their use of diagnostic systems in clinical practice, and the desirable characteristics of a classification of mental disorders. Participants expressed preference for a simpler system with 100 or fewer categories. Over two-thirds preferred flexible guidance to a strict criteria-based approach. Significant minorities of psychiatrists in Latin America and Asia reported problems with the cross-cultural applicability of existing classifications. Overall, ratings of ease of use and goodness of fit for specific ICD-10 categories were fairly high, but several categories were de-

scribed as having poor utility in clinical practice. This is being an important focus for the ICD revision.

Several WPA Member Societies and experts are being or will be involved in ICD-11 field trials and in the various translations/adaptations of the diagnostic system. The WPA is actively contributing to the process of harmonization between the ICD-11 and the DSM-5.

The WPA Past-President, M. Maj, who chairs the ICD-11 Working Group on Mood and Anxiety Disorders, recently reported (2) about the expected convergences and divergences in the ICD-11 and DSM-5 approaches to the classification of mood disorders. Among

the convergences, both systems are likely to include increased activation/energy as a defining symptom for mania, and to acknowledge that a manic/hypomanic syndrome emerging during antidepressant treatment, and persisting beyond the physiological effect of that treatment, qualifies for the diagnosis of manic/hypomanic episode. Furthermore, both systems are going to provide the clinician with the opportunity to acknowledge the occurrence of subsyndromal anxiety symptoms in a patient with a major depressive episode, by using a specifier (“with prominent anxiety symptoms” in ICD-11, “with anxious distress” in DSM-5). In ICD-11, bipolar II disorder is expected to be recognized as a distinct diagnostic entity, while in ICD-10 it is just mentioned among “other bipolar affective disorders”. Expected divergences between the ICD-11 and the DSM-5 will include a different characterization of mixed states and schizoaffective disorders. The DSM-IV bereavement exclusion in the diagnosis of depressive episode has been eliminated in the DSM-5, but two notes introduced in the text should attenuate the divergence from ICD-11, which is going to exclude from the diagnosis of depressive episode, in line with ICD-10, “normal bereavement reactions appropriate to the culture of the individual concerned”.

The Chairman of the WPA Section on Schizophrenia, W. Gaebel, who chairs the ICD-11 Working Group on Psychotic Disorders, recently reported (3) about the expected convergences and divergences in the ICD-11 and DSM-5 approaches to the classification of psychotic disorders. Among the convergences, both systems are going to deemphasize Schneider’s first-rank symptoms in the diagnostic criteria for schizophrenia and to omit subtypes of the disorder. These subtypes are going to be replaced by six symptom specifiers (positive symptoms, negative symptoms, depressive symptoms, manic symptoms, psychomotor symptoms, cognitive impairment) in the ICD-11 and by corresponding dimensional assessments in the DSM-5. Among the divergences, the ICD-11 is expected to

keep the one month duration criterion for the diagnosis of schizophrenia, and not to include functional impairment as a mandatory criterion.

World Psychiatry is one of the main channels through which the international psychiatric community is being updated about the ICD-11 development. A Special Article authored by the ICD-11 International Advisory Group, summarizing the philosophy of the entire process, has been published in the journal (4), as well as the first report of the Working Group on Intellectual Disabilities (5) and a review of evidence and proposals for the ICD-11 classification of feeding and eating disorders (6). Several papers produced by the Working Group on Mood and Anxiety Disorders have been collected in a special supplement to the journal (7). Many relevant contributions have appeared in recent issues of the journal (8–27). All these articles are available on the WPA website (www.wpanet.org).

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