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EDITORIAL

Keeping an open attitude towards the RDoC project

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In the 1970s, a programme was launched in the United States which had two objectives: a) to improve the reliability of psychiatric diagnoses under ordinary clinical conditions; b) to facilitate the elucidation of the pathophysiology of mental disorders. In order to pursue these different objectives, the same tool was regarded as appropriate: a diagnostic system based on operational criteria defining in an explicit and precise way the various mental disorders.

The first of the above objectives seems to have been achieved to some extent, although a conclusive research evidence, collected in ordinary clinical settings, is still lacking (1). The improved reliability of psychiatric diagnoses may have been attained, however, at the expense of an oversimplification of psychopathology (2) and a dehumanization of psychiatric practice (3). We may have lost part of the essence of some psychopathological constructs by translating them into operational terms, and we may have lost part of the essence of the psychiatric profession by reducing the diagnostic process to a check of the presence or absence of a series of symptoms.

The second of the above objectives has apparently not been achieved, as acknowledged by the leadership itself of the DSM-5 Task Force (4). In spite of four decades of intensive and costly research, the pathophysiology of mental disorders remains elusive. One could argue, however, that a bulk of neurobiological data has been indeed collected, and several models developed. The puzzle to be composed may be just much more complex than originally envisaged, and a declaration of failure may be actually premature.

If the programme has indeed failed to achieve its second objective, several interpretations are possible. The first, and the simplest, is that all mental disorders defined within the programme are not valid disease entities, i.e., the entire diagnostic system does not carve nature at its joints. The second is that, although some of those disorders may be valid disease entities, the level at which they have been described is higher than that at which meaningful pathophysiological correlates are likely to emerge, i.e., we need some intermediate entities on which to base our search for neurobiological mechanisms. The third is that absence of evidence should be regarded as evidence of absence, i.e., mental disorders may be not amenable to a pathophysiological explanation in the same sense as, say, cardiological or neurological diseases. Damage to the neural substrate may be not necessary for failure of psychological function (5,6) and/or a variety of higher-order processes may intervene between the level of neurobiological vulnerability and that of psychopathological manifestations, so that a bottom-up reductionistic approach becomes insufficient (7). The nature of psychopathology may be intrinsically heterogeneous in this respect, with higher-order processes accounting for the identity of some mental disorders (e.g., anorexia nervosa) much more than they do for others.

The Research Domain Criteria (RDoC) project is in conceptual continuity with the programme launched in the 1970s. One of its objectives is, again, to facilitate the elucidation of the neurobiological underpinnings of psychopathology. The other is to generate a diagnostic system which is more valid than that produced by the previous programme, being based, in analogy with the rest of medicine, on biological measures. In order to pursue these different objectives, the same tool is regarded as appropriate: a research framework including some functional domains, each consisting of behavioral dimensions that have been at least preliminarily related to a particular brain circuit or area.

The outline of the RDoC proposed dimensions available on the National Institute of Mental Health website is indeed impressive. Contrary to what might be inferred from the reports published in scientific journals, those dimensions do not only include “observable behaviors”, but also constructs such as “perception and understanding of self” and “understanding [others’] mental states”, so that the “experiential” component of psychopathology is also represented. The list of neurobiological variables is probably overinclusive, so that the reader is unable to identify the most promising ones (would some indication of the level of evidence available for each item be useful?). A (short) list of references is provided at the end of each section, but these references are not keyed to the proposed variables. Overall, however, the framework is remarkably informative for researchers.

Nevertheless, the gap between the proposed dimensions and the signs and symptoms that, as Cuthbert acknowledges, are “the actual clinical phenomena that bring patients to the clinic” (8) is sensible in several areas. If the problem with the DSM categories may be that they are too distant from the level of neuroscience, the problem with at least some of the RDoC constructs may be that they are somewhat distant from the level of clinical phenomena. Cuthbert seems to be confident that “sooner or later” it will be possible to explain even complex symptoms, such as delusions, “in terms of dysregulation in basic brain operations” (8). What happens, however, if some of those symptoms are found not to be explainable in neurobiological terms? Will they follow the fate of current diagnostic categories in being regarded as “invalid” constructs? Indeed, the RDoC project may be seen by some scholars as a

further step, after the introduction of operational diagnostic criteria, in the oversimplification of psychopathology and dehumanization of psychiatric practice. The concern may be raised that we are gradually departing from the essence of psychopathology rather than approaching it, and that we are further downgrading the humanistic component of the psychiatric profession just at a moment in which this component is being re-evaluated in the rest of medicine.

An alternative perspective, however, is that the RDoC project may represent a stimulus to a reconceptualization of some complex symptoms. Indeed, several elements of the current definition of delusions (i.e., that they represent "false beliefs", that they are based on an "incorrect inference", and that such an inference always regards "external reality") have been recently questioned, at least in the case of schizophrenia (9). What can be explained in neurobiological terms may not be the patient's metaphorical utterances, but the basic pathological experiences that the patient tries to convey through those utterances. A more in-depth exploration of those experiences may be therefore warranted.

The behavioral (and experiential) dimensions proposed by the RDoC project are expected to "cut across traditional diagnostic entities" (8). These latter entities would therefore be, in Jaspers' terms, "mosaic-like structures" consisting of the same recurring elements. This remains, however, a hypothesis. At least some of those dimensions may be found to have different nuances and neurobiological correlates in partial or full relationship to current diagnostic constructs. Hopefully, research designs within the project will allow distinguishing between these alternative possibilities. Cuthbert's argument that analyses "could be conducted in terms of the DSM factor, the RDoC dimension, and the interaction" (8) seems to point in this direction.

The RDoC project is stated to "depart markedly from the DSM and ICD processes", which were based on "extensive workgroup meetings" that "generated the sets of diagnoses" (8). One could argue, however, that the RDoC functional domains and the dimensions included in each domain have been identified through a similar process. They are at present the result of a consensus among experts. Of course, that consensus was based on the available research evidence and is going to be reconsidered throughout the process, but we should not forget that the same applies to current DSM and ICD constructs, several of which have been the subject of many hundreds of studies and have been repeatedly reconsidered and revised along the years on the basis of research evidence. Incidentally, an important feature of DSM and ICD workgroups has always been their international composition, while a recurring complaint has been that practicing clinicians, who might provide a useful viewpoint about the applicability of the proposed system under ordinary clinical conditions, were not sufficiently represented. It may be perhaps advisable to reflect upon this.

Overall, the RDoC project seems much more likely to achieve to some extent, in the foreseeable future, its first objective (i.e., to facilitate the elucidation of the neurobiological underpinnings of psychopathology), than the second, at least as currently formulated (i.e., to generate a diagnostic system "based upon neuroscience and behavioral science rather than descriptive phenomenology"). Achieving this latter objective, in fact, would require developing a set of behavioral and biological measures whose test-retest/inter-operator reliability as well as sensitivity/specificity in predicting outcomes (including response to various treatments) is at least the same as that of current symptom-based measures, and whose assessment is feasible and cost-effective in a reasonable range of clinical settings worldwide. Most likely, something not attainable even in the long term. It would be probably wise, therefore, to refrain from a polemic confrontation with the DSM and ICD which is unwarranted, disruptive to the field, and confusing to patients and families, to colleagues of other medical disciplines, to policy makers and to the public opinion.

It may also be appropriate to lay a greater emphasis on the less ambitious version of the second objective, which also appears in Cuthbert's paper, i.e., the development of neurobiological measures which may help in *subtyping* rather than *replacing* current diagnostic entities, in order to improve prediction of outcome and treatment response. As stated in a recent paper of which T. Insel was a co-author (10), "the real opportunity for psychiatry is to use the emerging advances in genetics, molecular biology, imaging and cognitive science to supplement, rather than replace, the symptom-driven diagnosis".

On the other hand, in consideration of all the above, it is probably advisable for all scholars to keep an open attitude towards the RDoC project. By interfacing more directly with the level of neuroscience, this project is likely to usefully complement the current diagnostic systems, which interface more directly with the level of clinical reality. Developing cross-walks between the two approaches, in a climate of reciprocal respect, is an endeavor that can only enrich psychiatry and related disciplines and increase their credibility.

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SPECIAL ARTICLE

Advantages and limitations of Internet-based interventions for common mental disorders

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Several Internet interventions have been developed and tested for common mental disorders, and the evidence to date shows that these treatments often result in similar outcomes as in face-to-face psychotherapy and that they are cost-effective. In this paper, we first review the pros and cons of how participants in Internet treatment trials have been recruited. We then comment on the assessment procedures often involved in Internet interventions and conclude that, while online questionnaires yield robust results, diagnoses cannot be determined without any contact with the patient. We then review the role of the therapist and conclude that, although treatments including guidance seem to lead to better outcomes than unguided treatments, this guidance can be mainly practical and supportive rather than explicitly therapeutic in orientation. Then we briefly describe the advantages and disadvantages of treatments for mood and anxiety disorders and comment on ways to handle comorbidity often associated with these disorders. Finally we discuss challenges when disseminating Internet interventions. In conclusion, there is now a large body of evidence suggesting that Internet interventions work. Several research questions remain open, including how Internet interventions can be blended with traditional forms of care.

Key words: Internet interventions, cognitive behaviour therapy, mood and anxiety disorders, dissemination

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Internet-based psychological treatments have a relatively short history, but extend on principles and evidence established by computerized interventions (1) and bibliotherapy (2).

Reflecting the evolving nature of the field, a broad range of terms have been used to describe Internet-delivered treatments, although consistency is emerging (3). We will use the term "Internet-based interventions" for treatments that are mainly delivered via the Internet with at least some therapeutic tasks delegated to the computer.

We will focus on psychological treatments delivered via the Internet. However, it should be noted that the Internet is also widely used by patients and their significant others to seek information about mental health issues (4), and may also be used by patients to engage in online support groups (5). Information seeking and online support groups are not the topic of this paper, but should be considered as important for psychiatry, since they may influence patient management (6).

The model of Internet-delivered treatment for which there has been most research activity is Internet-delivered cognitive behaviour therapy (ICBT) (7). However, other models of psychotherapy (e.g., psychodynamic and interpersonal psychotherapies) have also been delivered via the Internet to a much lesser extent.

During ICBT, patients login regularly to a secure website over a specified period to access, read and download online materials arranged into a series of lessons or modules (8). They receive homework assignments which they are expected to complete before the next module is available. They also regularly complete computer administered questionnaires relevant to their presenting problems, which allows a therapist to monitor progress, safety and outcomes.

Two dimensions which can be used to categorise ICBT are whether it involves therapist contact, and whether it aims to treat mental disorders or prevent their development. Internet interventions that involve therapist contact can be further divided into those that involve real-time (synchronous) or delayed (asynchronous) interaction with patients. Examples of the former include contact via telephone, video, or messenger services (9), while examples of the latter include secure e-mail communications. For pragmatic purposes, therapists may use a combination of synchronous and asynchronous communications during treatment.

The amount of time therapists spend working with patients varies considerably between studies, with some requiring therapists to spend considerable time reading and responding to writing assignments (8). Many programs, however, involve only minimal guidance via e-mail (or secure asynchronous communication system), which requires considerably less time than face-to-face therapy (9,10).

In this paper we discuss the advantages and disadvantages of Internet-delivered treatments for common mental disorders, with a focus on ICBT, although other forms of Internet interventions are also mentioned. We examine a broad range of issues regarding recruitment, assessments, the role of the therapist in guided ICBT, treatments for mood and anxiety disorders, management of comorbidity, and dissemination.

RECRUITMENT OF PATIENTS

Patients may be recruited for Internet-delivered treatments by multiple means that include advertising and promotions through online and traditional media, epidemiological surveys

(11), webpages, and less frequently, referrals from health practitioners.

Allowing patients to self-refer to Internet interventions offers multiple advantages. It is a well-known fact that many persons with mood and anxiety disorders never reach specialist clinics and sometimes hesitate to even mention their problems when consulting general practitioners, and by means of online recruitment the treatment versus demand gap can decrease (12). In other words, patients who may have remained untreated for many years may be given evidence-based psychological treatment for the first time. This is indeed an observation we have made, as research participants in our trials and clinics often have had their problems (for example social anxiety disorder) for decades. Furthermore, the format of Internet interventions makes it possible for prospective patients to reflect on the treatment before they make an informed decision to commit to it.

Online recruitment and particularly patient self-referral has, however, raised questions about whether the characteristics of patients using online services are similar to those accessing traditional face-to-face clinics. This is important from the perspective of determining whether this model of service delivery can be provided at a public health level. A common observation in Internet trials is that research participants tend to be better educated than the general population. This may reflect an artefact of the digital divide, i.e., the fact that access to the Internet reflects socio-economic characteristics, although such differences may attenuate as access continues to increase across social groups. However, it may be that, by virtue of increased levels of education and the self-selected nature of recruitment, online patients are more motivated to participate in treatment, and therefore are more responsive.

Our experience is that patients who use Internet-delivered treatments represent a broad range of people. These include people with both low and high levels of education and different cultural groups. This represents a challenge for the design and delivery of ICBT, though some initial steps have been taken in culturally adapting treatments (13). Patients also present with a spectrum of experiences with previous mental health services. Some have previously received traditional face-to-face treatments, while others have never sought treatment, despite years or decades of distressing symptoms. There is relatively little research on patient characteristics in ICBT versus other trials and regular clinics, but there is evidence to suggest that participants in Internet trials are more similar to persons in the general population who have the same problems than patients who are seen in specialist clinics (14,15).

There is also now an increasing number of effectiveness trials on ICBT, i.e., trials that have been conducted in regular clinical settings. A recent review identified four controlled studies and eight open studies that had been conducted in regular clinics (16). All studies clearly showed that the promising effects of ICBT in trials with patients recruited via advertisements can also be observed when the treatment is transferred to regular clinics.

INTERNET-BASED ASSESSMENTS AND DIAGNOSIS

Accurate and reliable diagnosis and measurement of symptoms is as important in Internet-delivered treatments as in traditional face-to-face treatments. An expanding literature concerned with how to collect patient data via the Internet has evolved (17), and it is timely to highlight the pros and cons of online data collection.

We can conclude from several studies that questionnaire data can be collected without compromising psychometric characteristics (18-20), but there is a need for a systematic review of this issue and it is commonly argued that norms need to be collected separately for paper-and-pencil and Internet administration (17). Advantages of Internet administration of questionnaires are that the risk of missing items can be reduced and that crucial items can be automatically highlighted for the clinicians (e.g., red flags in case of elevated suicide risk). Moreover, summary scores can be automatically generated and algorithms developed to help therapists monitor progress and actively intervene in cases of suspected lapse. Automated administration also results in reduced costs associated with scoring and posting questionnaires.

The cons of Internet administration include first and foremost security issues. This is relevant not only to data storage, but also to methods of collection. While most researchers and clinicians comply with information security frameworks similar to online banking standards, the recent advent of mobile smartphones reminds us of evolving issues in security associated with new technology. An additional con is the difficulty of checking accuracy of responses and of obtaining additional information. The former can be addressed to some extent by asking patients to confirm that responses are correct, while the latter can be managed by the adoption of clinical protocols that require telephone contact when clinically indicated. These procedures must be implemented within a governance framework acknowledging legal and informed consent issues.

A more critical question concerns limits of diagnosing patients via the Internet. Clearly, self-diagnosis would have many advantages, such as saving clinicians' time, but to date there is little to suggest that self-assessments can replace structured diagnostic interviews, and Internet administration does little to change this fact (21). On the other hand, if patients are required to first receive a diagnostic assessment at a face-to-face clinic, some of the advantages of Internet interventions may be reduced. Indeed, at the Internet psychiatry unit in Stockholm, this is the case when patients are diagnosed at the clinic (22).

In research, it is common to conduct structured psychiatric interviews such as the Mini-International Neuropsychiatric Interview (23) via telephone. This procedure is better than not obtaining any diagnoses at all and can generate valid findings (24). However, there are disadvantages with not seeing the patient, and information may unavoidably be lost. Again, the adoption of pragmatic clinical protocols requiring face-to-face assessments in the presence of

sufficient complexity of symptoms can address issues relating to diagnostic accuracy.

In summary, online questionnaires work well, but psychiatric diagnoses cannot be reliably made using self-report only. A compromise is to conduct interviews over the telephone. A secure online video conferencing platform could work as well, although research is needed to investigate the relative costs and benefits associated with this option.

THE ROLE OF THE THERAPIST IN INTERNET-BASED TREATMENTS

Important discussions in the field of Internet interventions concern the role of a therapist or professional compared to automated programs that do not include any interaction with a human (25). Reviews of the literature consistently show that treatments that include guidance lead to better outcomes than unguided treatments (26-28), but there are occasional exceptions, and unguided treatments are emerging that can work by means of automated reminders and similar solutions (29,30).

The available evidence indicates that indeed any contact with a clinician may improve outcomes. For example, a systematic review of Internet interventions for depression found a linear effect for the role of clinician contact, such that between-group Cohen's d effect size was of d=0.21 if there was no therapist contact either before or during treatment, of d=0.44 if there was therapist contact before treatment only, of d=0.58 if there was therapist contact during treatment only, and of d=0.76 if there was therapist contact both before and during treatment (31).

While some data indicate that, when given choice, patients may be more likely to opt for unguided treatments, there are important advantages to guided treatments. First, a therapist can make a diagnosis, to help determine the suitability of a treatment for a patient. Second, the intervention can be tailored and advice individualized following consultation with experienced clinicians: in fact, some support in ICBT is asynchronous, which means that clinicians can consult colleagues and other experts before answering and providing feedback to patients (32). Third, there are clear indications that support increases adherence and prevents dropout, an important issue given that at least some unguided interventions have suffered from unacceptably high dropout rates (33). Fourth, therapists can actively assist patients to access other services that may be required, including social, health and crisis services.

However, there are also outstanding questions about the optimum frequency and form of support that should be provided. First, there is no clear dose-response relation between support and outcome, and treatments in which substantial support is given do not appear to differ from treatments with minimal support (e.g., 10 minutes or less per client and week) (28). Second, while studies indicate that equivalent clinical outcomes have been obtained whether support is provided by a professional psychologist or a coach, providing the latter is under careful clinical supervision and the ICBT is highly structured (34-36), it is unclear whether similar outcomes would be obtained with less structured interventions. Third, while guided Internet interventions are cost-effective (37,38), the provision of guidance is indeed more costly than automated treatments, and unguided treatments with small effects can still be cost-effective (39). Thus, from a public health perspective, the minimal costs of providing Internet interventions without guidance can in some cases be justified if they are safe. A fourth outstanding question relates to the limited knowledge about therapist factors which are widely held to be important in face-to-face treatments (40). In addition to the findings regarding the role of technical versus more psychotherapeutic guidance (34-36), there are a few studies in which the therapist factor has been studied showing no or small effects (41,42).

On the other hand, the way guidance is provided seems to be important even if most of the communication tends to be of a supportive character (43). In a study in which the therapist correspondence was coded, it was found that a lenient attitude towards homework was associated with a worse outcome (10). Consistent with this, observations from our online research and clinical work indicate that better outcomes are associated with adherence to scripts which direct patients to key issues, while minimizing therapist drift.

Therapeutic alliance is another factor that is widely regarded as important in psychotherapy outcome research. Several studies on Internet interventions have collected data from patients on how they rate the therapeutic alliance with their online therapists (44). Most studies show no association with outcome, even if alliance ratings tend to be fairly high (45,46). There are, however, a few studies in which alliance early in the treatment predicted outcome (47,48).

In sum, and to date, most studies suggest that therapist contact is associated with better outcomes in Internet interventions. However, provided the content of the Internet treatment is of appropriate quality and sufficiently engaging for patients, therapist expertise may be less important than in face-to-face therapies. Thus, depending on the degree of structure in the model of Internet intervention adopted, guidance can be mainly practical and supportive rather than explicitly therapeutic in orientation. This offers advantages in terms of fidelity and efficiency of patient and therapist time. Indeed, the therapist can focus on supporting patients to master skills and overcome hurdles to the application of the intervention.

INTERNET-BASED TREATMENTS FOR MOOD AND ANXIETY DISORDERS

Most studies on Internet-based treatments have evaluated interventions for mood and anxiety disorders of mild to moderate severity (with the exception of some anxiety disorders

that can be regarded as severe). In a surprisingly short time, treatments have been developed and tested for a range of anxiety disorders, including panic disorder (49), social anxiety disorder (50-52), generalized anxiety disorder (53,54), post-traumatic stress disorder (8,55), obsessive-compulsive disorder (56,57), severe health anxiety (58), and specific phobia (59). Most studies have been on adults, but there are also studies on children/adolescents (60,61) and older adults (62).

The majority of studies of mood disorders have examined major depression and have evaluated different forms of CBT (35,63,64). In addition, several Internet intervention studies have evaluated other models of therapy, including psychodynamic psychotherapy (65) and physical activity (66). Direct comparisons of face-to-face CBT and ICBT have shown equivalent outcomes, with gains sustained in the long term (67), and this pattern of results was replicated in effectiveness studies (16).

Several advantages and disadvantages are emerging. Advantages include improved access to evidence-based treatments for patients as well as cost-effectiveness compared to face-to-face treatment. Furthermore, since patients can return to the program at their convenience to access treatment information, this may facilitate learning and retention. In addition, with the assistance of automated software features, therapists can monitor patient progress and outcomes and proactively support patients before a crisis develops. This means that patients in an Internet intervention may receive support from a therapist faster than would have been the case if they were receiving only weekly visits.

The main disadvantages appear to reflect the relatively new nature of the field. For example, there is limited knowledge about the characteristics of patients who are likely to benefit. Several studies have explored this issue, but few consistent predictors have been identified (68,69) and more research is needed. An additional and related topic requiring further information is the rate of negative outcomes and the risk that these are not detected. Negative outcomes following psychological treatments are a neglected aspect (70), and practically nothing has been written on this topic concerning Internet interventions.

From the perspective of integrating Internet interventions with existing mental health services, outstanding questions include the potential benefits of sequencing ICBT with face-to-face psychotherapy. One possible scenario may envisage the Internet intervention as a first step followed by more intense face-to-face treatments when needed (71). This sequence may be more frequently appropriate when the first step is unguided ICBT. On the other hand, we have seen patients who have failed face-to-face treatments and subsequently improve following ICBT, which may reflect issues associated with treatment readiness. More research is needed here, as not much is known regarding ICBT as a step in stepped care models.

In summary, there is a strong and consistent evidence base in favour of ICBT. Factors relevant to face-to-face treatments, including treatment readiness, are likely to be relevant. However, more information is required about the rate and determinants of dropout and non-response, as well as on the potential benefits of sequencing ICBT with face-to-face psychotherapy.

MANAGING COMORBIDITY

To date, the majority of Internet interventions have targeted specific disorders. However, a limitation of such interventions is the high prevalence of comorbidity (either co-occurrence of a mood and an anxiety disorder or co-occurrence of a mood or an anxiety disorder with other mental or physical disorders). Two recently developed strategies for addressing this problem are transdiagnostic and tailored Internet treatments. Both have received empirical support in controlled trials (65,72-74) and are associated with different pros and cons.

The main pros of transdiagnostic treatments include their high face validity with patients, who often report recognizing the relevance of learning about a range of symptoms; time saving for both patients, who do not have to work through different disorder-specific protocols, and therapists, who have to administer only one, rather than multiple interventions, which then allows capacity for individualizing therapy based on specific patient characteristics; and potentially reduced relapse rates due to increased emotional resilience. The main con are outstanding questions about whether patients with some diagnoses, such as that of social anxiety disorder, will benefit less from a transdiagnostic than from a disorder-specific treatment. This risk may be addressed by the provision of extra material which can be targeted towards specific needs (75).

The pros of tailored treatments include acknowledging and meeting patient preferences by providing a choice of treatment modules (76). Further, tailoring treatment content according to symptom profile does not only involve picking a suitable treatment program for the patient (like for example modules on generalized anxiety disorder, insomnia and problem solving), but also adapting the treatment according to the capacity of the patient (65). Finally, it is possible that tailored treatments are better suited to handle more severe disorders, which was indeed found in a controlled trial comparing standard ICBT versus tailored intervention in depression with comorbid problems (65). Among the disadvantages with tailored ICBT as it is currently set up, are the fact that the tailoring process is still based on best practice, since specific algorithms on how the tailoring should be made are being evaluated, and the risk of adding too much material, with the possible problem of overloading the patient.

Overall, there is now evidence to suggest that both transdiagnostic and tailored approaches to Internet interventions work, although their relative merits compared to diagnosis-specific treatments are less well known, with some studies reporting a superiority of the former (e.g., 65) and others reporting no difference (e.g., 76).

DISSEMINATION INTO CLINICAL SETTINGS

Several studies have examined the effect of Internet interventions delivered in regular clinical services (16). These studies consistently show that the promising results of Internet treatments found in efficacy studies (mainly with ICBT) are replicated in effectiveness studies, with moderate to large effect sizes.

There are advantages and disadvantages involved in the use of Internet interventions in regular clinical practice. First, because of the highly structured and often scripted nature of the intervention, therapist drift is less likely to occur compared to face-to-face therapies. Second, outcome monitoring is often embedded in the clinical implementation, thus facilitating the assessment of progress and safety (22). Third, Internet interventions can be organized as nationalized centralized health care (i.e., specialist centres), which reduces the need for duplication of resources and facilitates training and supervision. This frees up resources for other important activities, such as updating and adapting treatments to new needs (for example, delivering the treatments in different languages). Fourth, Internet interventions can also be delivered as local care in general practices and therefore be combined with other treatment options such as medication and face-to-face psychotherapy.

Among the disadvantages, the first and foremost is probably the common negative clinician and patient attitudes towards Internet interventions (77,78). Nevertheless, some surveys show that attitudes among people with mental disorders recruited from the general population may be more positive (79,80), and there are probably differences between countries depending on the level of Internet access. Furthermore, the skepticism of clinicians can be addressed through education (81).

A second related problem is that clinicians may feel threatened and fear losing their work as practicing psychotherapists if Internet interventions are disseminated. Given the scarcity of trained clinicians and the large number of people in need of evidence-based psychological treatments, this is likely not well founded, and Internet interventions should be regarded as a complement to other services rather than as a full replacement for face-to-face therapies (in particular for more severe patients).

Third, dissemination can be hindered or even made impossible by how legal and ethical regulations apply to online clinician-patient interaction (82). For example, in Norway, e-mail exchanges (even in secure closed systems) were not allowed, which had implications for the dissemination of a Swedish program in Norway (83), as guidance had to be provided by telephone (this has now been changed). Further, in countries like Germany, it has been considered inappropriate to provide psychotherapy over the Internet as a regular secondary care treatment, although this is gradually changing (84).

Fourth, dissemination into primary care depends on the willingness of practitioners to refer patients to Internet interventions. It may be difficult to coordinate local services (for example general practices) unless proper training is provided and diagnostic guidelines are well established rendering referrals safe. Stepped care procedures may be one solution, where Internet interventions are presented as one step in a stepped care process (85).

In conclusion, there are still few experiences of large scale dissemination of Internet interventions worldwide. While the evidence to date suggests that Internet interventions are effective when provided in regular clinical settings, and that more patients can get access to health care in that way either immediately or as part of a stepped care procedure, it is still the case that clinicians and patients need to know more about these interventions. Moreover, clinical guidelines need to be developed.

CONCLUSIONS AND FUTURE DIRECTIONS

With the number of studies on Internet interventions exceeding one hundred (86), there is now considerable support for the use of the Internet for delivering evidence-based psychotherapy for common mental disorders. The field has recently evolved to the point where several clinics are now providing such services as part of regular health care.

Conclusions that can be drawn from the work to date are that assessments using the Internet offer considerable advantages for patient care, in particular for monitoring safety, progress and outcomes, and for research purposes. However, because of uncertainty about the validity of online diagnoses, it is recommended that, when possible, patients with complex presentations be referred to existing face-to-face services rather than to automated online diagnostic systems.

Internet interventions for comorbid mood and anxiety disorders, including transdiagnostic and tailored treatments, have produced encouraging results. However, these interventions mainly target comorbidity between different forms of mental disorders, and there is a need to develop treatments that target also somatic disorders, as there are many studies on Internet intervention for common somatic disorders showing promising results (87).

Finally, recent reports indicate that Internet interventions work well in regular settings. We are currently in the process of disseminating Internet interventions and there are several challenges involved in this process. Questions have been raised about the possibility to develop and disseminate Internet interventions to better serve minority groups who may have less access to mental health services (13), and to persons in countries where mental health services may be less developed (88).

Likely areas for development and future research include exploring outstanding questions about the characteristics of those likely to benefit, how best to integrate Internet interventions with existing services, and optimal strategies for combining Internet interventions and medication. The latter question is pertinent given the common scenario in regular care of the prescription of selective serotonin reuptake

inhibitors for mood and anxiety disorders alongside psychotherapy, with such combinations often yielding better results than monotherapies (89).

Further work is also required to address the lack of studies on children, adolescents and older adults. Outstanding questions remain about the role of therapists and the optimum way to provide guidance during Internet interventions. There is also a need for integrating modern information technology with face-to-face therapy and this has not yet been the topic of much research (90).

In conclusion, we expect that the field of Internet interventions will continue to evolve at a rapid rate. While results of studies in this field have been very encouraging, we caution that efforts at dissemination must progress cautiously to ensure best outcomes for patients. We also expect further and considerable developments in the relevant research, as studies move from enquiring about effectiveness to exploring processes of change.

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Uses and abuses of recovery: implementing recovery-oriented practices in mental health systems

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An understanding of recovery as a personal and subjective experience has emerged within mental health systems. This meaning of recovery now underpins mental health policy in many countries. Developing a focus on this type of recovery will involve transformation within mental health systems. Human systems do not easily transform. In this paper, we identify seven mis-uses ("abuses") of the concept of recovery: recovery is the latest model; recovery does not apply to "my" patients; services can make people recover through effective treatment; compulsory detention and treatment aid recovery; a recovery orientation means closing services; recovery is about making people independent and normal; and contributing to society happens only after the person is recovered. We then identify ten empirically-validated interventions which support recovery, by targeting key recovery processes of connectedness, hope, identity, meaning and empowerment (the CHIME framework). The ten interventions are peer support workers, advance directives, wellness recovery action planning, illness management and recovery, REFOCUS, strengths model, recovery colleges or recovery education programs, individual placement and support, supported housing, and mental health trialogues. Finally, three scientific challenges are identified: broadening cultural understandings of recovery, implementing organizational transformation, and promoting citizenship.

Key words: Recovery, mental health services, peer support workers, advance directives, wellness recovery action planning, individual placement and support, supported housing, mental health trialogues, organizational transformation, promoting citizenship

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Understanding recovery as a return to symptom-free normality has been challenged in mental health services. People personally affected by mental illness have become increasingly vocal in communicating what helps in moving beyond the role of "patient". Recovery has been defined as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills, and/or roles" and "a way of living a satisfying, hopeful, and contributing life even within the limitations caused by illness" (1). This definition underpins mental health policy in the Anglophone world (2-6) and elsewhere (7).

At its heart, personal recovery is a subjective experience (8). There may be overlap between individuals, but there will be many subjective definitions of recovery, not least because the individual's understanding of his/her own recovery may change over time. Despite the policy consensus, it has proved challenging to develop a recovery orientation in mental health services which gives primacy to the individual's understanding. Indeed, some commentators suggest the concept has been "hijacked" (9) by professionals.

This paper sets out some recovery mis-uses ("abuses") and empirically supported pro-recovery approaches ("uses"). The authors comprise international experts from seven countries, and span lived experience (i.e. personal experience of mental ill-health), researcher, policy-maker and clinical perspectives.

We identify seven abuses of the concept of "recovery".

ABUSE 1. RECOVERY IS THE LATEST MODEL

With the spreading of the international movement towards recovery-oriented mental health services, organizations are increasingly trying to implement recovery-oriented practices.

Some organizations hire peers as a concrete manifestation of a recovery orientation. For example, thirteen states in the USA have committed to hire peers, and organizations in those states are now able to receive reimbursement for peer support services through a national insurance plan (10).

While consistent with recovery practice values (11), simply adding peers to the workforce of a mental health organization does not, by itself, create the paradigm shift needed. Indeed, a lack of organizational commitment can undermine the effectiveness of peer workers, if workers are disrespected or marginalized, or if roles are entirely assimilated into generic or clinical case work (12).

Implementing recovery-oriented practice should be person-centred and focus on helping individuals live a meaningful life (13), in contrast to setting clinical goals that are largely dictated by professionals (14). Shifting to practice that is built on equal partnership, hope-promoting and facilitating self-determination requires a transformation of services, practices and the paradigm within which they are delivered.

ABUSE 2. RECOVERY DOES NOT APPLY TO "MY" PATIENTS

The development of recovery ideology and practice has – like psychiatry – had a centre of gravity within psychosis. Some clinicians suggest that recovery as an approach is not relevant to the people they work with, because either the individuals are "too ill" or they do not have a psychosis diagnosis.

Neither stance is empirically defensible. Many pro-recovery interventions described in this paper are directly applicable to, and have been evaluated with, people in acute crisis. Similarly, empirical investigation of recovery has begun in many non-psychosis clinical populations (e.g., borderline personality disorder (15), forensic (16), eating disorders (17)) and various demographic groups (e.g., children (18), older adults (19), ethnic minorities (20)). Although the evidence base is less developed than in relation to psychosis, it is clear that recovery is at the least relevant to a wide range of clinical populations.

ABUSE 3. SERVICES CAN MAKE PEOPLE RECOVER THROUGH EFFECTIVE TREATMENT

Mental health professionals are often more accustomed to the clinical meaning of recovery than to personal recovery as it is understood by the recovery movement in mental health (1).

In clinical recovery, professionals diagnose and treat with the aim of curing people or reducing their symptoms. A review of all epidemiological studies with greater than 20-year follow-up showed that the majority of people with a diagnosis of schizophrenia attain clinical recovery (21), although the variance in this prevalence rate which is attributable to effective treatments is unknown. In personal recovery, the person leads his/her own journey towards a meaningful life and valued roles (22).

These two versions of recovery may be intertwined, but a person can experience one without the other. Traditionally, mental health services have been based upon either a clinical version of recovery or – at worst – a belief that recovery of any sort is not possible for many people. Mental health policy in many countries now requires services to build upon the personal version of recovery, and to give credence to the knowledge derived from lived experience of mental distress and recovery (23).

To support personal recovery, mental health systems will need to shift away from a dominance of institutional responses, drug treatments and coercive interventions. The focus needs to be on fostering hope and a belief in people, supporting self-determination, ensuring access to a broad range of community oriented services (including housing, education, employment, peer support, recovery education, crisis support, support in everyday living, drug treatments, talking therapies and advocacy), and promoting social inclusion and human rights (24). Treatment may help personal recovery, but it can also hinder it, especially if it is the dominant response and is associated with coercive practices.

ABUSE 4. COMPULSORY DETENTION AND TREATMENT AID RECOVERY

Compulsory treatment is promoted as an effective way to "take care" of individuals when they cannot take care of themselves. For example, in England, the introduction in 2008 of community treatment orders (CTOs) was intended to reduce the number of individuals compulsorily detained in hospital. Despite 4,220 CTOs being made in 2011/12, the rates of compulsory admission have actually increased (from 44,093 in 2007/08 to 48,631 in 2011/12) (25).

A systematic review of the literature on compulsory treatment orders found little evidence of effectiveness in terms of health service use, social functioning, mental state, quality of life or satisfaction with care (26). In addition, the review found that it would take 85 outpatient commitment orders to prevent one readmission, 27 to prevent one episode of homelessness and 238 to prevent one arrest.

Compulsory treatment appears to be a broadly used intervention which recent evidence suggests is ineffective at reducing readmission (27). In addition, it works against the recovery goal of reclaiming a meaningful life – a process that is based on self-determination and respect for the individual as a citizen of society. Indeed, a study of 136 acute inpatient mental health units in England found that a focus on control (reduced access to medical staff, more use of security guards, poor ward structure) was associated with increased use of manual restraint and shows of force by staff (28).

Many countries now fund initiatives to reduce the use of compulsion (29). For example, Norway has since 2006 had a national action plan to reduce coercion (30).

ABUSE 5. A RECOVERY ORIENTATION MEANS CLOSING SERVICES

A recovery orientation is not a valid justification for service cuts.

It is reasonable to assume that a meaningful life is not lived within the boundaries of mental health services, and increased contact with non-mental health agencies and natural forms of support are often seen by service users as more valuable than contact with formal services (31). Therefore, a gradual reduction in contact with formal mental health services, as part of a jointly agreed plan and with support to access natural community supports (friendships, peer contacts, community groups, employment, etc.), is likely to be helpful in supporting someone's recovery.

However, recovery is non-linear (32), and services have to be available to re-engage with people when needed.

Ineffective services should of course be replaced, but as an issue related to the improvement of mental health service delivery, not a matter of implementing recovery-oriented services. Reductions in services cannot be justified on the basis of meeting the goal of being supportive of recovery.

ABUSE 6. RECOVERY IS ABOUT MAKING PEOPLE INDEPENDENT AND NORMAL

The clinical framework underpinning most mental health services locates problems of exclusion largely within the individual. Clinical endeavours, therefore, focus on changing people through treatment (therapy, skills training, etc.), so that they "fit in", i.e., become "normal" and "independent" of support and services.

But recovery is not about "getting better" or ceasing to need support – it is about "recovering a life", the right to participate in all facets of civic and economic life as an equal citizen (33). This requires a framework predicated on a human rights and a social model of exclusion: "It is society that disables people. It is attitudes, actions, assumptions – social, cultural and physical structures which disable by erecting barriers and imposing restrictions and options" (34).

Inclusion and citizenship are not about "becoming normal", but creating inclusive communities that can accommodate all of us. Not about "becoming independent", but having the right to support and adjustments (in line with choices and aspirations) to ensure full and equal participation and citizenship (35).

The human rights of "persons with disabilities" – including those with mental health conditions – are outlined in the United Nations Convention on the Rights of Persons with Disabilities (36). These include the "right to live independently and to be included in the community" (Article 19). A right is not contingent on "getting better" or living without support, and explicitly includes the right to access the "assistance necessary to support living and inclusion in the community, and to prevent isolation or segregation".

Participation and inclusion do not involve changing people to fit in, but changing the world: "Having a psychiatric disability is, for many of us, simply a given. The real problems exist in the form of barriers in the environment that prevent us from living, working and learning in environments of our choice... [The task is] to confront, challenge and change those barriers... that impede and thwart our efforts to live independently and gain control over our lives and the resources that affect our lives" (37).

ABUSE 7. CONTRIBUTING TO SOCIETY HAPPENS ONLY AFTER THE PERSON IS RECOVERED

Work, whether it is paid, voluntary or household work, is the major way most people make a contribution to society. Work supports recovery (38). Most people who use mental health services are capable of working most of the time, yet 70-80% of people who use mental health services in most Western countries are unemployed, a higher proportion than any other disability group (39,40).

Self-stigma, anticipated discrimination and discrimination in services and society contribute to these high unemployment rates (41-43), as can deficit-based services with low employment expectations for people with major mental distress, and employers who lack knowledge of good employment practices for this group of people (44).

Currently, governments in many Western countries are attempting to reduce the numbers of people receiving welfare benefits or pensions, often with a punitive rather than incentive-based approach. Advocates who lobby against this approach to welfare have inadvertently created a discourse that focuses on the right to welfare over the right to work for people with mental distress.

Punitive welfare reform is not the fundamental injustice; it is the number of people who are out of work. The whole community benefits when it is assumed that people with mental health problems can work, when they have the same rights as others to determine their contribution, and when they have reliable access to welfare if or when they cannot work.

MAXIMIZING SUPPORT FOR RECOVERY

Is recovery just new wine in old bottles (45)? In other words, does supporting recovery mean more than just optimal implementation of what we already know is best practice? Certainly it is reasonable to assume that consistent implementation of best practice is better than inconsistent implementation, with some estimates that optimal treatment and coverage would avert 28% of burden (compared with 13% burden averted at present) (46). However, a systematic review has identified five key recovery processes as connectedness, hope and optimism, identity, meaning and purpose, and empowerment (the CHIME framework) (32). These recovery processes differ from traditional clinical outcome targets, and interventions targeted at these processes are needed.

We now describe ten empirically supported pro-recovery interventions. Inclusion criteria were interventions that target recovery outcomes such as the CHIME framework, and have emerging or established supportive empirical evidence based on experimental investigation. They are intended as illustrative exemplars rather than a prescriptive list of interventions. The aim is to identify the types of intervention which could be expected to be provided in a recovery-oriented mental health system.

Peer support workers

Peer support emerged from the user/survivor movement, and originally developed outside the mainstream mental

health system. It is based on recovery values of hope, self-determination over one's life, participation in the service, mutuality, and the use of lived experience knowledge to help each other.

Informal peer support comes from natural supports such as family and friends. By contrast, formal peer support involves workers who are either employed in autonomous peer-run services outside traditional mental health services, or partner with professionals within a traditional mental health or social service.

Peer support workers are individuals with mental illness who identify themselves as such, and who use their lived experience to support others to recover. Key features of their role are clear (47), and implementation guidelines are now available (48).

A substantial and positive evidence base now exists for peer support services (47), identifying the experience and benefits of being a peer support worker (49-51), changes in workplace structure made to sustain the delivery of peer support services (52-54), and description of changes initiated by peer support workers (55,56).

Evidence from seven randomized controlled trials (RCTs) evaluating the impact of peer support workers found consistent benefits in relation to clinical outcomes (engagement, symptomatology, functioning, admission rates), subjective outcomes (hope, control, agency, empowerment) and social outcomes (friendships, community connection) (57). RCTs on peer-led self-management interventions in the Netherlands (58) and USA (59,60) showed benefits in relation to having a recovery role model, pursuing recovery, hopefulness, self-perceived recovery, symptom scores and quality of life. A Cochrane review identified eleven randomized trials involving 2,796 people in three countries (Australia, UK, USA), showing equivalent outcomes from peer support workers compared with professionals employed in similar roles (61).

Advance directives

People with mental illness are almost by definition vulnerable to experiencing emotional crisis. Recent healthcare technologies support people to remain in control during crisis. For example, an advance directive involves specifying actions to be taken for the person's health if capacity is lost in the future. Actions may involve treatment or specify a proxy decision-maker.

Advance directives have strong empirical support (62). A variant increasingly used in a mental health context is joint crisis plans, which are developed in collaboration with the clinical team. RCT evidence about joint crisis plans in psychosis shows benefits for reduced compulsory treatment (63), service use (64) and increased control (65). Trials in other clinical populations are underway (66).

Wellness recovery action planning

Self-management of symptoms is a major trend across all chronic disease groups. The wellness recovery action planning (WRAP) tools and processes support self-management with a specific focus on recovery-oriented mental health services.

WRAP is used to create recovery plans, by guiding individuals and groups of people to reflect on what has assisted them to stay well in the past, and to consider strategies that assisted others with their recovery (67). Planning tools in the "wellness toolbox" focus on self-management, from identifying fundamental strategies that enhance daily well being, to recognizing and dealing with triggers to distress through crisis planning.

The focus is on approach motivation (defining wellness and supporting goal striving) rather than avoidance motivation (e.g., symptomatic relief), in line with the insight from positive psychology that positive ("approach") goals are more likely to be sustainably attained than negative ("avoidance") goals (68). The process relies on peer facilitation, to activate the hope-inducing benefits of authentic role models (69).

RCT evaluation of outcomes for participants (n=519) at eight outpatient community mental health centres in an eight-week peer led intervention, compared with usual care and wait-list for WRAP, showed benefits in symptom profile, hope and quality of life (60).

Illness management and recovery

The illness management and recovery program (IMR) is an empirically-supported standardized intervention to teach illness self-management strategies to people with a severe mental illness (70).

It can be provided in individual or group format, takes five to ten months to complete, and comprises five empirically based strategies: psychoeducation to improve understanding about mental illness and treatment; cognitive-behavioural approaches to improve medication adherence; training in the prevention of relapses; social skills training to buffer stress and strengthen social support; and teaching coping skills to reduce the distress and severity of symptoms.

The centrality of medication adherence and psychoeducation about mental illness in IMR can present a barrier to its use by people seeking to support recovery. Supporting recovery is not incompatible with diagnosis and medication, but a barrier arises when diagnosis and medication are assumed to come first in steps towards recovery (71) (see Abuse 3). However, IMR begins with and focuses on self-directed problem definition, problem solving and pursuit of personally meaningful goals, all vital elements of recovery support (72,73).

RCT evaluations indicate IMR can significantly improve symptomatology, functioning, knowledge and progress towards

goals for people in supportive housing (74), outpatient services (75), and community rehabilitation centres (76).

REFOCUS

The REFOCUS intervention increases the recovery orientation of community adult mental health teams.

The manualized intervention (77) is theoretically based (32,78). Staff are trained and supported through reflection sessions and supervision to use three working practices. First, to maximize person-centred care planning, staff discuss the values and treatment preferences of the service user, using conversational, narrative and visual approaches. Second, staff use a standardized assessment (79) to identify the service user's strengths, so that care planning will be focused on amplifying strengths and ability to access community supports, as well as on deficit amelioration. Third, staff support active goal-striving by the service user towards his/her personally valued goals. Additionally, the staff-service user relationship is targeted by training staff to use coaching skills.

The REFOCUS intervention is being evaluated in a multisite cluster RCT (80), which is using innovative approaches to assessing recovery support (81) and hope (82).

Strengths model

The strengths model of case management aims to help people with mental health problems to attain goals they set themselves by identifying, securing, and sustaining the range of environmental and personal resources that are needed to live, play, and work in a normally interdependent way in the community (83).

It has been used broadly and over decades in social care sectors in the USA, and in clinical services in Japan, Hong Kong and Australia (84). The evidence base comprises four RCTs (85-88) and several pre-post evaluations (89), showing improved psychosocial outcomes (especially for symptomatology and social functioning) and consumer satisfaction (84). Greater fidelity is associated with more improved consumer outcomes (90).

Recovery colleges or recovery education programs

People with psychiatric disabilities have emphasized the importance of education as a tool to assist them in gaining the competencies needed to assume full citizenship (91).

Recovery colleges or recovery education programs are an educational approach to supporting the recovery and reintegration of people with psychiatric disabilities. This model of service provision was pioneered at Boston University in 1984 (92), and is now being introduced in Italy, Ireland and England (93).

There is robust supporting evidence for several key features (94), including co-production (95) and supporting self-management through education (96). College-specific evaluation evidence is positive but limited (97).

Individual placement and support

People who cannot work should have easy access to welfare, and positive incentives to return to work. But most people with mental health problems want to work (98), though they need support in choosing, finding and keeping work (99).

Individual placement and support is an intervention which provides this support (100), and has a strong evidence base (101). A Cochrane review synthesized 18 RCTs of reasonable quality, and showed 18-month employment rates of 34% for recipients of the intervention, compared with 12% for prevocational training (102). For example, a six-country European RCT showed that individual placement and support was superior to the local alternative in each site, in terms of helping people find and maintain paid employment (103).

Follow-up studies conducted after 8-12 years confirm that the greater effectiveness of this intervention is sustained over the longer term (104,105), and there is evidence of cost savings through reduced mental health service use and lower reliance on welfare benefits (106,107).

Supported housing

Research suggests that around 30-40% of the urban homeless population live with a severe mental illness. Safe and secure permanent housing can act as a base from which people with a severe mental illness can achieve numerous recovery goals and improve quality of life (108,109). The housing first intervention involves rapid re-housing in independent accommodation. This approach has an emerging evidence base showing improved outcomes (110) and reduced costs (111).

People with a severe mental illness should have access to a range of housing options, with the capability to exercise choice regarding preferences.

Mental health trialogues

The active involvement of mental health service users, relatives and friends is essential for the development of recovery-oriented mental health practice and research (112). However, the idea that mental health is everyone's business, regardless of their background and experience, and accepting each other as equally entitled experts, remains a challenge. Trialogue groups (also known as psychosis seminars) are an approach to addressing this challenge.

A mental health trialogue meeting is a community forum where service users, carers, friends, mental health workers, and others with an interest in mental health participate in an open dialogue. Meetings address different topics, e.g. a task force on stigma-busting, or a work group on trauma and psychosis. In German-speaking countries, well over one hundred trialogue groups are regularly attended by 5,000 people (113), and international interest and experiences are growing (114).

Trialogues facilitate a discrete and independent form of acquisition and production of knowledge, and drive recovery-oriented changes in communication and structures.

REMAINING SCIENTIFIC CHALLENGES

Although the CHIME framework has been shown to apply across those cultures which produced guidelines included in the review (115), the generalizability of the concept of recovery remains a concern. Specifically, assumptions embedded in recovery may be "monocultural", and broader concepts of community and cultural resilience and well-being may be needed. For example, an important issue is the collectivist versus individualist value paradigm (116). In collectivist cultures, such as Maori (the indigenous people of New Zealand) and Chinese ones, emphasis is placed on interdependence among family members and relatives over and above the independence that is often promoted in Western cultures (117). Apart from culture, the mental health system and service context (118) are also important considerations. For example, middle- and low-income countries may not have the infrastructure, such as budget and community-based services, to support basic mental health care (119), let alone recovery approaches.

It is important to investigate how the concept of recovery is interpreted by service users and health professionals within a non-Western cultural context (120-123). Can recovery-related assessment and fidelity scales be applied with reliability and validity (124)? By investigating factors that facilitate or hinder recovery for individuals from diverse backgrounds, more culturally applicable recovery concepts can be developed which will better address service users' needs and rights.

An understanding of how to transform services is emerging. A synthesis of international guidance on supporting recovery identifies four levels of practice: supporting personally defined recovery (what interventions are offered), working relationship (how interventions are offered), organizational commitment (what is the "core business" of the mental health system?), and promoting citizenship (supporting the experience of wider entitlements of citizenship) (78). Most interventions reviewed in this paper address the first two of these levels. The Implementing Recovery – Organizational Change (ImROC) initiative across England addresses the culture of mental health services (93), using a learning set approach to helping organizations address ten key organizational challenges (125).

The final frontier is perhaps reducing and removing the barriers which prevent individuals experiencing full entitlements of citizenship (126). For mental health systems, this will involve transformation away from a "treat-and-recover" world view, in which priority is given to the provision of treatments with the aim that the person will then become ready to re-engage with his/her life. Empirical investigations of the concepts of "work-readiness" (in individual placement and support) and "housing-readiness" (in housing first) have found them to be inadvertently toxic concepts, which reduce hope and limit expectations. It has been argued that this change of emphasis applies more widely than just support for employment and housing (127).

However, the broadest – and most important – challenge is societal change, which will involve professionals and people with lived experience becoming partners (112) and social activists (128), to challenge stigmatizing assumptions that people with mental illness cannot, or should not, have the same citizenship entitlements as anyone else in their community.

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Social media's challenges for psychiatry

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The evolution of the Internet to include user-generated content, often referred to as Web 2.0, has altered our basic notions of privacy, connectivity, and communication. As more people are tweeting, blogging, posting on social media websites, and uploading personal videos, one consequence has been the blurring of boundaries between social and professional spheres. Whether as users of data posted by others or creators of information that others can access, psychiatrists are full participants in the social media revolution, creating a complex set of practical and ethical challenges for psychiatric practice.

Patients increasingly turn to the Internet to learn about their conditions, physicians, and treatments (1). Once online, they find not only health-related and professional information, but also the social "digital footprints" of their doctors. Physicians similarly have new access to the personal lives of their patients, including the potential to acquire information that patients have not revealed directly and may not want them to have. Here we consider some of the ways in which Internet-based social media may impact psychiatric practice, and address some of the issues that arise when psychiatrists consume and produce social media content.

PSYCHIATRISTS AS CONSUMERS OF SOCIAL MEDIA

Social media may be rich sources of collateral data that can be helpful in the diagnosis and management of psychiatric disorders, especially given the unreliability of information gathered in clinical interviews (2). Examinations of Facebook pages have shown the frequent inclusion of detailed, publically accessible postings describing depressive symptomatology (3) and ongoing patterns of substance abuse (4). Case reports have already demonstrated the potential clinical utility of web-based information for psychiatrists, for example altering the risk assessment for a suicidal patient in the emergency room (5).

Indeed, persons with psychiatric disorders may be overrepresented among those who frequently self-disclose online. For example, the Youth Internet Safety Survey of 1501 respondents aged 10-17 found that the 5% of subjects who reported symptoms of major depression spent more time online and were more likely to post identifiable information (if they were male) and pictures (if they were female) than those without depressive symptoms (6). Other studies have suggested that excessive Internet use may be correlated with social anxiety, depression, and introversion (7).

What should concern psychiatrists about pursuing the information newly available on social media sites and elsewhere on the Internet? As a foundational matter, the assumption that information on the Internet is necessarily accurate is clearly unwarranted. Researchers have demonstrated that people more readily engage in role-playing and fantasy in online user-generated content (8). These behaviors may be heightened by the "online disinhibition effect", promoted by the asynchronous nature of online communication, the minimization of centralized authority, and the increased anonymity inherent in the social framework of the Internet (9).

Even if such information is accurate, however, there are other concerns about psychiatrists accessing their patients' digital footprints, most notably intrusion on areas of patients' lives that they may consider off-limits to their therapists. The intrusiveness of accessing data from social media without patients' consent might be thought to be mitigated by patients' seemingly public behavior in posting the data on readily viewed, unrestricted websites. But a survey of 492 bloggers demonstrated that people often disclose information online with a particular audience and time period in mind, even though the information may then become broadly available for an indefinite period (10).

Misguided motives are another concern with regard to searching for patients' information. Mere curiosity, voyeurism or even self-interest may lie behind online searches. A case report of a psychiatrist assessing the financial status of a patient who was not paying his bill by looking at his house on GoogleEarth illustrates the self-serving impulses that can underlie attempts to access information about patients (11).

Finally, psychiatrists may not have thought through how they intend to use online information about patients. If the therapist wants to use the information in treatment, for example confronting a patient about continuing substance abuse documented on a social network site, its source presumably would need to be disclosed. The consequences of such revelations may be difficult to anticipate, but reflecting on how a psychiatrist would feel if a patient had surreptitiously accessed similar personal information might suggest an answer. If not disclosed, one might wonder about the corrupting effects of concealed knowledge on their interactions, especially in ongoing psychotherapy.

In sum, caution is called for in accessing patients' data online, especially sensitive personal information likely to appear on social media sites. Psychiatrists should be clear about how the information will benefit patient care, and a plan for use of the information should be thought through

in advance. Given the intrusion on patients' privacy, consideration should be given to getting patients' consent. Similar to other medical interventions, perhaps this requirement for consent should only be waived in an emergency situation where acute safety concerns are paramount. And, of course, before any use is made of the information obtained, its probable accuracy should be taken into account.

PSYCHIATRISTS AS PRODUCERS OF SOCIAL MEDIA

Psychiatrists and other physicians now also have a presence on the web, including in social media. This presence is complemented by patient-produced content about physicians, e.g., websites compiling patients' reviews of their doctors (12).

However, the content of postings by physicians, medical students, and other health care providers is often problematic. An examination of 271 blogs written by physicians and nurses found that 42% described patients and 18% described them negatively. Of those describing patients, 17% were judged to contain sufficient information for patients to recognize themselves or their doctors, and three blogs included recognizable photos of patients (13). In 2013, a cohort study of the Facebook pages of 200 senior medical students applying for a competitive residency match revealed that 16% of these pages contained unprofessional material clearly at odds with accreditation guidelines (14).

To what extent should patients' potential access to online information shape psychiatrists' use of social media? Disclosure of patient-related information, even when patients are not directly identified, can raise doubts among the public about the privacy of their medical interactions, increasing their reluctance to speak frankly with their physicians. When postings include negative comments about the healthcare system in general or a particular facility, they can shake patients' trust in the medical system and deter them from seeking care. Additionally, content showing doctors and other health professionals "behaving badly" may call their clinical judgment into question, raising doubts in patients' minds about the quality of the treatment they will receive. Such behavior can have negative consequences for the psychiatrist, including discipline by licensing boards (15).

Unreflective and excessive self-disclosure by psychiatrists, especially when they are engaged in psychotherapy, is another concern inherent in their use of social media. The model of the therapist as a "blank slate" dates back to Freud, who depicted the ideal analyst as "opaque to his patients and, like a mirror, [showing] them nothing but what is shown to him" (16). Though today various schools of psychotherapy embrace different approaches to self-disclosure, almost everyone agrees that disclosures should be rare, time-limited and made only when they are likely to have a positive therapeutic impact (17). In general, online disclosures lack most of these properties. Crucially, the psychiatrist may be wholly unaware if and when any self-disclosure has occurred, and therefore never be able to address its significance with the patient.

At the extreme, involvement in social media can contribute to a breakdown of boundaries in the physician-patient relationship. When medical professionals accept the offer of a patient to become their online "friend", the boundaries between the personal and professional become blurred (18). The terminology itself suggests that a transition in the relationship has occurred.

Although it is easy to focus on the negative consequences of social media for psychiatry, the positive role that these media can play ought not to be neglected. In addition to being used for social interaction, social media offer an opportunity for psychiatrists and other physicians to form groups of health professionals with similar interests; share resources with colleagues (e.g., the SlideShare website, which allows users to upload and share Powerpoint presentations and other educational materials); collect research data; and disseminate useful medical information to the general public (e.g., creating Facebook pages for education and discussion regarding specific psychiatric syndromes). Thus, it is not at all clear that abstinence is the right answer to the challenges presented by the social media.

We believe strongly that physicians do not have to shun social media so long as they use them prudently (19). Cautious online behavior includes taking advantage of appropriate privacy settings, which implies having a good reason for making personal information generally available. Equally important is the avoidance of unprofessional content, with the consequences that it can have for current and future patients and its liability implications for psychiatrists themselves. As a general rule, it may be helpful to ask oneself the question: "How comfortable would I be with my patients viewing this information?". Pejorative comments about facilities or patients have no place in social media. Not only should psychiatrists be aware of the content they have posted and to whom it is available; they should routinely scan the web for information about them posted by others, which may be inaccurate or overtly malicious.

With these precautions, which should be inculcated as part of psychiatric training (20), the twenty-first century psychiatrist should be able to be a cautious but vigorous participant in the social media revolution.

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Great expectations for participatory research: what have we achieved in the last ten years?

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Service user involvement in research used to be of the kind where individuals would be the "subjects" of research, implying a sense of exposure and even subjugation in a setting where all the power lies with the experimenter. It has now been more than ten years since P. Trivedi and I provided a guide on how to move research from individuals being passive subjects to becoming equal partners (1). It is certainly time to reflect on whether anything has changed.

The involvement of service users was thought to be beneficial in a number of different ways. In health care research, it makes the results more relevant to the community which it is aimed to benefit. Moreover, in the new world of reduced research resources, it is also likely to save money, because research involving consumers in formulating the questions, and particularly how they are asked, makes the research more valid and the science likely to proceed at a quicker pace.

In the last ten years, we have learnt one lesson: to call our subjects "participants". But is there any evidence that this has changed the power relationships? Does it mean more than learning to use the more politically correct term and one emphasized in most journals' publication style guidance? As well as examining whether naming has indeed affected research and particularly researchers, I also investigate whether there are data on how it might have affected our research outcomes.

Although the movement to more participatory research is of interest to the whole world, I have taken the UK as a central (and optimistic) example of how things can change with support and small financial investments. This is not just because of my personal research base, but also because there are few countries which have really taken the role of service user researchers and service user involvement as seriously as the UK, as judged by the number of reports in the peer reviewed literature.

TYPES OF RESEARCH PARTICIPATION

If you enter "participatory research" into a database such as Web of Knowledge, the search produces more than 1.8 million publications, but when you add the term "mental health" it reduces to less than 400. So, despite mental health disorders producing a high level of burden and being of interest to relatively large groups of researchers and policy makers, the number of papers on the topic is less than 0.02% of the total using this method. So, it is a scarce resource.

The definition of participatory research is also a problem when considering the literature. Many papers in my search called their methods participatory action research. This method was gleaned from work by Arnstein (2) on inner city regeneration, which produced a "ladder of citizen participation". This is a type of participatory research where the community suggests a research question which involves bringing about some change, and researchers provide expertise to the community on how to answer such a question. But work in mental health research is not always like this. The questions in general are set from a scientific perspective and are often about understanding a process rather than having specific change as the proximal goal. So, it is a long way from participatory action research. In fact, the methods appear to fall into the consultation variety (see below) and it is not clear that they do in fact fulfil Arnstein's expectation for community involvement.

I have drawn a new definition of participatory research from the work of an organization called INVOLVE, which is funded by the UK National Institute for Health Research (NIHR). INVOLVE supports public and patient involvement in research in the UK national health services, public health and social care (3). Three general levels of involvement were described in an early definition: consultation, collaboration and user-controlled research. But, before we even get onto this new ladder, we need to consider the least level of involvement. This is when a participant only provides data to researchers. Many people are happy to perform what may be lengthy, boring and sometimes unpleasant tasks for researchers on the understanding that these tasks will answer questions that may help others. In the UK, last year, more than 40,000 people agreed to take part in studies with a mental health component and many of these citizens presumably freely agreed to participate. This level of participation also needs to be celebrated, but several reports suggest that these individuals rarely discover what the research outcomes might be, unless they are so spectacular that they turn up in the newspaper or on television (4). This lack of dissemination might jeopardize future involvement and clearly needs to be high on the agenda of all researchers if we are to engage the next series of willing volunteers.

The INVOLVE level 1 involvement is *consultation*, and many studies carry out this task. It is clearly useful, as it may be that collaboration on the language of an information sheet, the acceptability of a particularly research design, or even the actual question asked, may aid the feasibility of study recruitment. What has also focused the minds of

many UK researchers on this activity is that funders now often demand a section in the grant proposal detailing these activities. But effective consultation requires work – it can only take place when researchers provide clear information on what is planned as well as offering options and listening to feedback (more information), with the real possibility that the researchers might actually change their research. Without these ingredients, the process of consultation is, as Arnstein suggests, mere tokenism or, using terms from Trivedi and Wykes (1), just lip service.

At the next level is *collaboration*, and this is much more difficult to carry out, as it requires both consultation and the development of mutual trust, since the partnership will continue to exist after the proposal is funded. This means encouragement of some additional ideas and options and deciding together the best way forward. Again, information and support is vital and requires patience by the researchers to ensure there is ample time to gain trust and resources – even financial ones – to encourage service user involvement.

The final level is *user led research*, when the power in the relationship is reversed, with mental health service users conceiving the research ideas and carrying out the research, sometimes in consultation with academic non-service user researchers.

Since P. Trivedi and I wrote our paper on issues to consider when working with service users in research, there have been tangible changes. In the UK, support for service user involvement has grown. It has taken three components: a) investment by the NIHR to garner early support, b) clear guidance to researchers on what is expected for public and patient involvement and c) an understanding that this is a significant part of the grant review process and that lay reviewers will consider it. For instance, an NIHR grant application poses two specific questions: how have the patients and public been involved in the development of the proposal, and how will they be involved in the conduct of the research. But unfortunately not all the text provided in forms is true! An examination of ethics proposals for research across the physical and mental disorders suggests that sometimes researchers have grand plans that are not put into practice (5). The good news in mental health, however, is that the situation is different. A recent audit of mental health studies thoroughly tested the involvement plans through interviews with service users and with study teams. The data demonstrate that for at least 85% of studies involvement plans were implemented (6).

GOOD EXAMPLES OF SERVICE USER INVOLVEMENT?

Clearly, if the research questions are generated by researchers, then there is little room for involvement of service users. But there are now examples of how research priorities are set with the involvement of all potential stakeholders. Some bring together large groups of local service users and by a process of voting and suggestion produce a list of priorities (7,8). Other systems involve more collaborative approaches, such as the process adopted by the James Lind Alliance in their Database of Uncertainties about the Effects of Treatments (DUETS) (see www.duets.nhs.uk). This database contains lists of priority questions posed by stakeholders (service users, families and clinicians). The process is to identify priorities from clinical and systematic reviews and add these to ones produced by service users and clinicians. There is then a priority setting partnership steered by representatives of patient groups, clinicians and academics. In developing questions to answer in the field of schizophrenia, there were 237 priorities identified, which through discussion were reduced to 26 highly ranked (via surveys). The next step was a face-to-face meeting where the list was reduced to 10 priorities of the form "what is the best way to treat people with schizophrenia who are unresponsive to treatment?" (9,10). These priorities are now being adopted by research funders (11).

Across the UK, support for user involvement is provided by the NIHR Mental Health Research Network (MHRN). The network has focused on ensuring that high quality research studies are designed through setting up a partnership similar to DUETS. The subsequent protocols are submitted for funding and can go through a second phase of involvement in the FAST-R (Feasibility And Support to Timely Recruitment) service. FAST-R is supported by MHRN and is a free seven-day turnaround service from a group trained in research protocols who also have experience of mental health difficulties. They advise on the protocol and suggest issues that might aid recruitment. So, for instance, as a minimum they might suggest some slightly different wording on the information sheet or a change in design to make it more acceptable to service users. MHRN also provides information on good practice for working with service users and carers through its website (www.mhrn.info).

In addition to this national support, there are also islands of good practice and innovation, and one such unit is the Service User Research Enterprise (SURE) at the Institute of Psychiatry, King's College London. This unit pioneered service users as researchers. It was founded by this author, who was its first director, but now (showing its maturity) is co-led with a service user researcher, D. Rose. Research in SURE is different from participatory action research, where the researcher is not part of the community but acts on behalf of the community in the research. In our model, service users have the skills of a researcher but, in addition, are considered part of the community under investigation, due to their status as someone who has used or is using mental health services. In addition to our general approach of employing service user researchers, SURE has also developed a number of different participatory methodologies. We understood the need for evidence of treatment outcomes, so we have a method for producing systematic reviews which includes service users with experience of the problem under investigation and the treatment being considered. Our first systematic review (12) on the outcomes of electroconvulsive

therapy (ECT) used peer reviewed literature, historical evidence from media libraries as well as Internet forums. It was steered by a group of individuals who had received ECT, and two of the researchers had also had this experience. Our conclusions had a large impact, because of novel findings which helped the understanding of the memory effects following treatment. It also changed clinical guidance across the UK.

What became clear in our examination of the ECT evidence was that some side effects had been missed or misinterpreted because of the lack of evidence from service user valued outcome measures. The outcomes of trials will be compromised if assessments are unappealing or misunderstood by service users or do not capture the essence of their experience. We approached this problem in two ways. First, service user panels reviewed and prioritized outcomes used in current clinical trials to ensure we could advise researchers on which of the popular ones were thought to be appealing and valued (13). Then we began to develop methods of user involvement to create novel measures (14,15).

Less than one third of clinical trials recruit to target (16) and one potential for service user involvement is to improve recruitment success. This potential tangible effect might motivate researchers (and funders) to make greater efforts with user involvement. We investigated the portfolio of clinical research studies kept on the MHRN database. We discovered that there had been an increase in service user involvement over the time that the database operated (about 8 years), with more collaborative studies and recently service user led studies. Some diagnostic areas clearly found involvement challenging, but this was limited to just one or two areas. But the most surprising result was that service user involvement did contribute to successful recruitment to the study. This occurred after taking into account the funder, the clinical study group under investigation, study design complexity, whether it was randomized, whether it had planned follow-up and whether it was interventional (17). This really is tangible evidence that researchers (and funders) would benefit from more involvement.

ARE THEIR LIMITATIONS OF SERVICE USER INVOLVEMENT?

There is a tendency to assume that service users need to be involved only when the research has a clear tangible clinical outcome such as a therapy or a service – effectively at the end of the translational pipeline. Some funders in the Ennis and Wykes (17) study did not encourage user involvement, such as the Medical Research Council. Their portfolio consists of earlier stage studies, often at proof of concept, and they might argue, as others have, that service user involvement is less necessary at this early stage. However, colleagues and I have suggested that involvement must start at an early stage even in the consideration of biomarkers and is one key to successful early translation (18). It is our contention that putting service users at the heart of translation will mean that less resource is lost through poor decisions made at this early phase. Currently only involvement at later stages of drug development is thought necessary. As Woolf (19) puts it, "bringing a drug to market without knowing how to bring it to patients undermines its larger purpose and can only diminish its profitability for investors". But we argue that the efficient use of resources and scientific direction can only be enhanced through service user involvement even at the stage of biomarker development (18). If we had input on which side effects are considered important and use this to determine the subsequent phases of drug development, then compounds might be more acceptable after reaching the final stages.

WHERE DOES THE FUTURE LIE WITH SERVICE USER PARTICIPATORY RESEARCH?

Clearly participatory methodologies will continue to develop into trials and epidemiology. With citizen research we might also reach out to the wider community to collate data to inform our science. For instance, the website PatientsLikeMe (www.patientslikeme.com) already harnesses the views of service users to increase our understanding of side effects and current use and acceptability of treatments. These data might be not only used for research and treatment development, but also for the important "back translation" to the initial phases to treatment. An extension of this is our new eMPOWERMENT study, which allows service users to have access to their electronic care records. The programme has been implemented with the full collaboration of service users. The final system collates information from hospital, community and general practitioners' records and provides useful links to important information on disability benefits and medication. But it also allows service users to input their own data into the mental health care record.

We are currently using participatory methods to develop measures of side effects and recovery to add to our measures of wellbeing, and will soon be embarking on further service user requested assessments. The hope is that the data produced by such a system will help to identify good (and poor) clinical outcomes of both treatment and services. Furthermore, it will provide large scale data which has great research potential for more subtle process measures and moderating factors important in defining the stratified medicine we aspire to.

CONCLUSIONS

In the past ten years there has been a qualitative advance (at least in the UK) not only in service user involvement but also in the available participatory methodologies. There is research support for involvement and I know that there are

researchers in the USA, Canada and Australia who are interested in these advances. We would like to see many more people move from interest to implementation, because we have found tangible benefits for researchers. We hope, however, that any adoption of the approaches outlined here will be because there is a genuine belief that there is value in user involvement (20) and not merely a response to requirements of funding bodies – although at least this would be a start.

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The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology

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In 2008, the National Institute of Mental Health (NIMH) included in its new Strategic Plan the following aim: "Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures". The implementation of this aim was named the Research Domain Criteria project, or RDoC. RDoC is a programmatic initiative that will fund grants, contracts, early-phase trials, and similar activities for the purpose of generating studies to build a research literature that can inform future versions of psychiatric nosologies based upon neuroscience and behavioral science rather than descriptive phenomenology. RDoC departs markedly from the DSM and ICD processes, in which extensive workgroup meetings generate final and finely-honed sets of diagnoses that are modified in field tests only if problems with clinical utility arise. Rather, in keeping with its provenance as an experimental system, the RDoC provides a framework for conducting research in terms of fundamental circuit-based behavioral dimensions that cut across traditional diagnostic categories. While an important aim of the project is to validate particular dimensions as useful for eventual clinical work, an equally important goal is to provide information and experience about how to conceive and implement such an alternative approach to future diagnostic practices that can harness genetics and neuroscience in the service of more effective treatment and prevention. This paper summarizes the rationale for the RDoC project, its essential features, and potential methods of transitioning from DSM/ICD categories to dimensionally-oriented designs in research studies.

Key words: Psychiatric diagnosis, Research Domain Criteria, RDoC, NIMH, DSM-5, translational research

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A spirited debate about psychiatric diagnosis broke out on the eve of the DSM-5 release following a blog post by the Director of the National Institute of Mental Health (NIMH), Dr. Thomas Insel, entitled *Transforming Diagnosis* (1). In the post, Dr. Insel reviewed the common consensus in the research community regarding the problems with the DSM system, i.e., diagnoses based upon presenting signs and symptoms that have acceptable reliability but have increasingly been shown not to represent valid disease entities. Instead, he stated that the NIMH would "re-orient" its research away from the DSM-5 toward the NIMH's Research Domain Criteria (RDoC) project, developed to explore ways of incorporating such methods as genetics, neuroimaging, and cognitive science into future diagnostic schemes based upon behavioral dimensions and neural systems. The ensuing online discussion was unfortunately misguided, in that the post was addressed to the research community (and in particular, to potential peer reviewers of RDoC research grant applications) rather than to observers of the DSM-5, and the debate subsided following a joint press release by the NIMH and the American Psychiatric Association that reaffirmed the agencies' shared interests in psychiatric diagnosis and the important role played by the DSM in clinical use (2).

The scientific significance of the discussions, however, remained: the DSM-5 shows almost no influence of the remarkable advances in new technologies and substantive knowledge in neuroscience and behavioral science since the DSM-IV release in 1994, in spite of a decade-long literature review by committees of experts for the new revision. Dr. David Kupfer, the respected head of the DSM-5 process, was essentially correct in stating: "The problem that we've had in dealing with the data that we've had over the five to 10 years since we began the revision process of DSM-5 is a failure of our neuroscience and biology to give us the level of diagnostic criteria, a level of sensitivity and specificity that we would be able to introduce into the diagnostic manual" (3). His comment raises the obvious question: how does the field go about changing directions to remedy this pressing problem?

Students of nosology have considered at some length the kinds of research that need to be conducted in order to move toward more scientifically-informed conceptions of diagnosis and etiology. Considering the impressive range of disciplines that such commentaries represent, there is a remarkable consensus, as shown in the following small sample of quotations: "the DSM's descriptive criteria are designed to be transitional until research reveals etiologically distinct disorders among current syndromes" (4, p. 27); "empirical data have been quite consistent with the possibility that terms that are routinely used in clinical inquiry, from neuroticism and extraversion to depression and posttraumatic stress disorder, do not in fact represent meaningful, cohesive psychological constructs; rather, they represent combinations of constructs" (5, p. 281); "a more powerful approach is to move

beyond simply rearranging symptom constellations, and to configure how known facts across the genomic, enviromic, endophenomic and phenomic domains may be reassembled to identify clusters of etiopathologically meaningful and empirically testable entities while remaining agnostic to traditional, phenotypic boundaries" (6, p. 11); "the field will have to collect data across the current diagnostic categories, focus on comparing across disorders as much as comparing across normal controls and will need to collect and curate data, so that it can be widely shared and collated" (7, p. 4). As a national funding agency charged with envisioning and implementing the future, the NIMH's goals are very much in harmony with such visions.

These insightful commentaries unfortunately omit one very inconvenient fact in the well-reasoned calls for new research directions: the DSM/ICD system has become the international *de facto* standard for submitting research grant applications to both private and public funding agencies, and conservative review processes are typically quite unforgiving of any deviations from orthodoxy. Further, the system has served so well for clinical, services, administrative, and legal purposes that any changes are now fraught due to the ripple effects that even the smallest changes in categories or criteria may have upon eligibility for mental health services, insurance payments, secular trends in prevalence rates, health care costs, research using the categories, and so on. Thus, the system's own success has become one of the largest barriers to change. In this light, the research enterprise is presented with a paradox. In order to attain groundbreaking nosological approaches in the future that are based upon genetics, other aspects of neurobiology, and behavioral science, a requisite literature is required that can inform these innovations in classification and measurement. However, such a research literature cannot be created as long as studies are conducted solely within the constraints of ICD/DSM categories. This is the rationale for the development of the RDoC project.

THE RDoC PROJECT

What does RDoC involve? The official statement of the RDoC goal – "Develop, for research purposes, new ways of classifying mental disorders …" – could be inferred to mean that NIMH has created a fully-fledged new nosology that is now ready for field trials. This is misleading. In fact, the goal of RDoC is to foster research to validate dimensions defined by neurobiology and behavioral measures that cut across current disorder categories, and that can inform future revisions of our diagnostic systems. In other words, RDoC is intended to support research toward a new classification system, but does not claim to be a completed system at the current time. To the contrary, RDoC represents a *framework* for conducting research on psychopathology in ways that diverge markedly from current standards. The ultimate goal is to build a research literature that reflects advances in genetics, other areas of neuroscience, and behavioral science to provide a foundation for precision diagnosis and treatment of mental disorders.

Research applications for the RDoC project are evaluated in the usual NIMH manner – through committees that conduct peer review and give high scores to the applications deemed most meritorious. To date, NIMH has relied upon a combination of funding set-asides and investigator-initiated applications to support RDoC research.

The development and overall organization of the RDoC project has been reviewed thoroughly elsewhere (8,9) and will not be covered in detail here. In brief, an NIMH workgroup was convened in early 2009 to devise an approach for the new system. The workgroup determined that five major domains of functioning would serve as an organizing rubric for subsuming the various dimensions. The five domains are: negative valence systems (i.e., those that respond to aversive situations), positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems. A workshop was held for each of these five domains with representative experts from basic and translational areas. Each workshop accomplished three tasks on the basis of available basic and clinical literatures: a) determine the dimensions to be included in the domain, starting with a list of candidates nominated by the NIMH workgroup; b) provide a definition for each dimension; and c) for each dimension, specify various elements (as supported by relevant data) that could be used to characterize the dimension at each of several Units of Analysis (see below). Dimensions were included in the matrix if the workshop members deemed that they met two stringent criteria: a) there had to be evidence for the dimension as a validated behavioral function, and b) there had to be evidence for a neural circuit or system that plays a preponderant role in implementing the function.

STRUCTURE OF THE RDoC MATRIX

The major elements of this organizational scheme can be represented as a two-dimensional matrix (Figure 1, see also www.nimh.nih.gov/research-priorities/rdoc/index.shtml). The various dimensions referred to above appear in the rows of this matrix. They are formally termed "constructs" to denote their status as non-computable concepts based on convergent sets of data, whose precise functional significance changes as increasing amounts of data are compiled to inform our understanding (see 5). The constructs are grouped within the superordinate domains (the "Research Domains") as noted above, reflecting significant relationships among constructs within each domain besides providing a heuristic organizing scheme.

The seven columns of the matrix represent various classes of measure-

			UNITS OF ANALYSIS					
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Affiliation/attachment								
Social communication								
Perception/understanding of self								
Perception/understanding of others								
Arousal/Modulatory Systems								
Arousal								
Biological rhythms								
Sleep-wake								

Figure 1 Research Domain Criteria matrix

ment that could be used to assess each construct, and are termed "Units of Analysis" (there is also a column to represent various paradigms used to assess the construct). As noted above, entries for each cell – as defined by the intersection of a row (dimension) and a column (Unit of Analysis) – were nominated and vetted by the workshop participants. The center column refers to measurement of particular brain circuits; the three columns to its left denote respectively the genes, molecules, and cells that comprise circuits, while the columns to the right can be thought of as various circuit outputs (behavior, physiological responses, and verbal reports or clinician-completed instruments). The latter three columns include measures that could be used to assess signs and symptoms from various self-report or interviewer-based instruments.

The matrix includes two other dimensions that are critical to the RDoC goal, and should be considered integral parts of the structure. These two dimensions, often interacting strongly, comprise developmental trajectories and environmental effects (broadly considered). Most mental illnesses are now viewed as neurodevelopmental disorders, and maturation of the nervous system interacts with a wide variety of external influences beginning at conception. There has been considerable research on multiple risk factors, in such disparate areas as prenatal infections and early life abuse/neglect, that can constitute risk for later disorders. However, the current diagnostic systems do not necessarily promote an integrative account of developmental patterns that may differentially lead to resilience or to disorders, nor a precise understanding of why a particular insult may lead to different disorders (e.g., that early life stress represents a risk variously for depression, posttraumatic stress disorder (PTSD), or borderline personality disorder). A major goal of RDoC is to focus research on relevant systems to document the unfolding of trajectories as they interact with various events – not only in childhood, but across the life span.

Some writers have commented that RDoC embodies a reductionistic approach that is exclusively focused on genetics and biomarkers to the exclusion of social influences (e.g., 10). In fact, as some astute commentators have observed (e.g., 11), this is not the case. There is a strong emphasis on developing a more mechanistic understanding of how such factors as life events and the social environment interact with development to produce a range of observed outcomes.

As mentioned above, RDoC is a framework that is designed and intended to both foster and accommodate new research findings on a continual basis. How is this envisioned, given the current structure of the matrix? The constructs should be regarded as particularly promising dimensions that could be studied within the overall experimental scheme, as vetted by workshop participants for

their potential applicability to various clinical problems. So, the current constructs serve both as particularly good candidates for investigators wishing to conduct RDoC-themed research, and as examples for researchers interested in conducting studies to validate a new construct. The RDoC workgroup is committed to updating the matrix periodically, but this is not actually necessary, because investigators are always free to submit grant applications for new constructs (or revisions of the current constructs). As always, the merit of these new ideas is evaluated through the NIMH/National Institutes of Health (NIH) peer review system.

MAJOR POSTULATES OF RDoC

RDoC adopts very different perspectives compared to traditional systems in considering psychopathology. As some of the implications are nuanced and subtle, additional elaboration will be useful regarding its workings.

One of the controversies surrounding the DSM-5 has revolved around the issue of whether disorders may be considered as qualitatively different from normality (e.g., 12) or fall along a continuum with no sharp distinction between normal functioning and disorder (e.g., 13). Resolution of this ongoing debate would obviously be informed by data regarding the overall distribution of "normal" with respect to adaptive, mildly impaired, and severely impaired functioning. Unfortunately, historically there has been little consensus about the domains of normal functioning in cognitive and emotional spheres, or how to measure them. However, over the last few decades, as a result of increasingly advanced technologies for structural and functional analyses of brain circuits, and equally increasing sophistication of behavioral measurements, the major systems of the brain have been delineated and related to their functional outputs. Comparative research has implicitly mitigated the views of human exceptionalism that supported problematic mind-brain dichotomies, and demonstrated the surprising conservation of genes, neurotransmitters, and behavioral functions across evolution – even in model animals such as fruit flies and zebrafish, let alone mammalian species such as rodents and primates (14).

To give just three examples: a) the crude "reward system" identified by Olds and Milner (15) has given way to the increasingly sophisticated explication of dorsal and ventral striatum and the associated differentiation of functions for experiencing reward, seeking reward, learning contingencies for reward, and developing habits (e.g., 16,17); b) responses to acute threat and potential threat have been distinguished behaviorally and related to distinguishable circuits along with components that dynamically regulate these responses (18,19); and c) systems that implement the cognitive operations of working memory first posited on the basis of behavioral studies in the late 1960s and 1970s have been reliably characterized (20,21). Importantly, many paradigms have been developed that can provide measures both of behavioral performance and of related functional brain activity in a large population, thus providing some sense of the normal distribution of behavior; obviously, this capability, in turn, permits a quantitative specification of the extent to which various aspects of functioning deviate from normality. Importantly, these new developments are not confined only to laboratory tasks, but also to psychometrically-derived inventories that relate strongly to real-world functioning (e.g., 22).

In terms of the RDoC system, several consequences ensue from these developments. First, RDoC adopts a translational approach to disorders, construing (for these experimental purposes) pathology in terms of deviations in fundamental functional systems. While translational research has become almost a cliché in contemporary research, RDoC marks a subtle but significant shift in direction for psychiatry. The standard approach to psychiatric illness has been to define a mental disorder (on the basis of signs and symptoms) and then seek a pathophysiology relating to those symptoms. In contrast, RDoC asks the following questions: "What is the normal distribution for a certain trait or characteristic; what is the brain system that primarily implements this function; and, how can we understand, at various levels of mechanism (23), what accounts for the development of dysregulation or dysfunction in these systems along normal-to-abnormal dimensions?". This strategy has obvious advantages in terms of applying basic research at all levels of analysis to clinical problems, as the translation is relatively straightforward. On the other hand, it may be more difficult for clinical researchers, since the symptoms that they are accustomed to study literally do not appear in the RDoC matrix. A further implication of the translational approach is that RDoC is agnostic to current disorder categories. There is no claim to "understand" or "explain" DSM/ICD disorders in terms of these functions; rather, the aim is more simply to seek an understanding of how these various systems may become dysregulated to various extents and to relate such dysregulation to relevant symptoms.

On a related point, RDoC incorporates a dimensional approach to psychopathology, inherently examining, to quote the NIMH Strategic Plan for RDoC, "the full range of variation, from normal to abnormal, among the fundamental components [dimensions] to improve understanding of what is typical versus pathological". In fact, the framework intentionally omits any disease definitions, disorder thresholds, or cutpoints for various levels of psychopathology. Because such boundaries can bias the way research is conducted (particularly given the inertia of ICD/DSM-determined disorder categories), the aim is simply to gather data about the dimensions that will support future decisions in this regard, made on the basis of quantitative data rather than clinical consensus. Further, the availability of reliable and valid quantitative

measurements could permit adjustments over time consequent to epidemiological studies of risk and outcome, as has happened frequently over the years in such areas as hypertension (24).

One important point in this regard is that there is no assumption that the relationships between various measures of a particular construct are linear, as might be presumed under a simple severity model. Indeed, the search for points of disjunction and non-linear functions is a major reason for a purely empirical approach. One instance of this phenomenon is the classic inverted U-shaped curve relating arousal and performance (25). In another intriguing study, Tucker et al (26) recorded a cortical event-related potential termed the error-related negativity (ERN), which in this case demonstrated a larger response when the subject was given feedback regarding task-related errors. As predicted, patients with depression showed larger ERNs than controls; however, the unexpected finding was a quadratic relationship with depression severity, such that the large ERNs were seen only in patients with moderate (but not mild or severe) depression scores.

Some observers might object that this translational emphasis over-simplifies the richness of psychopathology, or that complex psychiatric symptoms are not yet ready to be explained in such a direct translational manner. For instance, one hears informal comments at conferences that psychosis is a "black box" in RDoC. The rejoinder to this view holds that, if the field is ever to establish a diagnostic system based upon neuroscience, sooner or later it will be essential to explain complex symptoms in terms of dysregulation in basic brain operations (as exemplified in the quotations above). For instance, hallucinations might be broached in part via a consideration of systems that represent the integration of perceptual information (27), while networks that mediate functions involved with language, working memory, declarative memory, and learning would appear to be promising avenues for the study of delusions (28). The growing realization that some degrees of psychotic phenomena are present in the normal population (29), and also in broad ranges of psychiatric outpatients (30), is consistent with a view of these symptoms as dimensionally arrayed in the population and not simply a manifestation of qualitatively distinct severe pathology. Thus, an essential component of an experimental classification system involves challenging investigators to depart from traditional ways of thinking about disorders in order to seek promising new experimental ideas.

Another issue concerns the relationship of the various RDoC measures to presenting signs and symptoms, since of course the latter are the actual clinical phenomena that bring patients to the clinic. Establishing mechanistic relationships by which disruptions in the functioning of one or more constructs (as assessed by various Units of Analysis) result in specified symptoms or impairments is considered as a central task for the RDoC project, and a major component of the grant funding program. Notwithstanding the translational research approach, the RDoC project is very much directed toward an understanding of the impairments that patients experience in their lives, and this desideratum was emphasized by the RDoC workgroup in nominating constructs.

The concern about the current diagnostic environment has not been so much with the symptoms themselves, as with the way in which they are clustered into disorders in the polythetic DSM system. Particularly in research and in treatment development (where the diagnostic category is preeminent as an independent variable or treatment indication, respectively), the polythetic algorithms serve to deemphasize individual symptoms because they are important only insofar as they contribute to diagnosis. Thus, a strong RDoC research project will focus upon a specific clinical problem that can be better explicated through a research design that combines appropriate Units of Analysis to illuminate the mechanisms of dysfunction.

TRANSITIONING FROM ICD/DSM TO RDoC

What would a prototypical RDoC design look like? Such an experiment would include subjects with a wide range of normal-to-impaired functioning with respect to the dimensional construct(s) of interest. While many studies would employ enriched sampling of subjects who evince levels of impairment consistent with current diagnostic criteria, the focus would be exclusively on the RDoC constructs without recourse to ICD/DSM diagnoses in the design. (It is acknowledged that, for the foreseeable future, these diagnoses will be needed for medical records and insurance purposes). At the extreme, for example, samples for a study of reward circuit activity (as relevant to anhedonia and/or mania) might be drawn from virtually the entire population of treatment-seeking adults – mood/anxiety spectrum, psychotic spectrum, eating disorders, personality disorders; for appropriate exploration of dimensionality, the sample would also include relatively minor psychopathology such as an adjustment reaction diagnosis as well as those individuals who do not meet criteria for any diagnosis. A similar approach might be used to study executive function in children across a range of autism spectrum, attention-deficit/hyperactivity disorder, and mood/anxiety disorders (and once again, those who do not meet criteria for any disorder).

There are two highly important caveats that are necessary to place this sort of design in context. First, there are the obvious considerations for appropriate inclusion and exclusion criteria. The usual exclusions for neurological conditions or injuries, intellectual disability, extensive substance abuse in adults, etc. would still apply; on the other hand, one tactic for ex-

ploring dimensionality is to broaden the inclusion criteria for control subjects by permitting more prior or current psychopathology. For both adults and children, it is also critical to account for normative developmental stages (e.g., cognitive and physical development in children, cognitive slowing in later life), given the emphasis on normative measurement. Second, studies of this type may be more informative when they build upon a prior basis of research with the relevant constructs and research designs; for example, studies that have established consistent results for an anhedonia dimension across the mood/anxiety spectrum will have a much firmer foundation for extension to psychotic and other disorders.

Designs such as those above (vastly oversimplified here for brevity) may be considered the "gold standard" in terms of RDoC's instantiation of the corresponding goal in the NIMH Strategic Plan. Accordingly, a critical aspect of the RDoC program is helping researchers make the transition – both conceptually and practically – from the ICD/DSM to a dimensional outlook. This has been a matter of ongoing concern for the NIMH workgroup, as the DSM/ICD system has been used for so long in research and clinical practice that some transition is needed to consider psychopathology from other perspectives. These issues would depend not only on becoming accustomed to the significance of new scale values (e.g., for anhedonia or working memory), but also on achieving a "mental model" for patients seen through the RDoC lens. The same psychopathology would be present, of course, but conceived and measured in distinct ways.

The general approach to this transition would incorporate various combinations of RDoC constructs and DSM/ICD disorder categories in experiments. While these steps may be useful in transition, there are potential drawbacks as well. One problem is the temptation for the disorder categories to remain privileged with respect to the dimensions: investigators might continue to regard the diagnostic thresholds as demarcation points for ill versus well, and also continue viewing pathology through the DSM/ICD lens rather than acclimating to the idea of neural systems-based functional constructs. There is also the obvious potential bias in sampling mostly patients who meet current diagnostic criteria, in treatment-seeking samples or with other recruiting strategies, thus short-circuiting dimensional exploration. In short, these transitional steps pose the risk that investigators will continue to regard their patients – both clinically and in terms of research designs – in familiar DSM terms, failing to grow a sufficient appreciation of the precision-medicine *zeitgeist* that RDoC is intended to facilitate. For these reasons, transitional research designs are best regarded as temporary heuristics for a limited number of studies if the full potential of the RDoC framework is to be reached.

With these caveats in mind, there are two broad approaches that investigators might use for transitional designs. The first would be studies that explore RDoC dimensions within multiple diagnostic groups. The simplest form of this type would specify in the design two or three distinct DSM disorders, each recruited for a sufficient N to achieve acceptable statistical power. The analysis could then be conducted in terms of the DSM factor, the RDoC dimension, and the interaction. Where the N's are too small to permit an interaction design, the numbers might at least be large enough to conduct tests of the separate main effects of the DSM factor and the RDoC dimension(s). Important additions to these designs would include subjects that contribute to exploring a broad range of the dimensions under study. As mentioned above, control groups with liberal inclusion criteria would be important; others could include treatment-seeking individuals who just fail to meet criteria for a DSM diagnosis (as by coming up one symptom short in the polythetic list, or *forme fruste*), or patients with not otherwise specified (NOS) diagnoses. As with all DSM-based studies, this type of design suffers from the problem of how to accommodate and analyze varying numbers and patterns of co-morbid DSM diagnoses – a continuing obstacle that has been a major rationale for the RDoC approach.

An alternative approach, somewhat more compatible with an RDoC design, would be to include subjects from all diagnostic groups in one of the chapters of the new "metastructure" crafted largely in common between DSM-5 and the upcoming ICD-11, without targeting a specific N for each category. These chapters generally include a number of disorders varying in severity – for instance, the Schizophrenia Spectrum chapter contains schizotypal disorder, schizophreniform disorder, brief delusional disorder, etc. As above, inclusion of subjects with subsyndromal pathology or unaffected relatives, in addition to control groups as described above, would contribute to the dimensional objectives. As an added benefit, inclusion of these more varied groups represents potentially a significant contribution to public health, in that these are patients with palpable impairments who are typically excluded from most pathophysiology and treatment studies due to their failure to fit one of the modal diagnoses. To our knowledge, there are no good estimates of the percentage of patients in these shadow groups, nor estimates of the magnitude of the public health significance posed by their symptoms and impairment. Finally, a number of studies have demonstrated palpable impairments on various laboratory tasks in clinically unaffected relatives of probands (e.g., 31). While such studies have been used to demonstrate heritable risk, there has been insufficient attention to date on how such results could inform the actual pathophysiological differences that (as quoted above) "improve understanding of what is typical versus pathological".

A broader version of this alternative sampling strategy would involve subjects with primary diagnoses from different chapters of the ICD/DSM meta-

structure, again without constraining the subjects to two or three specified categories. Such groups might initially include disorders of somewhat comparable psychopathology, e.g., schizophrenia spectrum/bipolar spectrum or unipolar mood/anxiety disorders. The goal, however, would not be to distinguish particular groups as is typically done, but rather to explore the underlying dimension(s) so as to gain a more comprehensive understanding of the pathological mechanisms. In this regard, for instance, Craddock and Owen (32) posited a gradient of neurodevelopmental pathology, ranging in a continuous fashion that begins with intellectual disability and progresses through autism, schizophrenia, schizoaffective disorder, bipolar disorder, and unipolar depression. Each disorder is seen not as a unitary disease entity, but rather as a particular range within the overall gradient. (It is worth noting that, if one selects subjects from two adjacent ranges of a larger gradient, a statistically significant result is virtually guaranteed; it is clearly highly misleading, at best, to conclude that these represent two qualitatively distinct disease entities).

The second broad type of transitional designs might simply employ a single ICD/DSM group in the usual fashion. However, the investigators would propose analyses of various dimensions within the group that might provide more information about subtypes or ranges along relevant dimensions than data from symptom-based efforts (e.g., the modest success for understanding or treating vegetative signs or atypical depression within the overall category of unipolar depression). In most cases, this type of design will have less potential relative to the ultimate goals of the RDoC scheme, because it cannot contribute to an understanding of specified constructs or mechanisms that could represent cross-cutting diagnostic criteria in future nosologies. However, this approach may represent a useful way for investigators with research programs directed toward a single ICD/DSM disorder to initiate the transition toward studying RDoC dimensions. To repeat a point made earlier, one component of such studies (as with any RDoC design) might profitably explore developmental trajectories so as to understand how individual differences in neuroplasticity over time contribute to heterogeneity in presenting symptomatology and activity in relevant systems.

RDoC AND TREATMENT DEVELOPMENT

While the above steps have been oriented toward psychopathology, there are relatively near-term possibilities for using RDoC concepts in treatment as well. The common element for any treatment trial in RDoC will require the development of a valid set of measures that can reliably distinguish a particular subtype, or critical location along a dimension, to predict successful treatment outcomes. As one example, given the well-known heterogeneity of ICD/DSM categories, establishing mechanistically-based subtypes of current disorders may enhance matching of patients to treatments. For instance, PTSD is often regarded as a prototypical "fear circuit" disorder. However, many patients with PTSD show a blunted affective response to affective challenges (33), which may relate to multiple traumas and/or a chronic course (34). Accordingly, classic exposure therapies for PTSD might be predicted to be effective only for highly fear-reactive patients (where the fear can be extinguished), while different therapies may be indicated for those with a blunted response pattern. Appropriate assessments for measuring the fear response in a reliable, idiographic manner, for which there are multiple potential candidates but no validated methods, would permit a test of this hypothesis – which appears to hold for other anxiety disorders as well (34).

Similarly, development of new treatments may be facilitated by the identification of more homogeneous subgroups of patients. As a group of industry scientists noted, "by increasing the mechanistic understanding of disease and matching the right treatments to the right patients, one could move from one-size-fits-all to targeted therapy and increase the benefit-risk ratio for patients" (35). In other words, new treatments that target a mechanism associated with one particular symptom may have a low probability of success in a trial for a DSM/ICD indication, because the particular symptom is not shared by all patients with the diagnosis. By contrast, an exemplary research topic in RDoC might involve an enhanced understanding of how various aspects of reward-related systems relate to clinical anhedonia (a symptom of depression which itself may be a multi-faceted clinical construct). If a new anhedonia treatment were developed that targets a novel mechanism based upon such research advances, the prediction would be that the treatment has therapeutic effects only for those depressed patients with anhedonia, but should be efficacious for patients with other diagnoses who have measurable anhedonia. Once again, "measurable anhedonia" is a key phrase that necessitates prior validation of widely-accepted procedures for this type of trial.

CONCLUSIONS

As noted at the outset, RDoC is a long-term funding project designed to inform future versions of classification systems. The goal is for research conducted under the aegis of RDoC to make a definitive contribution toward precision medicine in psychiatry, through identification of relationships among aberrations in fundamental neural systems and functional impairments – and notably including an emphasis upon neurodevelopmental trajectories and environmental factors.

Perhaps the most important point about RDoC is that its essence is to provide a broad framework for conducting research on mental disorders from a wholly new perspective. In this sense, what is most important about RDoC is not the list of constructs and

the matrix per se – although thousands of person-hours have been devoted to crafting the overall organization and its specific elements – but the idea of freeing up investigators to pursue exciting translational research questions driven by neuroscience and behavioral science rather than by constraining sets of symptom clusters.

The main notion of the RDoC matrix is to provide guidance to investigators in how they might set about taking the first steps down the long and arduous road that must be traversed to reach a point when neuroscience-based nosologies are possible (and intermediate research designs such as the steps discussed above reflect the fact that some period of transition is to be expected). Perhaps the outcomes for RDoC might be assessed by the number of research programs that, freed from the strictures of current diagnostic guidelines, outstrip the RDoC matrix to move in entirely new directions that transcend the organization of the current system. Such a result would be a testament to the imagination and scientific prowess of the clinical research community, which will play the largest role in how research conducted in the spirit of the RDoC approach contributes to progress in understanding and treating mental disorders in the years ahead.

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RDoCs redux

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We are delighted to share in the debate about the RDoC program, as we feel some responsibility for its birth. Indeed, the notion articulated in RDoC to inform "future versions of psychiatric nosologies based upon neuroscience and behavioral science rather than descriptive phenomenology", by providing "a framework for conducting research in terms of fundamental circuit-based behavioral dimensions that cut across traditional diagnostic categories" (1), is a direct outgrowth of studies that began in the Clinical Brain Disorders Branch of the Intramural Research Program of the National Institute for Mental Health (NIMH) at St. Elizabeth's Hospital in the early 1980s.

This body of work led to the creation of the Genes, Cognition and Psychosis program, an interdisciplinary research program which in its title recognized that the biology of psychopathology was not linked to diagnostic nomenclature. The work of this program in identifying mechanisms in the brain by which risk factors influenced biological susceptibility was a foundation of the Strategic Plan launched by the NIMH in 2008 and in which the RDoC plan was proffered.

Given our experience with work that forms so much of the rationale for RDoC, we should be enthusiastic. So, why are we not?

Actually, the debate between "lumpers" and "splitters", whether in the realms of descriptive psychopathology or in brain imaging measurements or in genetics, has been going on literally for over a century in psychiatry. The RDoC project claims to be a new and enlightened way to split and then lump, because it argues that the neuroscience and genetics of psychiatric disorders open new arenas for such progress. This sounds really good, but to paraphrase a popular beer advertisement in the USA, does it taste great?

We see the main concerns about the RDoC mindset not with its conceptual foundations, but with its reliance on the presumed validity of the behavioral, neural functional and genetic dimensions it highlights as fundamental to a revision of psychiatric nomenclature. Ultimately, any revision of psychiatric diagnosis, which clearly is the RDoC goal, must be better than the existing system, better in the sense of what diagnosis is about. Diagnosis is primarily an instrument used by clinicians for two primary purposes: to predict the natural history of an illness and to predict the most appropriate treatment. This will be the standard also for RDoC, if its long-term goal of replacing existing diagnostic practices is to be realized.

Even clear and important dimensions of behavior and its reward-based underpinnings may have unexpected complexities when viewed through the RDoC lens. In an incisive and elegant study, Gold et al (2) demonstrated that negative symptoms in schizophrenia are associated with overestimating the cost (or effort) involved in attaining an outcome. One could easily view this as a metric or dimension, suggestive of "degrees" of negative symptoms. One can imagine elegant neuroimaging studies of effort estimation showing varying engagement of prefrontal, insular, and striatal function.

Cuthbert's suggestion that a good research study would be to explore such behavioral and neural system dimensions across current diagnostic groups and in subjects without psychiatric diagnoses presents a daunting conundrum. For example, "overestimating the cost (or effort) involved in attaining an outcome" also seems to be a suitable operational definition of laziness, as used by lay individuals. Thus, an important question is whether this or any of the RDoC dimensions have the same meaning when associated with schizophrenia qua schizophrenia, or if they are observed across other diagnoses and in a spectrum of otherwise normal, albeit, lazy individuals. Moreover, would the neural systems and genomics that are associated with this set of behaviors be the same in all cases? Several recent papers focus on this issue. They suggest, for example, that mechanisms for auditory hallucinations in otherwise healthy functioning individuals (so called "voice-hearers") may be different than the mechanisms associated with such symptoms in schizophrenia (3).

It has become increasingly popular to believe that similar patterns of brain activity in patients with psychiatric illness and in some non-psychiatric research samples underlie RDoC-type dimensions of psychopathology. These studies are based on specific protocols that elicit physiological responses critically dependent on the context. It is an old saying in the functional neuroimaging research lexicon that functional neuroimaging data reflect what the brain was doing during the imaging protocol, but the challenge for the investigator is to figure out what the brain was actually doing. The meaning of this saying is that patterns of engagement of brain functional systems during an imaging experiment do not necessarily reflect a specific or even definable brain state. A clear illustration of this is the current fascination with the so-called resting state functional magnetic resonance imaging (fMRI) experiment, where subjects, including diverse samples of psychiatric patients, are allowed

to lie in the confining and noisy environment of the MRI scanner for five to ten minutes doing nothing. This is said to be a resting or unstimulated state and the pattern of activity typically seen in normal subjects after they have acclimatized to the scanner environment is called the "default network". Part of the appeal of this paradigm is that it is easy to do and easy to find differences between patient and control samples.

Patients with a variety of psychiatric diagnoses have been observed to have deviations from the default pattern, and it is often stated that they show a deficiency or abnormality of the default network as if this is some sort of neural defect. Clearly, the relative engagement or lack thereof of the default network is a dimension putatively linked to a neural circuit. Do we imagine that patients currently diagnosed with schizophrenia, or children with autism, or patients with Alzheimer's disease, all of whom may show similar patterns of default network deviations, share pathology in this dimension? Sounds good, but does it taste great? In fact, it is highly implausible that patients with schizophrenia or with autism will experience the MRI environment analogously to a paid healthy volunteer and it is unlikely that they will each experience it the same, either. The different ways in which they are liable to think and feel about the noise and the confinement will interfere with the so-called default system, producing a potentially similar degree of abnormality on this dimension, but based on dissimilar reasons.

The current approach to caseness is rooted in many decades of clinical observation and detailed description of clinical course and natural history, and many academic debates about how best to represent clinical reality. This rich history has also witnessed many self-proclaimed enlightened movements to change the scheme. In the absence of pathognomonic findings, diagnosis is imprecise and multidimensional, as it is in other fields of medicine. The idea that RDoC is a blueprint for research to fill in this multidimensional landscape is appealing and attractive. But, as an approach to ultimately revise the concept of caseness, it has a much more difficult task.

One of the most important components of any diagnostic scheme that is conspicuously missing from the RDoC phenomenology matrix is the dimension of time. The DSM-5 regards time as an essential aspect of most diagnostic categories. In neurology, it is said that time is the best diagnostician. Good psychiatric clinicians know that cross-sectional phenomenology is problematic, and what looks like obsessive-compulsive disorder today, may turn out to be psychosis tomorrow. What looks like schizophrenia early on in the course of a patient's history turns out to be bipolar disorder down the road. Were these examples to have been treated based on the RDoC dimensions, the outcome might not be optimum, to say the least. Indeed, as much as there is overlap phenomenologically and perhaps genetically in what we call schizophrenia and what we call bipolar disorder, and patients across these categories will share many RDoC dimensions, it is indisputable that for some patients with the latter diagnosis, lithium is as miraculous as any treatment in psychiatry, yet it is entirely without antipsychotic effects in patients with the former diagnosis.

There is good evidence that diagnosis per se is a social construct and is dependent on where on a continuum some relatively arbitrary threshold a caseness call gets made (4). The DSM system has always recognized that having symptoms is not sufficient for a clinical diagnosis. There must also be disability. Illness and disability or functional compromise are inseparable concepts. Regardless of the in vogue phenomenology, illness begets disability. Even between mild cognitive impairment and Alzheimer's disease there is a grey area. An unbiased way at looking at symptoms, cognition, etc., involving threshold-free dimensions, has been thought to be a valid alternative. However, this fails to account for notable differences at the severe ends of the spectrum that may encompass multiple dimensions and the possibility that "disease" neurobiology can accelerate.

It's a no brainer that psychiatric diagnosis is imperfect, subjective and not based on pathophysiology or causation, and the field is eagerly anticipating a future where this would be different. Psychiatric practitioners are faced with real world patients with real world problems and their decisions are not readily informed by rarefied fMRI paradigms and weak genetic associations. They use diagnosis to help them organize the complex clinical landscape.

Most clinicians know that the diagnoses they apply are approximations, that they refer to syndromes not distinct disease entities, and that they do not express distinct boundaries. They understand that our diagnoses are constructs, and that patients do not *have* schizophrenia or bipolar disorder, per se; they are given these diagnoses. These realities seem to have surprised researchers, many of whom unfortunately know about psychiatric illnesses only from what they read in the literature or on their computer screens.

Our current approach to psychiatric diagnosis is the result of many decades of deep clinical experience and scholarly debate. As imperfect as it is, it is a practical and clinically useful tool that has helped transform psychiatry from subjective, impressionistic categorization of clinical syndromes to more objective, diagnostically reliable definitions. The field would be dramatically enhanced by a better system, as would many other fields of medicine. But, the adoption of an alternative phenomenology must be viewed with caution and it must result in something better than what we have. This means more clinically valuable to practitioners and to patients.

We suspect that RDoC will be liberating to some researchers, because they will be encouraged to move beyond current diagnosis in designing clinical research projects. Does this require a major NIMH initiative that co-opts the grant review process and has the unintended consequence of actually reducing creativity by its very mandate and also of potentially undermining clinical practice? One might hope that researchers and clinicians alike are continuing to think outside the box and are exploring

new ways of solving old problems without the NIMH telling them that they are not.

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Wittgenstein's nightmare: why the RDoC grid needs a conceptual dimension

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RDoC attempts to finesse an existential dilemma facing psychiatry: psychiatry is most persuasively a medical field if mental disorders are understood as brain disorders, but brain disorders seem to fall under neurology. The RDoC attempts to resolve this dilemma by distinguishing brain circuit malfunctions as the distinctive domain of psychiatry: "the RDoC framework conceptualizes mental illness as brain disorders; in contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits" (1). RDoC further locates brain circuit function within a grid of analytical and developmental levels and dimensions that together are supposed to replace DSM/ICD categories with more valid diagnoses.

Wittgenstein famously said: "In psychology there are experimental methods and *conceptual confusion*... The existence of the experimental method makes us think we have the means of solving the problems that trouble us; though problem and method pass one another by" (2). RDoC is a paradigmatic expression of Wittgenstein's concerns. It joins an ambitious empirical research program with a conceptual framework so weak that it is difficult to envision success. I consider below some of the RDoC's apparent conceptual challenges.

RDoC embraces brain-circuit construct validity without addressing conceptual validity, thus gets the relationship wrong between itself and the DSM/ICD. The RDoC sees the DSM/ICD's failures when it comes to construct validity (i.e., each diagnosis identifying one etiological category), but fails to appreciate DSM/ICD's essential role in psychiatric legitimacy. The DSM/ICD identifies conditions that, judging from surface symptoms, context, and background knowledge of normal human functioning, fall under the concept of disorder. Correctly distinguishing between disorder and normality is what I have labeled *conceptual validity*. Conceptual validity is independent of construct validity: a DSM/ICD disorder category can encompass ten different disorders and thus lack construct validity, but be conceptually valid if it encompasses only disorders, and it can be construct valid but identify a non-disorder and thus be conceptually invalid. Most criticisms of DSM-5 were accusations of conceptual invalidity, that criteria encompassed normal variations. Whatever its errors, DSM/ICD remains an attempt to delineate the domain of psychological conditions that fall under the concept of disorder. RDoC offers nothing to replace the DSM/ICD efforts to delineate the domain of disorders and provide a target at which construct validation can aim. DSM/ICD provides the only thoughtful guidance to what conditions the RDoC must explain in terms of malfunctioning circuits.

RDoC pays inadequate attention to context. RDoC's grid includes environmental influences, but by this RDoC means environmental risk factors like early traumas or disturbed attachment relations that influence the trajectory of disorder development. Nowhere in the RDoC grid is there adequate recognition that human psychological mechanisms are biologically designed to respond sensitively to the social and environmental context. No diagnostic scheme can be valid without building ample contextual references into diagnostic criteria, as does the DSM (3).

RDoC is confused about which of two meanings of "etiology" is pertinent to disorder diagnosis. Ultimately, etiology individuates disorders. This is why, when multiple etiologies are discovered in formerly unified diagnostic entities, they divide into several disorders, as in recent developments regarding breast cancer. But, what is an etiology? In the context of mental disorder, "etiology" is ambiguous, having a broader and narrower meaning (4). In the broad sense, "etiology" refers to the causal story by which a disorder comes about. Such causal histories can encompass anything that led to the disorder, including risk factors, environmental events, common genetic variations, and other factors that are not in themselves disordered but were part of the pathway that led to the disorder. As indicated in its grid, RDoC studies the entire developmental trajectory that leads to disorder, adopting what I call a "kitchen sink"

approach advocated by some anti-essentialist theorists (5,6). The diagnosis thus includes the entire history of contributory risk factors that caused the disorder within the omnibus diagnosis. The problem is that most of those factors are perfectly normal. Introducing them into the diagnosis does not correspond to how we think about disorder as harmful dysfunction (7), and is usually about as diagnostically informative as listing "gravity" when trying to explain a plane crash. Diagnosis concerns etiology in a narrower sense: among the myriad causal factors, what exactly went wrong? That is, what is the current dysfunction that is responsible for the symptoms? Broad etiology is useful for prevention but generally not for diagnosis or treatment. One can get cholera from contaminated water, but once one has cholera, diagnosis and treatment involve identifying and eliminating the infectious agent; the water supply remains relevant only regarding prevention of future re-infection.

Inadequate emphasis on the centrality of meaning and conscious experience. Even if research shows that human exceptionalism is a mistake, the human meaning system is still a uniquely complex entity. Yet, meaning, subjective experience, and mental representations are downplayed by RDoC, except for their entering into the "cognitive" domain which, given the emphasis on circuits, seems a bit of window dressing. But meanings are real and their functioning is part of our biological design. There is nothing less medical about dealing with disordered meaning processing. What makes this RDoC oversight particularly problematic is the instability of behavior under small perturbations in the meaning system. One's sexual desire circuits may be highly activated, but just one additional belief, such as "this is wrong because I am married" or "he/she may have a venereal disease", may override those circuits and alter your behavior. The traditional "virtues" were simply such abilities to overcome natural biological tendencies based on beliefs about what is right. Perhaps all such phenomena concern one activated circuit overpowering others. However, we are nowhere near knowing how to identify and assess the power of single beliefs at the brain level that interact with standard circuit activations. This imposes limits on how predictive the RDoC can be.

Confusing high circuit activation with disorder. Particularly pernicious is the lazy notion that disorder is simply high circuit activation. Anyone who has been terrified at imminent danger or experienced an orgasm knows that this can't be right. One might object that RDoC sees *atypical* or *impairing* high activation as disordered. But, depending on how you select your dimensions, you can make anything atypical. It is statistically typical to sleep, but the circuit activation during sleep is highly deviant from normative circuit status when awake, and it is highly socially impairing. No RDoC cell will tell you that sleep is a biologically designed condition and not a disorder. For that you need an evolutionary dimension, lacking in RDoC. Is the fidgeting child who is thereby socially disruptive and impaired in schoolwork suffering from a dysfunction of attentional mechanisms, or is he a normal but high-energy boy caught in an overly constraining modern school environment? Either way, the fidgeting child's brain and behavior will look different from those of other kids. Evaluating these alternative hypotheses requires an understanding of the concept of disorder beyond statistically deviant impairing brain activation.

Valid disorder cutpoints may not emerge from RDoC dimensional empiricism alone. RDoC cites the standard examples of hypertension and hypercholesterolemia to demonstrate that dimensions are a scientific medical approach. In fact, these are controversial as to their disorder versus risk factor status, and the vast majority of medical conditions are categorical. The notion that conceptual validity will emerge from the empiricism is reminiscent of D. Regier's suggestion that DSM-5 would dimensionalize severity and then conceptually valid cutpoints would emerge. Several problems beset such a strategy. First, severity is not always the test of disorder (childbirth pain, illiteracy, and normal grief are more severe than arthritic pain, mild dyslexia, and mild depressive disorder, respectively, but the former are normal and the latter disorders). Second, the point at which a dimensional feature turns into disorder does not always emerge as a literal discontinuity, but rather may require theory to identify an underlying conceptual boundary.

RDoC reorganizes diagnosis according to shared risk factors, but risk of disorder is not disorder. Sharing risk factors does not necessarily mean two disorders are the same disorder (although at times they might be). For example, the fact that people with high genetic loading for neuroticism have a higher risk for developing both major depression and generalized anxiety disorder (8) does not mean that those two disorders are the same disorder. They may involve quite divergent dysfunctions both made more likely by the common genetic risk factor. This ought to be obvious from the physical disorder domain: the fact that smoking is a risk factor for both cancer and cardiovascular disease does not mean that those are the same or even similar disorders.

DSM-5 demonstrated how well-intentioned efforts can go embarrassingly wrong if there are conceptual missteps. Oddly enough, RDoC seems to be repeating DSM-5's error. The DSM-5 Task Force Chairs rejected a proposal for a conceptual committee to clarify conceptual assumptions and address conceptual disputes (9). The subsequent objections to DSM-5 were mainly conceptual.

All mental processes take place in brain tissue, therefore mental disorders must be brain disorders, we are repeatedly assured. The analogy to computer software/hardware (software runs in hardware, but not all software malfunctions are hardware malfunctions) suggests the inference is invalid. However, even accepting the inference, the fact remains that all normal psychological processes equally occur in brain tissue. Thus, studying the brain does not evade the conceptual challenge of distinguishing disorder from normality, it just

moves the problem inward. The RDoC lacks any serious conceptual component that might effectively connect its ambitious empiricism with the conceptual problems of diagnosis it aims to resolve.

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Will RDoC hasten the decline of America's global leadership role in mental health?

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Two recent events have substantially increased the perceived global importance of mental health and provide hope that mental health problems will, finally, be allocated the financial and other resources commensurate with their importance to the health of communities. The December 2011 release of the new Global Burden of Disease Study (GBD) results demonstrates the growing importance of mental health problems as a major component of public health in both high-income and low- and middle-income countries (1,2). And in May 2013 the World Health Assembly – the annual World Health Organization (WHO) meeting of ministers of health from around the world – passed a major global mental health initiative, the Mental Health Action Plan 2013–2020 (3).

At this high point for global mental health, the RDoC initiative of the US National Institute for Mental Health (NIMH) unequivocally declares that the traditional basis for identifying mental health problems – ICD and DSM diagnoses – are fundamentally flawed and need to be completely redrawn (4). Despite proclamations to the contrary (5,6), the clear take-home message of the RDoC initiative for the mental health community is that the considerable effort the American Psychiatric Association put into generating the DSM-5 and the effort the WHO is still expending to create the mental health section of the upcoming ICD-11 are misguided and of little use for the promotion of mental health.

If this internecine struggle is taken seriously by the GBD consortium and by ministers of health in leading countries, the NIMH position could make them rethink the rationale for recommending expansion of mental health efforts. The GBD data about mental illnesses are based on epidemiological studies using DSM diagnostic categories, and an important component of the WHO global mental health plan is the Mental Health Gap program (7) which is based on providing treatments for a core group of ICD-defined conditions. If the GBD findings and the proposed WHO interventions are based on flawed constructs, why not wait until the mental health community gets its house in order before reallocating scarce resources to deal with these problems?

The RDoC initiative, though intellectually appealing (to neuroscientists), is tone deaf to the current global trajectory of mental health. The world is clamoring for fixes to the clinical and administrative problems that are limiting the access to care and the quality of care for the vast numbers of individuals with mental health problems (8). This high-profile focus of NIMH funding on the very long-term goal of establishing biologically-based diagnostic categories – which may ultimately prove impossible for a large proportion of the persons we currently treat – will distance NIMH research efforts from the central concerns of clinicians and mental health administrators, particularly those in low- and middle-income countries.

The world will not throw away the current diagnostic system for mental illnesses based on the say-so of the NIMH. There needs to be convincing evidence that any proposed major changes would dramatically improve outcomes. A much better incremental approach would be for the NIMH to emphasize the need to identify dimensional neuroscience measures to help

develop more targeted treatments for individuals classified according to current diagnostic systems. This will allow the research to remain relevant to the needs of clinicians and health care systems (which need stable diagnoses to function) and, thus, continue to receive the political support it needs to get sustained funding. Once this approach has generated evidence of its ability to improve treatments by identifying distinct subgroups within current diagnostic categories, NIMH will then be in a much better position to recommend changes in the diagnostic system focused on regrouping conditions that respond to (or can be prevented by) similar interventions.

A diagnostic system is first and foremost a *cultural* product, a community's attempt to create meaning, to categorize phenomena of interest in ways that facilitate predicting and, possibly, changing future outcomes. Many institutions within a community – ideological, cultural, social, economic, and scientific – participate in the process of classifying and managing health conditions considered departures from "normal". Scientific research is only one of many stakeholders in this process and it does not operate independently of the other stakeholders; both the outcomes of scientific research about health and the utilization of these outcomes are heavily influenced by the socioeconomic environment in which they arise and are used. The involvement of a wide range of stakeholders in the development of both DSM-5 and ICD-11 is a clear example of this process. In contrast, the RDoC initiative will attempt to develop a diagnostic system with as little input as possible from the non-neuroscientists: the not-so-implicit message is that economic realities, social factors and cultural preferences should wait until the neuroscientists have discovered the "truth" and then fall into line accordingly. This biological reductionist approach is naïve about the role of diagnostic systems in the real world. A diagnostic system must serve the ever-changing needs of *all* stakeholders. Moreover, these stakeholders need to be integral to the process of developing successive iterations of the diagnostic system, not bystanders.

Will major mental health funders in other countries follow NIMH down the RDoC road? In the past, the economic strength of America and its ability to attract leading specialists from around the world has allowed it to maintain intellectual leadership in many fields, including mental health. But as middle-income countries gradually increase their research funding for mental health and as other high-income countries increase their funding for multinational mental health projects, the proportional contribution of NIMH to global funding for mental health research will inevitably decrease. As this happens, it is likely that the intellectual leadership in global mental health will become increasingly multipolar. At present, it remains unclear how this gradual changing of the guard will affect priorities in global mental health research.

The siren call of biological fixes for biopsychosocial problems has dominated medical research for several decades, so mental health research priorities in other countries may follow the NIMH Pied Piper. But the new emphasis on the public health burden of mental disorders highlighted by the GBD findings and the urgency of the need to resolve these pressing problems highlighted by the WHO Mental Health Plan may induce some countries to disengage from NIMH at the RDoC juncture, and allocate increasing proportions of mental health research funding to the universal problems of expanding the range, quality and utilization of services. If that happens, the inevitable slow decline of American intellectual leadership in global mental health will accelerate.

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Approaching human neuroscience for disease understanding

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In psychiatric research, neuroscience knowledge is growing at a record rate, in both the acquisition of facts and the development of mechanistic understanding, at the level of the molecule, the synapse, the cell and the neural system. Whereas, only 20 years ago, we talked about brain function in terms of a "black box", today we understand many dimensions of brain function mechanistically, especially where molecules and physiology support characteristic behaviors (1). It is not only within genetics and synaptic function where

knowledge is growing, but also in identifying postsynaptic signaling pathways, cognition mechanisms, epigenetic modifications and systems neuroscience, to name just a few areas.

Translational scientists are challenged to keep up with relevant new knowledge. Science administrators are thoughtful about motivating the field to use basic knowledge both for the purpose of understanding normal brain function and to identify disease-causing perturbations in disease. There never has been a better time for neuroscience growth or for developing biomarkers and molecular targets for brain diseases. The RDoC system challenges every brain scientist focusing on psychiatric diseases to synthesize and apply relevant brain facts to advantage mechanistic disease understanding (2).

There already exist methodologies to examine *in vivo* brain function in humans histologically, molecularly and phenotypically, enabling measurements of human brain-based behaviors (3). Cognition is a good example of this, since cognitive capacity can be assessed experimentally and is routinely used to make inferences about functioning of the brain itself. Other approaches, like human brain imaging and evoked potential analyses with electroencephalogram (EEG), all use measures of brain molecular, metabolic or electrical activity to represent neuronal activity regionally. Then, also, some experimental approaches use human postmortem brain tissue for histological or molecular analyses directly, albeit in non-living brain tissue. Regional gene expression, generating region- or cell-specific proteins, could be critical for capturing complex brain function and its regional dysfunction in disease. And animal models, if carefully verified, can contribute improved experimental models.

Then, how do perturbations of these normal human-based systems associate with mental symptoms? Again, here is where the RDoCs system comes in. What the RDoC framework contributes is a system for generating and categorizing brain facts as they relate to putative cross-cutting basic behavioral states or functions of brain, leaving to experimental observation the identification of those perturbed in brain pathology.

It would be incorrect to conceptualize RDoC as a diagnostic system. It is, rather, an approach for systematizing brain knowledge to make it pertinent to functional and dysfunctional systems in the brain as they relate to behavioral outcomes. Nor is RDoCs ready to transform psychiatric diagnosis for all of the practically purposes that ICD and DSM are used for. But, the RDoC system does call attention to the essential need in translational neuroscience to base diagnosis on disease understanding and to tether molecular target development to a detailed and demonstrated disease pathophysiology.

The emphasis in the Cuthbert paper on developing dimensional approaches within mental illness is represented within the domain of psychosis by the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) project. References to "psychoses" have been made in the literature for many years, creating an expectation for measurable overlap of biomarkers in brain diseases with prominent psychotic features. Recently, the BSNIP study, using dense biomarkers to characterize psychosis, including schizophrenia, schizoaffective disease and bipolar disorder with psychosis, was launched to explore the dimension of psychosis with modern biomarkers (4).

The study recruited individuals with psychosis and phenotyped them densely, using cognition testing, evoked potential evaluation, eye movement assessment, brain imaging and resting EEG assessment, in addition to a full clinical assessment. The resulting phenotypic characterization of the psychoses diagnoses has created a rich database which can be analyzed for the purpose of creating biological markers for diagnosis.

The BSNIP study showed how biomarkers clustered within and across current DSM diagnoses and, in general, across the psychosis dimension. The high variability and the broad overlap of the biomarkers across diagnoses suggest that our DSM diagnoses are biologically heterogeneous. The additional surprise in these data was the considerable overlap in clinical and diagnostic characteristics. The current BSNIP question is how to move from the present state of partial knowledge in clinical phenomenology and emerging neurobiology, to a state of biological understanding in our psychiatric conditions, a research agenda in the field.

The implication of the BSNIP outcomes and RDoC predictions is that, if we examine current diagnostic groups of psychosis using ideal neural biomarkers, we are still likely to be unsuccessful at defining pathophysiology, because of the gross heterogeneity of the identified groups (5). If we approach disease with a dimension, instead of a single diagnosis, we anticipate, in fact utilize, the marked heterogeneity of the group to recognize biologically similar clusters within the dimension and use the clustering of biomarkers to generate biologically-defined disease groups. The development of validating characteristics for the clusters is the research challenge, namely a common systems understanding or a unifying molecular pathology for these biomarker clusters. The BSNIP approach begins dimensionally, using dense biomarker characterization, to form biologically common clusters, potentially useful as disease identifiers with biological targets.

On the other hand, as Cuthbert suggests, we can also approach disease definitions biologically through identifying the genes, molecules, cells and circuits of normal behaviors, then see which normal functions could be altered when these systems are perverted. The framework of the RDoC system, as it is currently articulated, starts at a detailed level of knowledge of domains for normal behaviors (6). Several of these domains are already relatively well understood. Examples are the constructs of "declarative memory", "acute threat" and probably also "reward learning". These normal systems, if abnormally executed, could manifest themselves as "psychosis", "post-traumatic stress disorder" or "drug abuse", respectively, if the normal tract is perverted.

In our current state of knowledge which lacks even basic biological clues

about the nature of psychiatric illnesses, let alone biological targets, it is not an over-extension to say that we should involve both approaches in discovery and use overlap as concept demonstration.

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RDoC: a roadmap to pathogenesis?

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> "*It is now necessary to turn away from arranging illnesses in orderly, well defined groups and to set ourselves instead the undoubtedly higher and more satisfying goal of understanding their essential structure*" (1).

In the last few years we have witnessed unmistakeable signs of a sea change in psychiatric genetics and basic neuroscience. Genome-wide association studies, conducted by large international consortia and using data from more than 100,000 individuals, have, *inter alia*, identified common polymorphisms shared by seemingly unrelated disorders, including schizophrenia, bipolar disorder, autism, attention-deficit/hyperactivity disorder and possibly certain forms of intellectual disability and epilepsy (2). This provides a strong argument for pleiotropy as a rule, rather than as an exception in the genetic underpinnings of psychiatric disorders.

Next-generation sequencing of exomes and whole genomes of psychiatric patients, gathering speed owing to the increased affordability of advanced technologies, may eventually supply the final answer. The ENCODE project is providing novel information on the regulatory network of transcription factors, which is crucial for interpreting personal genome sequencing and understanding basic principles of human biology and disease (3). The recently launched Brain Activity Map Project (4) aims to achieve over the next 10 years a comprehensive mapping of the activity of single neurons and their connectivity by applying nanotechnologies and large-scale computation techniques.

Against this rapidly changing background, the clinical practice of psychiatry is hampered by a knowledge gap which obstructs the translation of such groundbreaking advances into "personalized" diagnostic formulations and targeted prevention or treatment. While part of the reason is the forbidding complexity of psychiatric disorders, another part is the "reification" of current diagnostic and classificatory schemes, whose basic postulate of discrete nosological categories remains essentially unchanged since the times of Kraepelin and Bleuler.

All of the above underpins the motivation and rationale of the National Institute of Mental Health initiative to propose and implement the Research Domain Criteria (RDoC) project as a strategic science alternative (or counterpart) to the DSM/ICD classification. Its "seven pillars" (5) include: primacy of translational research; integration of neuroscience and behavioral science; a quantitative dimensional approach to psychopathology; development of interviews and measurement scales allowing studies of the entire range of variation from normal to abnormal; sampling strategies unbiased by DSM/ICD diagnoses or any fixed definitions of disorders; and a selective approach to the independent variables which may be chosen among any one of the "units of analysis" or "constructs" of the conceptual model.

There are obvious and appealing strengths in the RDoC design. The study of fundamental processes that cut across the conventional diagnostic boundaries will reveal unexpected patterns of associations with symptoms, personality traits and behavior. The mapping of clinical phenomenology onto specific brain dysfunction will result in a "functional psychopathology" (6) that may add substantially to recasting the taxonomy of mental disorders. Thus, RDoC sets a common agenda and framework for psychiatric and neuroscience researchers that could unify and focus the efforts towards the ultimate goal of reconceptualizing our understanding of the "essential structure" of psychiatric disorders. If and when achieved, this would align psychiatry with other medical disciplines, such as cardiology and oncology, which are considered to be pioneers in translation research.

Yet there are uncertainties, challenges and caveats along the road of the RDoC project. First, the relationship between the RDoC philosophy and clinical reality is ambiguous. Patients

entering the psychiatrist's office present with their phenotype and not with their genotype or biosignature. It is unlikely that making diagnostic sense of their stories would ever evade the necessity of a first-line, sound phenomenological approach and assignment of a categorical, rule-based diagnosis to be followed by a referral for laboratory investigations and a treatment plan – both supported by the best available evidence. Thus, both categories and dimensions are likely to continue co-existing as two sides of the same coin, reminiscent of the "particle-wave" paradigm in physics. The utility of any future versions of DSM/ICD will therefore depend on the extent to which they deliver non-trivial information about prognosis, likely treatment outcomes and/or testable propositions about biological and social correlates (7,8).

Second, there is at present a huge explanatory gap in genetic research between findings of statistical associations of common genomic variants with particular disorders, symptoms or traits and the demonstration of causality. Considering that the vast majority of such associations have minuscule effect sizes, recent data suggest that many hundreds of genes make statistically significant but minor contributions to the estimation of disease risk. It remains uncertain if rare variants, such as copy number variations, "private" point mutations and genomic sequences, would provide in the individual case more than a probabilistic assessment of risk rather than a deterministic aetiological *causa prima* of the disorder. In contrast, future refined neurophysiological measurements and neuroimaging are more likely to yield reliable endophenotypes and biomarkers, thus being of pragmatic utility in the evaluation of patterns of individual pathogenesis.

Lastly, the present five domains of the RDoC framework require conceptual enrichment in at least two of its components. The "self-representation areas" need further elaboration to include disorders of self-awareness which are at the core of psychotic disorders (schizophrenia, acute transient psychotic disorders), as well as of neurological disorders such as temporal lobe epilepsy with complex partial seizures: depersonalization and derealization experiences, identity confusion, thought interference, ambivalence and loss of the sense of agency (9). Furthermore, common symptoms, such as auditory hallucinations, are complex and heterogeneous and need to be decomposed into several phenomenological features, each mapping onto a range of cognitive and social processes (10).

In conclusion, notwithstanding such caveats, the RDoC will provide a "roadmap" towards a better understanding of the pathophysiology and pathogenesis of mental illness by integrating knowledge across different fields of research and lead the way to improved diagnosis and treatment. Its focus should not only be on what neuroscience and genetics can offer, but even more on the interaction between biological, psychological and social research.

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The journey from RDC/DSM diagnoses toward RDoC dimensions

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Successive revisions of the DSM and the ICD have served to improve reliability of psychiatric diagnoses. In particular, the development of the Research Diagnostic Criteria (RDC, 1) led to the major revisions in DSM-III toward this goal. However, these classifications continue to suffer from heterogeneity within disorders, blurred boundaries between disorders, frequent use of "not-otherwise specified" (NOS) categories, and high levels of comorbidity. All these have served to limit clinical utility. Importantly, validity, the holy grail of psychiatric classification, remains elusive, and accounts for the lack of biomarkers for diagnosis in psychiatry (2).

Heterogeneity is not unique to psychiatry; many common medical disor-

ders are heterogeneous, with diverse risk factors and complex pathophysiology (e.g., hypertension, non-insulin dependent diabetes (NIDDM)). However, the latter group of disorders is not ensnared in debates such as those seen in psychiatry, because biological measures known to be relevant to the disorder are now available for clinicians. It is not surprising that some patients with NIDDM develop kidney failure while others go blind and still others have coronary artery disease or need a lower extremity amputation, as long as glucose, insulin, or hemoglobin A1C levels can be measured to show that these are diverse presentations of the same underlying metabolic abnormality. Psychiatric neuroscience research seeks exactly these kinds of measure to aid in psychiatric classification. While there is no dearth of biomarkers in psychiatry, they simply lack specificity, because symptomatic diagnoses, such as DSM and ICD categories, are inadequate as gold standards to validate such biomarkers (2).

To address this impasse, Cuthbert (3) offers a visionary outline of the steps needed for psychiatry to march ahead in the difficult road from symptom-based typology toward a neuroscience-informed nosology using the Research Domains Criteria (RDoC) framework. The key goal for the field is how to transition from the current DSM classification (DSM-5) toward a neuroscience-based dimensional approach (4). The impressive advances in knowledge of neurobiology and genetics of psychiatric disorders in recent years makes this goal timely and offer unprecedented opportunities. In our view, some key steps are critically needed for such efforts to bear fruit.

The first is incorporating RDoC measures in clinical practice. The DSM-5 has made a significant, yet modest effort toward a dimensional approach by including cross-cutting symptom measures (Section III). This allows assessment of a comprehensive set of psychopathological domains (similar to the review of systems in medicine) that may or may not fit neatly into the diagnoses suggested by the presenting complaints. For example, cognitive impairment, one of DSM-5's proposed dimensions of psychosis severity, is rated on a 0-4 scale based on extent of deviation from age appropriate norms. To rate this, the clinician would have to carry out a cognitive battery of assessments that include key domains such as working memory, verbal memory, attention, etc., already well known to be widely prevalent, persistent, and predictive of outcome in schizophrenia (5). Cognitive measures such as working memory are RDoC domains, and their neurobiological and genetic correlates are being worked out rapidly (6). Thus, we might already be in a position to incorporate some of the specific RDoC domains into the clinician's practice. However, DSM-5 did not go far enough (4), and includes a global cognitive measure only in an optional section of the manual. Thankfully however, DSM is a "living document", and hopefully the DSM and RDoC measures will synergize in the near future. Once implemented in clinical practice and field trials, such measures can provide dimensional data that can then be examined in relation to pathophysiological and etiological measures, thereby moving toward a neuroscience based classification.

As stated earlier, lack of validity remains the major limitation in the ICD/DSM approach to classification. A key direction to address this in future research is proposed by Cuthbert, i.e. to examine RDoC-like relationships between behavioral and neurobiological domains within a given DSM disorder, within and between related groups of disorders in the DSM/ICD metastructure. Pathophysiological and etiological (genetic and environmental) correlates of symptom domains across RDoC units of analyses elucidated in this way are then expected to pave the way toward etiologically based classification of mental disorders (7). However, etiopathology is only one of the key external validators toward a clinically meaningful classification; the clinician needs to be able to diagnose disorders that are sufficiently demarcated from each other, to characterize pre-morbid antecedents and predict natural course and outcome as well as treatment response (8). The RDoC dimensions will therefore have to be mapped on to etiological, as well as clinical, outcome and treatment response validators in future research. We here outline some potential directions.

RDoC dimensions can potentially inform disease-related variations between individuals that map on to premorbid developmental trajectories better than symptom-based categories. Thus, it may be worth asking whether neurocognitive RDoC domains may better track with premorbid cognitive and learning disorders, while aberrations in positive or negative valence might more likely be associated with temperamental difficulties that suggest impaired affect regulation.

A useful research design for outcome prediction, for example, would be to longitudinally characterize RDoC domains in first episode psychosis patients across the DSM/ICD spectrum (schizophrenia, schizoaffective and psychotic affective disorders) and examine the DSM, RDoC dimension and interaction effects on putative outcome/treatment response measures (e.g., cognitive decline, persistent negative symptoms, lithium response). A similar design could be used in young relatives at risk for major psychotic disorders to see whether one can predict emergent psychosis, affective episodes, or both during follow-up in the critical risk period of adolescence.

Another potential value of the RDoC approach may be to help treatment response prediction to identify subgroups of patients within the same disorder who may respond differentially to one treatment over another. Thus, an impairment in one RDoC domain in schizophrenia such as working memory might indicate treatment with one approach such as cognitive remediation, while another RDoC domain alteration such as heightened negative valence might indicate a different approach, such as cognitive bias training. Identifying neuroscience based predictors and markers of treatment response might therefore be valuable.

A longitudinal approach to investigating RDoC domains can also resolve

the oft-stated problem of diagnostic stability, i.e. clinical diagnoses being not always stable over time (9). Neuroscientific inquiry can provide convergent evidence about whether this instability is due to the inadequacy of our diagnostic system to capture disease presentation over time, or whether there is genuine evolution of disease presentation. Why clinical presentations change in the same patient over time is one of the many unsolved questions in our field where the neuroscience-based approach can supplement the work that has been done to date.

The goals of clinical and neuroscience based approaches to classification of psychiatric disorders are convergent. As these silos get broken down, time becomes ripe for the two traditions to come together. The road from RDC (and DSM) toward RDoC may be long, but will have promise for the practice of psychiatry.

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The RDoC program: psychiatry without psyche?

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Cuthbert's dense synopsis of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) proposal (1) raises a lot of questions. I will restrict myself to a few, quite general, theoretical and psychopathological issues.

The RDoC proposes to develop "psychiatric nosologies based upon neuroscience and behavioral science rather than descriptive phenomenology", i.e. "based on dimensions of observable behavior and neurobiological measures". The RDoC's theoretical underpinning appears to be a neurocentric "type-type" reductionism: specific chunks (types) of mental life (e.g. hallucination, anhedonia) are identical with, or nothing else than, certain specific chunks (types) of neural activity (say, a certain configuration of interactions between dysfunctional neural networks). It is hard to follow the logic of Cuthbert's assertion that the RDoC is *non*-reductionistic when he repeatedly emphasizes a "mechanistic understanding" as the RDoC's ultimate goal. "Type-type" reductionism is, of course, a legitimate theoretical position, but one that is far from being universally shared and is perhaps even obsolete (2).

There is no concern in the RDoC that biological reductionism, so successful in somatic medicine, may be confronting in psychiatry the complications of what philosophers call the "explanatory gap" (3), "the hard problem of consciousness" (4) or the defiant distinctiveness of the ontology (nature of being) and epistemology of human consciousness (5). These issues cannot be adequately addressed by an outright denial of "human exceptionalism" because of the genetic continuity between fruit flies and humans. The RDoC is programmatically silent on the issues of consciousness and subjective experience. Although acknowledging, *in passim,* that "verbal report" is the patient's primary gesture in a clinical context, the RDoC does not offer any suggestion on the nature of psychopathological enterprise that is needed to decode the pathologies of subjectivity expressed through such "verbal report".

Cuthbert claims that conventional clinical concepts (e.g., post-traumatic stress disorder) are not "cohesive psychological constructs", but he fails to specify what a "cohesive" psychological (or biological) construct might be.

The etiological project in psychiatry presupposes a serious study of the *explanandum* itself, i.e., consciousness and its pathologies, because "without some idea... of what the subjective character of experience is, we cannot know what is required of... (reductive) theory" (6). The object of psychiatry is the patient's altered experience, expression and existence, associated with suffering in self and/or others. A psychiatrist treats a *person* and not a brain circuit. We will therefore continue to need a classification anchored in phenomenology, and into which the brain enters in so far that the neural pathology is diagnostically or therapeutically *relevant* to this suffering and not because

the brain *de jure* is of principal interest for psychiatry.

The RDoC's target constructs, believed to reflect simple, natural-kind like behavioral functions and instantiated in circumscribed neural networks (previously called "modules"), will in all likelihood fall short from becoming an exhaustive or even a relevant *explanans* of the disorders of rationality, worldview, symbolization, self-awareness, and personal identity, which are the hallmarks of the most serious psychiatric disorders. Would clinically typical schizophrenic and bipolar patients suffer from *the same mental disorder* (i.e. share *the same* future "precision diagnosis") if they exhibit identical profiles of neurobiological and neuropsychological dysfunctions?

The justification for launching the RDoC was a failure to translate the advances of basic neuroscience into actionable psychiatric knowledge. This failure has been ascribed to the (DSM-IV) phenotype-based classification: with the passage of time, the diagnostic categories became "reified", i.e., they came to be dogmatically considered as "true" and valid entities, monopolizing research, and preventing scientists to ask novel questions, outside the DSM prescribed space (7). Yet it is also quite possible, and in my view, even likely, that the lack of progress is less related to the existence of phenotype-based classifications as such but more importantly linked to the concrete nature of DSM-III+ operational classifications.

The "operational revolution" entailed a behaviorist, subjectivity-aversive stance and oversimplified psychopathology to a lay level, depriving it of any conceptual or phenomenological framework, and resulted in inadequate or deformed phenotypic distinctions. The "operational" criteria are in fact not "operational" in any theoretically significant sense (8). Rather, the diagnoses, based on "symptom counting" and neglecting the prototypical-gestaltic structures of mental disorders, *necessarily* resulted in meaningless comorbidity, arbitrary diagnostic thresholds and hindered dimensional considerations.

The effects of "operational" simplification may be easily illustrated. An essentially *experiential-felt* origin of the schizophrenic delusion has been systematically ignored by all successive DSM/ICD definitions; perhaps because delusion cannot be grasped through a commonsensical lay definition, but always requires an embededness in a more overarching phenomenological framework (8). Hallucination is another example: what is called auditory verbal hallucinations is phenomenologically (qualitatively) so markedly heterogeneous (9) that treating those hallucinations as a homogeneous phenotype is likely bound to undermine empirical research. In other words, empirical research is crucially dependent on the adequacy of the employed phenotypic distinctions, adequacy that cannot be achieved through a simplistic behaviorist checklist approach.

The RDoC is legitimate as a *neuroscientific research program*, but it is hazardous as a "grand design", a totalizingly *prescriptive paradigm* for psychiatry. Reification, i.e. confusing a *concept* or idea for a really existing *thing*, deplored in the context of DSM-IV (7), will in all likelihood repeat itself with the RDoC, yet this time with perhaps even more serious consequences. We risk what Jaspers anticipated as "psychiatry without psyche". Psychiatry will survive as a therapeutic activity because the patients will not vanish. However, psychiatry that neglects its psychopathological foundations, i.e. an interdisciplinary, theoretical and empirical study of subjectivity, risks disappearing as an academic medical discipline (10).

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RDoC is necessary, but very oversold

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The past half century has witnessed heroic advances in the basic sciences of brain research, genetics, and molecular biology. But there has also been a surprising and disappointing paradox: none of the exciting scientific findings has had any impact whatever on the everyday practice of clinical psychiatry. Fortunately, we have available effective treatments for most mental disorders, but there have been no real breakthroughs in our understanding of psychopathology and ways of treating it.

Why the gaping disconnect between a basic science enterprise that is remarkably dynamic and a clinical practice that is relatively static? In fact, psy-

chiatry is really not that different from the rest of medicine in this regard. All the medical specialties have faced (and so far have largely failed to negotiate) a similar bottleneck in translational research. It turns out to be lots easier to discover the fascinating secrets of bodily functioning than to turn these to any great clinical advantage.

And because the brain is so much more complicated than other organs, psychiatry confronts by far the most challenging of all translational leaps. Our three pound brains manage to contain more neurons than there are stars in a galaxy, each connected to a thousand others and firing a thousand times a second, and with hundreds of proteins mediating the busy traffic at 100 trillion synapses. It is amazing that a machine with so many moving parts works as flawlessly as usually it does. By comparison, the breast is the most straightforward of organs, many orders of magnitude simpler than the brain. If, despite decades of intensive research, we are still early days in understanding breast cancer, why be surprised that we haven't yet gotten much of a handle on schizophrenia.

When we published DSM-III in 1980, the research future for psychiatry seemed bright and likely to deliver a quick payoff for our patients. We had great hopes that deep understanding and practical solutions would emerge quickly from the happy conjunction of powerful new research tools, generous funding from National Institute of Mental Health (NIMH) and drug companies, and the availability of a reasonably reliable diagnostic system that provided specific targets for study and treatment. Soon enough, the journals were filled with seemingly exciting findings on the genetics of mental illness and were decorated with pretty pictures that purported to show brain malfunctioning in the different mental disorders.

NIMH was at the center of the neuroscience enthusiasm, dubbing the 1990s the "decade of the brain" and betting the house on a narrow biological agenda to replace what previously had been a more balanced portfolio of research into not only the basic sciences, but also into treatments and health services. In effect, NIMH turned itself into a "brain institute" rather than an "institute of mental health". Its efforts have succeeded in producing wonderful science, but have failed in helping patients. The brain has revealed the secrets of psychopathology only in frustratingly small packets, many of which do not replicate and none of which has been powerful enough to generate a diagnostic test or a treatment advance that would actually improve clinical practice.

NIMH has grown understandably frustrated by this lack of progress and rightly has decided to switch to the new RDoC research track that is described in Cuthbert's paper (1). Rather than continue to study the hopelessly heterogeneous categories of DSM mental disorders, it will instead focus its attention on much simpler dimensions of mental functioning, hoping that these will yield clearer biological answers.

Although the RDoC strategy is sound and necessary, the way it was recently announced to the public was badly muddled – misleading, poorly timed, and damaging to the credibility of both NIMH and the practice of clinical psychiatry. A provocative, widely reported press release came just three weeks before the publication of DSM-5. NIMH explicitly trashed all existing psychiatric diagnosis and instead offered RDoC as a better, biologically based, alternative approach. This unwise over-promising about the future blithely ignored the sobering lessons of the past and the glaring needs of our patients in the present. Lost in the bombast of the NIMH press release was that RDoC has absolutely nothing to offer in the present except an untested research tool. RDoC will almost certainly deliver nothing of practical import within this decade. My guess is that it will consist of a slow, steady slog of tiny steps, more characterized by frustrating blind alleys than by any great leaps forward.

Granted that descriptive psychiatry (as embodied in both DSM and ICD) has limited specificity and almost no explanatory power, the fact remains that it is currently the only helpful approach to psychiatric diagnosis and continues to be essential and surprisingly useful in clinical practice. Take "schizophrenia" as an example. Our current construct is clearly a research nightmare: heterogeneous, overlapping with near neighbors, no uniform course or treatment response, and no clear pattern of gene or brain findings. Eventually this final common descriptive pathway – "schizophrenia" – will probably turn out to have hundreds of different causes and will require dozens of different treatments. But for now "schizophrenia" does very much inform clinical practice and RDoC has no replacement for it.

Moreover, it is a dangerous myth to assume that patients who meet criteria for "schizophrenia" suffer only from a brain disease. Contextual forces play a large role in the onset of schizophrenia and very often are the most crucial elements in its successful management. A supportive environment, a decent place to live, and therapeutically encouraged engagement with school, work, and social activities are now, and always will be, absolute essentials.

NIMH has had its attention so distracted by glorious dreams of a future research revolution that it has completely lost touch with the desperate suffering of schizophrenic patients in the present. It pays no attention to, and takes no responsibility for, the mess that is US mental health care. During the same fifty years that witnessed a basic science research revolution, the US has closed one million psychiatric hospital beds. But having provided too little care and housing in the community, we have been forced to open one million prison beds for psychiatric patients who were arrested for nuisance crimes, preventable had they received adequate community services and housing. These patients are suffering greatly not so much for lack of knowledge on how to care for them, but because of a lack of attention and inadequate resources. Patients with severe psychiatric illnesses are worse off in the United States than in other developed countries and their wholesale imprisonment is a throwback to the barbarity of two centuries ago.

Meanwhile, NIMH has sat silently on the sidelines ignoring this shameful transinstitutionalization. It should, but does not, feel a strong responsibility to improve the lives of our patients right now – in all the many concrete ways that are already available to us if only there were adequate funding for them. NIMH should advocate in Congress for patients, not just for its own research budget. And the NIMH research budget should support a balanced portfolio across the entire spectrum – from bench to treatment and from treatment to community services.

Gambles on brain research are certainly necessary for a better future, but should not dominate so completely over current need.

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Road to nowhere

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B. Cuthbert presents a model aimed to integrating neuroscience and psychopathology, that may yield improvements in assessment and treatment outcome (1). The claim is that this approach is substantially different from those endorsed in the past decades, that were unable to produce biological tests which could be routinely used in diagnosis and treatment of mental disorders (2). There are no preliminary findings, however, to suggest that this is the case, nor clinical exemplifications of the usefulness of this model. Indeed, a number of problems emerge.

The model endorses a "blanket" approach: all possible biological and behavioral measurements are utilized, even though they may be highly redundant in nature, under the misguided assumption that nothing will be missed with such a strategy and innovative classification systems will ensue automatically. Quite to the contrary, conflicting results are likely to occur, with findings that may be difficult to interpret.

The model is clearly the reflection of an intellectual crisis in psychiatry, that can be attributed to a decline of clinical observation as the source of fundamental scientific challenges (3). As Feinstein remarked, in clinical medicine, "all the fundamental scholarly ideas come from elsewhere, and clinicians apparently have nothing important to contribute beyond their work in applying the basic ideas" (4). Neurosciences have exported their conceptual framework into psychiatry much more than serving as an investigative tool for addressing the questions addressed by clinical practice.

Major clinical challenges are left without appropriate independent research supported by public sources. For instance, there is insufficient research on the frequent and vexing problem of loss of clinical effects during long-term antidepressant treatment, including exploration of its neurobiological correlates, despite the practical implications that research in this area would entail (5). Another example is that antidepressant drugs have become increasingly popular as first-line treatment of anxiety disorders, despite lack of any evidence to support their superiority (6). K. Rickels, the father of modern pharmacotherapy of anxiety disorders, wonders whether a specific study investigating comparative efficacy and differential responsiveness of newer antidepressant drugs versus benzodiazepines will ever be funded by a public source (7). In the same vein, an editorial in Nature (8) judged studies on psychological treatments "scandalously undersupported", despite their "potential to make a substantive difference to patients". It concluded that "many funding agencies around the world are too keen solely to support mechanistic investigations with potential long-term payoffs, and too unwilling to appreciate that part of their portfolio should be oriented towards identifying immediately effective psychological interventions" (8).

In 1967, A. Feinstein (9) urged clinicians to develop a "basic science" of their own – to study the clinical phenomena directly, to specify the importance of different types of clinical data, to create appropriate systems of taxonomy for classifying the information, and to develop intellectual models and pragmatic methods that would articulate the clinical process and use the results for quantified analyses. Such line of research, that is often subsumed under the rubric of clinimetrics, has been neglected (10). The fact that clinicians browsing a journal issue may no longer find any article relevant to their practice is a direct consequence of such neglect.

Exclusive reliance on diagnostic criteria has impoverished the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice (10). Psychopathology and clinical judgment are discarded as non-scientific and obsolete methods. Yet, in their everyday practice, psychiatrists use observation, description and classification, test explanatory hypotheses, and formulate clinical decisions. In evaluating whether a patient needs admission to the hospital (or can be discharged from it), in deciding whether a patient needs treatment (and in case what type) and in planning the schedule of follow-up visits or interventions, the psychiatrist uses nothing more than the science of psychopathology and clinical judgment. The clinimet-

ric perspective provides an intellectual home for the reproduction and standardization of clinical intuitions, such as subtyping and staging (10). A large amount of clinical research is derivative: methods are often applied in clinical studies simply because they have become available. If the clinical problem itself is poorly defined, the focus of neurobiological research is set for random effort and misunderstanding.

Engel (11) identified the key characteristic of clinical science in its explicit attention to humanness, where observation (outer-viewing), introspection (inner-viewing) and dialogue (interviewing) are the basic methodological triad for clinical assessment and for making patient data scientific. The exclusion of this interaction by medical science's continuing allegiance to a 17th century scientific world view makes this approach unscientific. Unlike 20th century physics, "the human realm either has been excluded from accessibility to scientific inquiry or the scientific approach to human phenomena has been required to conform to the reductionistic, mechanistic, dualistic predicates of the biomedical paradigm" (11). This restrictive ideology characterizes the Research Domain Criteria. It is time to substitute the fashionable popularity of strategies developed outside of psychiatry with creative research based on the insights of clinical judgment.

A major problem in the development of the Research Domain Criteria project has been the fact that its strong ideological endorsement by leading figures of the National Institute of Mental Health has resulted in suppression of an adequate debate. How many investigators who are likely to submit funding applications to that agency may afford disclosing that the emperor has no clothes and that the strategy may be a road to nowhere?

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The only one or one of many? A comment on the RDoC project

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It is always a surprise and a pleasure to see a meaningful coincidence in science and medicine, such as the publication of the article by B. Cuthbert (1) on the 100th anniversary of the first edition of Karl Jaspers' monumental work on psychopathology (2). H. Helmchen (3) called Jaspers' book "the methodological conscience of psychiatry" for a reason that is directly relevant to the RDoC approach which Cuthbert describes: Jaspers advocated a methodologically clearly defined descriptive as well as interpretative approach to the total of the psychopathological phenomena seen in their psychological, biological and social contexts and in the light of their consequences.

Cuthbert states that the goal of the RDoC approach is to "develop for research purposes new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures". While the in-depth exploration of dimensions of behavior as well as the use of neurobiological measures in studying mental functioning are both laudable approaches, the ultimate goal of the RDoC project does need additional and more careful attention: is the RDoC about to develop a classification for research that will be different from the classification of mental disorders for clinical work? And from some other classification that will be recommended for use in training different categories of staff in mental health services? And will this RDoC based classification be the only one that will have to be used when applying for grants of one of the mightiest non-commercial sources of support to research in psychiatry? Clinical practice operating with diagnosis based on symptoms emerging from observation and patients' reports has in all fields of medicine been a source of inspiration for researchers: will it be possible to translate ideas gained in the clinical field using diagnosis into hy-

potheses whose confirmation will be based on RDoC matrices?

And the RDoC approach, if understood in this way, also raises the question of the best way to satisfy Jaspers' requirement that we should not only describe but also try to understand and interpret the meaning of the components of psychopathology in their social, biological and psychological context. The study of dimensions and their measurement are only the beginning of the process of approaching the creation of meaningful prototypes corresponding to individuals in their context. It is to be hoped that the RDoC project has foreseen a way to do this, starting with it in parallel to the acquisition of data about the research domains.

Another issue that should be kept in mind is the emphasis on the collection of data concerning the domains that have been defined on the basis of a consensus of a limited number of experts who met in 2009. The consensus which they reached directed the work of five workshops that followed the first meeting in order to define the dimensions to be included in the domain, provide definitions of these dimensions and specify elements that could be used to characterize each dimension. It is possible that another group of experts would have selected another set of domains which would have oriented the research into another direction. This is particularly true for the domain of "systems for social processes" but also holds, possibly to a lesser degree, for the domains of "positive valence systems" and "negative valence systems". The workshop participants also "nominated and vetted" the various classes of measurement. There is nothing basically wrong with this approach, unless working along those lines uses all the available resources and the approach becomes the dominant theme for the National Institute of Mental Health, which has been such a very important player in the governance of research and its orientation not only in the USA but also globally. Another group might perhaps choose a different set of domains, containing a different set of dimensions, possibly more helpful: there should be room and support for such a project. It will therefore be important to remember that the basic premise of the RDoC project is the consensus of a relatively small group of experts about the area that should be explored.

A third important issue which is not explicitly addressed in the fine paper that Cuthbert has written is that of measuring the development of the units of analysis over time. Physiological indicators related to "acute threat" and any other dimension included in the RDoC change over time, and the longitudinal profile of this change might be just as revealing as its correlation with other factors and characteristics of the individual. To capture the impact of these factors, it would probably be useful to construct a three-dimensional matrix involving domains, manners of investigation, and age, gender and other characteristics of the persons whose dimensions are being measured, all of this along the axis of time and longitudinal development of the phenomenon.

The same argument applies, in a slightly different form, to the decision to avoid funding research that will be based on DSM or ICD diagnostic categories. Research using categories created on the basis of observations of behavior and the development of the disorder over time is as justified as other approaches. Diagnostic categories have never been more than hypotheses about the nature of the disorder that medical practitioners meet. These hypotheses should continue to be explored and their definitions should continue changing over time and in the light of information about the reaction of the disorders to treatment, about long-term outcome, about brain structures and functions recorded by modern means.

In summary, we should congratulate the National Institute of Mental Health and thank it for deciding to fund work proceeding along a well-defined new avenue of research, hoping at the same time that this departure will not block the funding of alternative ways of examining human behavior and its basis in health and in disease.

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An integrative approach to psychiatric diagnosis and research

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Much attention has been paid to revisions of psychiatric classification systems. Nevertheless, there remains significant dissatisfaction with the nosology. From a neuroscience perspective, diagnostic criteria have failed to incorporate neurobiological data, and a focus on "circuit-based behavioral dimensions" (1) will improve diagnosis. From a more critical perspective, given that psychiatric disorders do not represent valid disease entities (1), diagnosis merely medicalizes problems in living.

These specific debates echo larger debates about classification in medicine, in which many emphasize notions of disease, arguing that clinicians must

be scientists who understand physiology, while others emphasize the experience of illness, stating that clinicians must be humanists who understand suffering (2). An integrative medicine and psychiatry arguably recognizes each of these aspects of being a good diagnostician and researcher (3,4).

From an integrative perspective, ongoing work on nosological systems is needed to optimize diagnostic validity and utility. To the extent that the RDoC framework leads to research that allows such progress, it should be supported. However, I worry that many DSM-5 and ICD-11 critics may have unduly high expectations of diagnostic systems. Insofar as the RDoC framework sets unrealistic goals for nosology, caution is needed. Along these lines, I would emphasize the following points.

First, a clear goal of medical and psychiatric classification is clinical utility, which is only partly related to underlying pathophysiology. In medicine, the diagnosis of a syndrome, such as cardiac failure, may provide little information about precise etiology, but nevertheless may help guide treatment (5). In psychiatry, many entities are syndromic. While syndromes may have multiple causes, blurry boundaries, and absent biomarkers, they also are clinically useful.

It may be counterargued that much of medicine focuses on specific etiologically-based entities, e.g., viral pneumonia. Psychiatry too has specific diseases, such as psychosis due to neurosyphilis. But these exceptions prove the rule; many diagnoses in medicine and psychiatry reflect the fact that patients present with variegate symptoms underpinned by multiple mechanisms (6). Some cases of hypertension, headache, and depression are due to single gene variants or other circumscribed pathophysiologies; the majority reflect multiple influences.

Second, given that multiple mechanisms play a role in producing psychiatric signs and symptoms, foregrounding any particular diagnostic validator, such as "circuit-based behavioral dimensions", has both pros and cons. Science has progressed from Hippocrates's account of the "humors" to theories of the neurocircuitry basis of positive and negative valence, but it is possible that, a century from now, circuitry concepts will be considered rudimentary. On the other hand, the construct of depression, which is based on several other validators, may continue to resonate with eons of clinical descriptions.

DSM-5 distinguishes between anxiety and obsessive-compulsive related disorders partly on the basis of the different neurocircuitry underpinning these conditions. But there are also strong arguments for lumping these disorders on the basis of considerations such as response to serotonin reuptake inhibitors and cognitive-behavioural treatments (7). We need to accept that diagnostic systems cannot "carve nature at her joints". Rather, facts and values need to be continually re-assessed, to try optimize classifications.

Third, given the multiple mechanisms underlying psychiatric complaints, and the many considerations relevant to treatment decisions, we should be cautious in our expectation that diagnostic criteria or thresholds will ultimately be based on behavioral dimensions or biological markers. Simple assessments, such as blood pressure measurement or mental status examination in medicine and psychiatry, can provide important information. Still, such information is partial. In medicine and psychiatry, deciding on whether and how to intervene necessarily requires a complex assessment of a range of factors, including understanding the function of symptoms, their social context, and the risks versus benefits of treatment.

One set of factors sometimes neglected by critics of nosology emerges from a public health perspective. Psychiatric classifications focus on individual disorders, where underlying "endophenotypes" may be relevant. However, it may be as important to address "exophenotypes", i.e., societal phenomena, such as interpersonal violence, that crucially contribute to the burden of disease (8). Furthermore, decisions about thresholds for psychiatric intervention may need to include not only facts about underlying neurobiological mechanisms, but also considerations such as the cost-effectiveness of particular interventions.

Given that the RDoC framework encourages research on a broad range of phenomena and mechanisms, it is hard to be overly critical. By adopting a translational approach that encompasses different levels of investigation, RDoC may well contribute to advancing personalized medicine. Still, we need to be cautious of medical strawmen, such as the physician who relies solely on laboratory tests to determine diagnoses, or the public health practitioner who eradicates pathogens using simple interventions such as handwashing. No matter how many dollars we pour into behavioral neuroscience, we may have to accept that there are few diagnostic biomarkers for psychiatric disorders, and few mosquito nets to combat them (9).

Indeed, given the complexity of medicine, psychiatry provides a number of approaches worth emulating. Thus, a physician faced with a patient with headache should be able, after a careful history and examination, to diagnose a particular headache syndrome (indeed, headache classification takes a DSM-like approach (10)). Then, based on neuroscience knowledge, as well as a range of other considerations, one or another intervention may be chosen. Similarly, a physician faced with a complex public health problem, such as substance abuse, knows that the causes are complex, that a range of responses are needed (and that, as in much of psychiatry, there is no mosquito net).

For the foreseeable future, an integrative approach to psychiatric diagnosis and research ought to incorporate DSM/ICD, RDoC, and a broad range of other constructs.

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Preserving the clinician-researcher interface in the age of RDoC: the continuing need for DSM-5/ICD-11 characterization of study populations

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For the past 35 years, clinicians and researchers in the United States have utilized essentially the same diagnostic system for the purposes of describing patients' symptomatic presentations.

Having common diagnostic definitions for both research and clinical practice has had a number of advantages. It has made possible the transfer of information between the ever growing clinical research literature and clinical practice. Because the same criteria are used for diagnosing patients in both settings, it is easier to translate findings of a research paper to the diagnosis and treatment of the next patient that one might see in an office practice. This approach also ensures greater clarity of communication within and among areas of psychiatric practice. Most importantly, this approach facilitates the necessary dialogue and mutual influence between clinicians and researchers.

Recognizing the value of operationalized diagnostic criteria for facilitating communication among clinicians and researchers and improving the reliability of diagnostic assessment, in 1980 the American Psychiatric Association adopted diagnostic criteria as the centerpiece of the DSM-III classification. The expectation was that, in addition to improving clinical assessment, they would be widely adopted by the research community.

Subsequently, most of the psychiatric research literature since DSM-III has been keyed to DSM categories, thus facilitating its application to clinical practice. The hope was that iterative refinement of the diagnostic criteria sets through successive validation studies would eventually elucidate their underlying etiologies (1,2). However, despite years of intensive investigation, researchers using the current DSM paradigm have "failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder" (3, p. 33). While much of this lack of success reflects the enormous complexity and relative inaccessibility of the human brain (4), undoubtedly a major contributor is the fact that the DSM categories are a poor mirror of nature.

Although it has become increasingly evident to researchers over the past 20 years that the DSM categories do not represent valid disease entities, the entrenched hegemony of the DSM system and the conservative nature of review processes has led to researchers being pressured to use the DSM-IV categories "in order to satisfy most grant-making bodies, journal reviewers and editors, and organizers of scientific meetings" (5, p. 156).

One of the main goals of the National institute of Mental Health's RDoC project is to release the research community from the shackles of the DSM/ICD categorical system by providing an alternative framework for conducting research in terms of fundamental circuit-based behavior dimensions. Given its role as the premier governmental body funding psychiatric research in the United States, the NIMH is uniquely positioned to incentivize researchers to adopt such a framework and thus it is likely that most NIMH-funded research over the next decade will adopt the RDoC framework.

While this has the potential to be a positive step that facilitates the development of the requisite research literature "to attain groundbreaking nosological approaches in the future that are based upon genetics, other aspects of neurobiology, and behavioral science" (6), it has the potential drawback of impeding clinicians' ability to make clinical sense of such research and apply it to their patients, whose clinical presentations will likely continue for the foreseeable future to be thought of in terms of the DSM/ICD-type categories.

Indeed, one of the central thrusts of RDoC is to discourage the use of the DSM/ICD syndromal constructs by researchers in either research design or subject selection, except insofar as is necessary during the research community's "transition" from the DSM/ICD to RDoC. As noted by Cuthbert, many if not most of the symptoms that form the basis for DSM psychiatric assessment and treatment do not appear in the

RDoC matrix, impeding clinicians' ability to relate to RDoC-themed research studies.

So what can be done to mitigate this situation? Although in his paper Cuthbert repeatedly discusses the need for a "transition" from DSM/ICD to RDoC and provides concrete suggestions for how this may be done (e.g., incorporating "various combinations of RDoC constructs and DSM/ICD disorder categories in experiments"), according to Cuthbert such "transitional research designs are best regarded as temporary heuristics for a limited number of studies".

Rather than viewing the retention of elements of the DSM/ICD system as heuristics to be phased out as soon as possible, it should be a required part of any RDoC-oriented research project to provide linkages or crosswalks between the RDoC design and the DSM/ICD classifications. At a minimum, study populations used in RDoC-themed protocols should also be described in terms of DSM-5/ICD-11 diagnoses, if for no other reason than to provide a touchstone to the clinician for appreciating the types of subjects included in the study.

For example, according to Cuthbert, a "prototypical RDoC design... would include subjects with a wide range of normal-to-impaired functioning with respect to the dimensional constructs of interest". It would be relatively straightforward to diagnostically assess these subjects, not for the purposes of the experimental design but to characterize the study population in terms understandable by clinicians.

Only by explicitly building bridges between the DSM/ICD and RDoC worlds can the field continue to promote some level of communication and interaction between clinicians and researchers.

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RDoC+: taking translation seriously

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Cuthbert's paper gives a helpfully detailed introduction to the RDoC framework for assimilating neuroscientific findings, aimed, ultimately, at more effective translation of research into practice (1). In this commentary, I take a step back from the details to look at RDoC's underpinning theory and at the implications of that theory for RDoC's translational aims.

The theory underpinning RDoC is that mental disorders are analogous to disorders in other areas of medicine such as cardiology. Cuthbert, for example, compares RDoC's dimensions with (the also dimensional) hypertension (1). Insel, too, draws on the analogy at several points in his blog introducing RDoC as Director of the National Institute of Mental Health (NIMH). "Imagine – he writes, referring specifically to DSM's failure to translate research into practice – deciding that EKGs were not useful because many patients with chest pain did not have EKG changes" (2).

The implication, then, is that, in focussing on pathological mechanisms, RDoC takes the analogy with medicine more seriously than DSM. The concern, though, is that by the same token RDoC is at risk of neglecting the symptom side of the theory. Medicine is of course concerned equally with symptoms and with underlying mechanisms. Neglecting *either* side of the theory, therefore, neglecting either symptoms or mechanisms, could prove equally fatal to effective translation of research into practice.

To be clear, the concern here is not that symptoms (broadly construed) are actually excluded from RDoC. True, the particular symptoms on which DSM is based are not in RDoC (1). But "observable behavior" was included in NIMH's original strategic brief; symptoms are covered in RDoC itself (respectively by "self reports" and "behavior"); psychopathology is flagged in the title of Cuthbert's commentary; and, as Cuthbert indicates (1), "impairments that patients experience in their lives" were important in the development of the RDoC framework. So, the concern is not that symptoms are excluded but rather that, compared with mechanisms, RDoC is at risk of not taking them seriously enough.

Thus, Cuthbert's examples – reward, threat and memory (1) – although certainly showing the value of more precise understanding of symptoms as well as of brain mechanisms, all regard relatively straightforward aspects of subjectivity compared with the subtleties of such staples of mental disorder as belief, perception, volition and emotion. Insel, similarly, in his reference to EKGs, writes as though heart disease were diagnosed clinically by chest pain as such, whereas it is specifically *anginal* pain that is diagnostic of heart disease,

which, indeed, may not be in the chest at all but in the throat or left arm. Again, Cuthbert is well aware of the complexities of subjectivity. The concern is that, compared with mechanisms, these complexities fail to make it into RDoC's headlines. The relevant units of analysis, indeed, "self reports" and "behavior" – if the lists of instruments given in NIMH's domain workshop reports are any guide – rely heavily on questionnaires and rating scales no different in principle from those on which the DSM itself was originally constructed. So, with nothing essentially new on the symptom side of RDoC, there is a clear risk that it too, like the DSM, will fail to support effective translation of research into practice (3).

That said, Cuthbert emphasizes that RDoC is an inclusive, not exclusive framework. It will be measured, he says, "by the number of research programs that. . . outstrip the RDoC matrix to move in entirely new directions" (1). Scientifically, this promissory note towards an RDoC+, as it might be called, is perhaps the most important statement in Cuthbert's article. Progress in science, as the philosopher of science Karl Popper pointed out (4), depends on bringing together imaginative conjectures with the disciplines of trial by experiment. Social science research has identified similar conditions for creativity (5). It is just this vital combination of imagination and experiment that an open and inclusive RDoC of the kind Cuthbert anticipates will support.

If RDoC fails to deliver on this promissory note, it will not be for lack of resources. There is a veritable raft of new sciences of the mind that could be added to the neuroscience-focussed RDoC to give a symptom-enriched RDoC+. Prominent among these new sciences of the mind, in this centenary year of Karl Jaspers' *General Psychopathology*, is the continuing importance of phenomenology (6). Cuthbert is right to dismiss the merely "descriptive phenomenology" (1) of the DSM. But there are other more clinically realistic phenomenologies available for an RDoC+. Among these, "naturalized phenomenology" (7) connects philosophical phenomenology seamlessly with all the resources of cognitive science, which, in turn, as Cuthbert and others involved in planning RDoC were clearly aware (ref. 9 in 1), provides a natural bridge to the neurosciences (8). These resources, furthermore, together support computational approaches to psychopathology (9) that are directly conformable to the dimensional structure of the RDoC framework and the "precision medicine" (1) it is intended to foster.

In his book *The First Three Minutes*, the Nobel-laureate theoretical physicist Stephen Weinberg warned that in science "our mistake is not that we take our theories too seriously but that we do not take them seriously enough" (10). In rebalancing symptoms with mechanisms, RDoC takes the analogy between mental disorders and disorders in other areas of medicine such as cardiology more seriously than DSM. Taking the analogy seriously enough for successful translation of research into practice means adding to RDoC the resources of the new sciences of the mind.

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Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis

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We conducted a meta-analysis of randomized trials in which the effects of treatment with antidepressant medication were compared to the effects of combined pharmacotherapy and psychotherapy in adults with a diagnosed depressive or anxiety disorder. A total of 52 studies (with 3,623 patients) met inclusion criteria, 32 on depressive disorders and 21 on anxiety disorders (one on both depressive and anxiety disorders). The overall difference between pharmacotherapy and combined treatment was Hedges' g = 0.43 (95% CI: 0.31-0.56), indicating a moderately large effect and clinically meaningful difference in favor of combined treatment, which corresponds to a number needed to treat (NNT) of 4.20. There was sufficient evidence that combined treatment is superior for major depression, panic disorder, and obsessive-compulsive disorder (OCD). The effects of combined treatment compared with placebo only were about twice as large as those of pharmacotherapy compared with placebo only, underscoring the clinical advantage of combined treatment. The results also suggest that the effects of pharmacotherapy and those of psychotherapy are largely independent from each other, with both contributing about equally to the effects of combined treatment. We conclude that combined treatment appears to be more effective than treatment with antidepressant medication alone in major depression, panic disorder, and OCD. These effects remain strong and significant up to two years after treatment. Monotherapy with psychotropic medication may not constitute optimal care for common mental disorders.

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

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Anxiety and depressive disorders are highly prevalent (1,2) and are associated with a substantial loss of quality of life for patients and their relatives (3,4), high levels of service use, substantial economic costs (5-7), and a considerable disease burden for public health (8). Effective treatments are available for these disorders, including several types of psychotherapy and antidepressant medication (9-11). Although psychotherapy and antidepressants are about equally effective for most anxiety and depressive disorders (12), there is some evidence that combined treatments may be more effective than each of these treatment alone (13-15). At the same time, however, an increasing proportion of patients with mental disorders in the past decade have received psychotropic medication without psychotherapy (16,17). It is important, therefore, to examine whether this has negative effects on the quality of care.

We conducted a meta-analysis of studies comparing pharmacotherapy alone with combined psychotherapy and pharmacotherapy. Although some earlier meta-analyses have examined this question, these were all aimed at one disorder, especially depression (13-15) and panic (18,19). For some other disorders – e.g., social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD) – several primary studies have been conducted, but these have not yet been integrated into meta-analyses. The main goal of this paper, therefore, is to provide an overall meta-analysis of studies comparing antidepressant medication with combined treatment for anxiety and depressive disorders. We also examined whether differences between combined treatment and placebo only were larger than those between combined treatment and pharmacotherapy, in order to determine the relative contribution of psychotherapy and pharmacotherapy to the effects of combined treatments.

METHODS

Identification and selection of studies

We used several strategies to identify relevant studies. We searched four major bibliographical databases (PubMed, PsycInfo, Embase and the Cochrane database of randomized trials). We first developed a search string for psychotherapy with text and key words indicating the different types of psychotherapy and psychological treatments. This search string was combined with search strings indicating each of the disorders we included: major depression; dysthymia; generalized anxiety disorder (GAD); SAD; panic disorder; OCD; post-traumatic stress disorder (PTSD). We limited our search to randomized controlled trials. We also checked the references of 116 earlier meta-analyses of psychological treatments of the disorders (Figure 1).

We included randomized trials in which the effects of treatment with antidepressant medication were compared

	Depression	GAD	SAD	Panic	OCD / PTSD	Total
21,729 references identified by literature search						
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
⇓						
After removal of duplicates						
	9860	1562	1228	2032	221	14903
⇓						
Earlier meta-analyses checked for references						
	42	7	14	26	27	116
⇓						
Full-text papers retrieved						
	1344	136	247	493	58	2278
⇓						
Reasons for exclusion						
No correct comparison	243	49	86	170	29	577
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	1312	135	243	483	52	2226
⇓						
Included in meta-analysis	32	1	4	10	OCD: 4 PTSD: 2	52

Figure 1 Selection and inclusion of studies. GAD – generalized anxiety disorder, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder, SAD – social anxiety disorder

to the effects of a combined antidepressant medication and psychological treatment in adults with a depressive disorder, panic with or without agoraphobia, GAD, SAD, OCD or PTSD. Only studies in which subjects met diagnostic criteria for the disorder according to a diagnostic interview – such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), the Composite International Diagnostic Interview (CIDI), or the Mini-International Neuropsychiatric Interview (MINI) – were included. 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. Studies in English, German, Spanish, and Dutch were considered for inclusion.

Quality assessment and data extraction

We assessed the validity of included studies using the "Risk of bias" assessment tool, developed by the Cochrane Collaboration (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 assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses). Assessment of the validity of included studies was conducted by

two independent researchers, and disagreements were solved through discussion.

We also coded participant characteristics (disorder; recruitment method; target group); type of antidepressant that was used (selective serotonin reuptake inhibitor, SSRI; tricyclic antidepressant, TCA; serotonin-norepinephrine reuptake inhibitor, SNRI; monoamine oxidase inhibitor, MAOI; other or manualized treatment including several antidepressants); and characteristics of the psychotherapies (format; number of sessions; and type of psychotherapy). The types of psychotherapy we distinguished were cognitive behavior therapy (CBT), interpersonal psychotherapy (IPT), and others. Because most CBT therapies used a mix of different techniques, we clustered them together in one large family of CBT treatments. 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 (such as psychodynamic therapies).

Meta-analyses

For each comparison between a pharmacotherapy and the combined treatment group, the effect size indicating the difference between the two groups at post-test was calculated (Hedges' g). Effect sizes were calculated by subtracting (at post-test) the average score of the pharmacotherapy group from the average score of the combined treatment 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 aimed at patients with depressive disorders, we used only those instruments that explicitly measured symptoms of depression. In studies examining anxiety disorders, we used only 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 used the above-mentioned software. Because we expected considerable heterogeneity among the studies, we employed a random effects pooling model.

Because the standardized mean difference (Hedges' g) is not easy to interpret from a clinical perspective, we transformed these values into the number needed to treat (NNT), using the formulae provided by Kraemer and Kupfer (22). The NNT indicates the number of patients that have to be treated in order to generate one additional positive outcome (23).

We also calculated the relative risk (RR) of dropping out from treatment in pharmacotherapy compared with combined treatment. To compare the long-term effects of the two treatments, we calculated the RR of having a positive outcome at follow-up.

As a test of homogeneity of effect sizes, we calculated the I^2 statistic, which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (24). We calculated 95% confidence intervals around I^2 (25), using the non-central chi-squared-based approach within the Heterogi module for Stata (26).

We conducted subgroup analyses according to the mixed effects model, in which studies within subgroups are pooled 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 publication bias by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure (27), 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.

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 further consideration. We excluded 2,226 of the retrieved papers. The flow chart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. A total of 52 studies met inclusion criteria for this meta-analysis (28-79). Selected characteristics of the included studies are reported in Table 1.

Characteristics of included studies

In the 52 studies, 3,623 patients participated (1,767 in the combined treatment conditions and 1,856 in the pharmacotherapy only conditions). Thirty-two studies were aimed at depressive disorders (22 on major depression, including one that was aimed at patients with both major depression and OCD; 5 on dysthymia; and 5 on mixed mood disorders) and 21 at anxiety disorders (10 on panic disorder with or without agoraphobia; 4 on OCD; 4 on SAD; 2 on PTSD, and one on GAD). Most studies (n = 32) recruited patients

Table 1 Selected characteristics of studies comparing treatment with antidepressant medication to combined treatment with psychotherapy and medication

Study	Disorder	Psychotherapy	Medication	Ncom	Nmed	Quality*	Country
Azhar (28)	PAN	CBT	SSRI	17	17	− − − −	Other
Barlow et al (29)	PAN	CBT	TCA	65	83	− − + +	USA
Bellack et al (30)	Mood	Other	TCA	17	18	− − + −	USA
Bellino et al (31)	MDD	IPT	SSRI	16	16	− − + −	Europe
Berger et al (32)	PAN	Other	SSRI	35	38	− − − −	Europe
Blackburn et al (33)	MDD	CBT	TCA	22	20	− − − −	USA
Blanco et al (34)	SAD	CBT	MAOI	32	35	+ + + +	USA
Blom et al (35)	MDD	IPT	SNRI	33	30	− − + +	Europe
Blomhoff et al (36)	SAD	BT	SSRI	98	95	+ + + +	Europe
Browne et al (37)	DYS	IPT	SSRI	122	117	+ + + −	Canada
Burnand et al (38)	MDD	DYN	TCA	33	38	− − + −	Europe
Crits-Christoph et al (39)	GAD	CBT	SNRI	17	24	− − + −	USA
Davidson et al (40)	SAD	CBT	SSRI	42	39	+ + + +	USA
De Jonghe et al (41)	MDD	DYN	Prot/Other	83	84	− − + +	Europe
De Mello et al (42)	DYS	IPT	MAOI	11	13	− − + −	Other
Dozois et al (43)	MDD	CBT	Prot/Other	21	21	− + − −	Canada
Finkenzeller et al (44)	MDD	IPT	SSRI	23	24	+ − + +	Europe
Foa et al (45)	OCD	BT	TCA	19	27	− − + −	USA
Hautzinger et al (46)	Mood	CBT	TCA	32	24	− − + +	Europe
Hellerstein et al (47)	DYS	Other	SSRI	18	17	− − − +	USA
Hollon et al (48)	MDD	CBT	TCA	25	57	− − + +	USA
Hsiao et al (49)	MDD	Other	Prot/Other	24	26	+ − + +	Other
Keller et al (50)	MDD	Other	SNRI	226	220	+ + + +	USA
King et al (51)	PAN	CBT	Prot/Other	25	25	− + + −	Other
Koszycki et al (52)	PAN	CBT	SSRI	59	62	+ + + +	Canada
Lesperance et al (53)	MDD	IPT	SSRI	67	75	+ + + +	Canada
Loerch et al (54)	PAN	CBT	MAOI	14	16	− − + +	Europe
Lynch et al (55)	MDD	Other	Prot/Other	15	16	− − − −	USA
Macaskill & Macaskill (56)	MDD	CBT	TCA	9	9	− − − −	Europe
Maina et al (57)	MDD, OCD	DYN	SSRI	25	29	+ + + +	Europe
Markowitz et al (58)	DYS	IPT	SSRI	21	24	+ + + +	USA
Misri et al (59)	Mood	CBT	SSRI	19	16	+ − + +	Canada
Mitchell et al (60)	Mood	Other	Prot/Other	45	53	+ + + +	USA
Murphy et al (61)	MDD	CBT	TCA	22	24	+ + − +	USA
Mynors-Wallis et al (62)	MDD	PST	SSRI	35	36	+ + + +	Europe
Naeem et al (63)	MDD	CBT	SSRI	17	17	+ + + +	Other
Otto et al (64)	PTSD	CBT	SSRI	5	5	− − − −	USA
Prasko et al (65)	SAD	CBT	MAOI	22	20	− − + −	Europe
Ravindran et al (66)	DYS	CBT	SSRI	24	22	+ + + −	Canada
Reynolds et al (67)	MDD	IPT	TCA	16	25	− − + +	USA
Rothbaum et al (68)	PTSD	BT	SSRI	34	31	− − + +	USA
Shamsaei et al (69)	MDD	CBT	SSRI	40	40	+ − + −	Other
Shareh et al (70)	OCD	CBT	SSRI	6	6	− − − −	Other
Sharp et al (71)	PAN	CBT	SSRI	29	29	− − − −	Europe

Table 1 Selected characteristics of studies comparing treatment with antidepressant medication to combined treatment with psychotherapy and medication *(continued)*

Study	Disorder	Psychotherapy	Medication	Ncom	Nmed	Quality*	Country
Sirey et al (72)	MDD	Other	Prot/Other	21	24	− − + +	USA
Spinhoven et al (73)	PAN	CBT	SSRI	20	19	− − − +	Europe
Tenneij et al (74)	OCD	BT	Prot/Other	34	46	− − + +	Europe
Thompson et al (75)	MDD	CBT	TCA	36	33	− − − +	USA
van Apeldoorn et al (76)	PAN	CBT	Prot/Other	36	37	+ + + +	Europe
Weissman et al (77)	MDD	IPT	TCA	23	20	− − + −	USA
Wiborg & Dahl (78)	PAN	DYN	TCA	20	20	+ + + +	Europe
Wiles et al (79)	Mood	CBT	Prot/Other	14	11	+ + + +	Europe

*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

BT – behavior therapy, CBT – cognitive behavior therapy, DYN – psychodynamic therapy, DYS – dysthymic disorder, GAD – generalized anxiety disorder, IPT – interpersonal psychotherapy, MAOI – monoamine oxidase inhibitor, MDD – major depressive disorder, Mood – mixed mood disorder, Ncom – number of patients in the combined treatment condition, Nmed – number of patients in the pharmacotherapy condition, OCD – obsessive-compulsive disorder, PAN – panic disorder with or without agoraphobia, Prot/Other – other antidepressant or protocolized treatment with antidepressants, PST – problem-solving therapy, PTSD – post-traumatic stress disorder, SAD – social anxiety disorder, SNRI – serotonin-norepinephrine reuptake inhibitor, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant

exclusively from clinical samples, and 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 belonged to the family of cognitive and behavioral therapies, while nine studies examined IPT, and the remaining 10 examined other therapies (including psychodynamic therapies). The number of treatment sessions ranged from 5 to 56, with most therapies (n = 36) having between 10 and 20 sessions. The antidepressants that were examined in the studies included SSRIs (n = 22), TCAs (n = 13), SNRIs (n = 3), MAOIs (n = 4), and treatment protocols with different types of antidepressant medication (n = 10).

Most studies were conducted in the US (n = 20), or Europe (n = 19). Two papers were published in German, the rest in English.

Quality assessment

The quality of the studies varied (Table 1). Twenty-one studies reported an adequate sequence generation, while the other 31 did not. Nineteen studies reported allocation to conditions by an independent (third) party. Thirty-nine studies reported blinding of outcome assessors or used only self-report outcomes, whereas 13 did not report blinding. Thirty-one 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). Thirteen studies met all four quality criteria, another six studies met 3 criteria, while the remaining 33 studies met two criteria or less.

Effects of combined treatment versus antidepressants only

The overall mean effect size indicating the difference between pharmacotherapy only and combined treatment of pharmacotherapy and psychotherapy at post-test for all 52 studies was 0.43 (95% CI: 0.31-0.56) in favor of the combined treatment. This corresponds to a NNT of 4.20. Heterogeneity was moderate to high ($I^2 = 64$; 95% CI: 52-73). After exclusion of three possible outliers with extremely large effect sizes ($g > 1.5$; Table 2), the effect size was somewhat smaller ($g = 0.37$; 95% CI: 0.27-0.47; NNT = 4.85), but heterogeneity was reduced to a moderate level ($I^2 = 48$). The results of these analyses are reported in Table 2. A forest plot of the studies and their effect sizes is given in Figure 2.

For specific disorders, we found evidence that combined treatment was more effective than pharmacotherapy alone in major depression ($g = 0.43$; 95% CI: 0.29-0.57; NNT = 4.20), panic disorder ($g = 0.54$; 95% CI: 0.25-0.82; NNT = 3.36), and OCD ($g = 0.70$; 95% CI: 0.14-1.25; NNT = 2.63). We also found some indication that combined treatment may be more effective than pharmacotherapy in SAD ($g = 0.32$; 95% CI: −0.01-0.71; NNT = 5.56), although this was not significant ($p<0.1$). Insufficient evidence was found for dysthymia, PTSD, and GAD.

Inspection of the funnel plot and Duval and Tweedie's trim and fill procedure pointed at some risk of publication bias. After adjustment for possible publication bias, the overall mean effect size was reduced from $g = 0.43$ (NNT = 4.20) to $g = 0.29$ (95% CI: 0.15-0.43; NNT = 6.17; number of imputed studies: 10). Egger's test of the intercept also indicated significant publication bias (intercept: 1.33; 95% CI: 0.24-2.42; $p<0.01$).

Table 2 Effects of combined therapy for adult depressive and anxiety disorders compared with antidepressant medication only

		Ncomp	g	95% CI	I^2	95% CI	p	NNT
Depressive and anxiety disorders		52	0.43	0.31-0.56	64	52-73	0.81	4.20
Possible outliers excluded (g > 1.5)		49	0.37	0.27-0.47	48	28-63		4.85
Depressive disorders		32	0.41	0.28-0.54	50	25-67	0.17	4.39
Major depression		23	0.43	0.29-0.57	30	0-58		4.20
Dysthymia		5	0.20	−0.21-0.60	0	0-79		8.93
Mixed depressive disorders		5	0.56	0.12-0.99	73	32-89		3.25
Anxiety disorders		21	0.47	0.23-0.71	75	61-84	0.66	3.85
Panic disorder		10	0.54	0.25-0.82	82	68-90		3.36
OCD		4	0.70	0.14-1.25	67	5-89		2.63
SAD		4	0.32	−0.01-0.71	65	0-88		5.56
PTSD		2	0.31	−0.39-1.00	0	-		5.75
GAD		1	−0.51	−1.42-0.40	-	-		(3.55)
Subgroup analyses								
Medication	SSRI	22	0.34	0.15-0.53	76	63-84	0.45	5.26
	TCA	13	0.46	0.22-0.71	9	0-47		3.91
	Other/protocol	17	0.51	0.31-0.72	41	0-67		3.55
Recruitment	Clinical samples	32	0.49	0.34-0.64	63	46-75	0.09	3.68
	Community	16	0.28	0.08-0.47	45	2-70		6.41
Target group	Adult in general	43	0.44	0.30-0.57	65	51-74	0.89	4.10
	Specific group	9	0.41	0.12-0.71	64	27-83		4.39
Type of therapy	CBT	33	0.51	0.35-0.66	70	58-79	0.20	3.55
	IPT	9	0.24	−0.05-0.53	32	0-69		7.46
	Other	10	0.37	0.09-0.64	10	0-50		4.85
Number of sessions	5-9	11	0.67	0.40-0.93	86	76-91	0.10	2.75
	10-12	16	0.24	0.03-0.46	48	8-71		7.46
	13-18	18	0.47	0.26-0.67	4	0-52		3.85
	>19	7	0.41	0.06-0.76	33	0-72		4.39
Treatment format	Individual	42	0.46	0.32-0.59	68	55-76	0.35	3.91
	Group	9	0.29	−0.02-0.60	40	0-73		6.17
Quality score	<3	32	0.49	0.33-0.66	62	44-74	0.23	3.68
	3 or 4	20	0.35	0.16-0.54	67	47-79		5.10

CBT – cognitive behavior therapy, GAD – generalized anxiety disorder, IPT – interpersonal psychotherapy, Ncomp – number of comparisons, NNT – number needed to treat, OCD – obsessive-compulsive disorder, PTSD – post-traumatic stress disorder, SAD – social anxiety disorder, SNRI – serotonin-norepinephrine reuptake inhibitor, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant

We found no indication that combined treatment resulted in lower dropout from treatment than pharmacotherapy alone. The RR of dropping out of treatment, in the 35 studies in which dropout was reported, was RR = 0.99 (95% CI: 0.95-1.03; I^2 = 24; 95% CI: 0-50).

Subgroup analyses indicated no significant differences between the effects sizes of depressive and anxiety disorders, between the different depressive disorders (while excluding anxiety disorders), and between the different anxiety disorders (while excluding depressive disorders) (Table 2). We also found no indication that the effect sizes differed according to the type of medication (SSRI; TCA; other or protocolized), target group (adults in general or more specific target group), psychotherapy treatment format (individual or group), type of therapy (CBT; IPT; other), number of treatment sessions (5-9; 10-12; 13-18; >19); and quality of the studies (meeting 3 or 4 criteria versus less than 3 criteria). We did find a trend ($p<0.1$) indicating that the effect size may be higher in clinical samples (g = 0.49) compared with samples that included patients recruited from the community (g = 0.27).

We examined whether baseline severity was associated with outcome in the 20 studies examining depressive disorders. Mean baseline severity according to the Hamilton Depression Rating Scale (HAM-D) was moderate in 16 of the

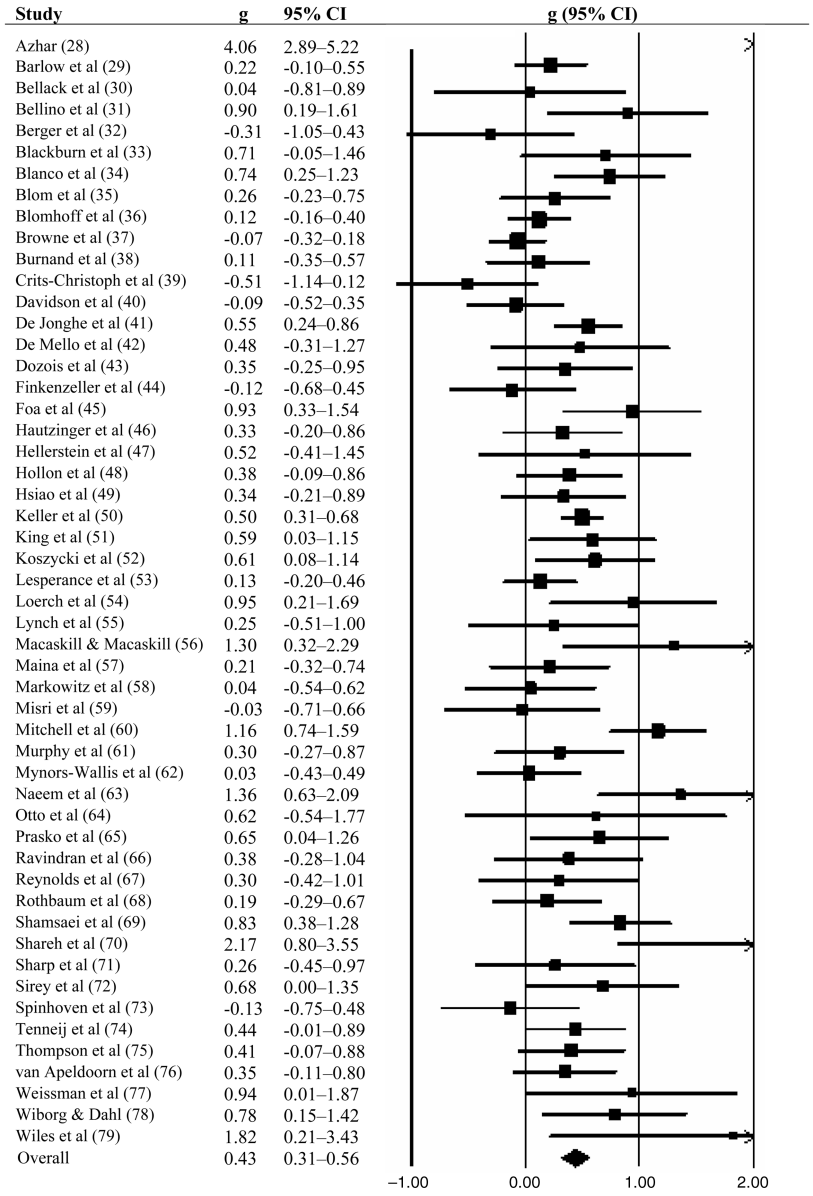

Figure 2 Effects of pharmacotherapy compared to combined treatment with pharmacotherapy and psychotherapy (Hedges' g)

20 studies (score 18-24), severe in three studies (score >24), and mild in one study (score <18) (80). In a meta-regression analysis, we did not find any indication that the effect size of difference between pharmacotherapy and combined treatment was associated with baseline severity of depression (slope: 0.007; 95% CI: −0.022-0.038; p = 0.63).

Combined treatment versus placebo

In 11 of the 53 studies, the combined treatment could be compared to a pill placebo control group. All of these studies also included a psychotherapy-only condition (with or without a pill placebo), as well as a pharmacotherapy-only condition. This allowed us to calculate the effect sizes indicating the

Table 3 Direct comparisons between psychotherapy, pharmacotherapy, combined psychotherapy and pharmacotherapy, and placebo in anxiety and depressive disorders (Hedges' g)

	Ncomp	g	95% CI	I^2	95% CI	NNT
Combined vs. placebo	11	0.74	0.48-1.01	65	33-82	2.50
Pharmacotherapy vs. combined	11	0.37	0.12-0.63	43	0-72	4.85
Pharmacotherapy vs. placebo	11	0.35	0.21-0.49	0	0-60	5.10
Psychotherapy vs. combined	11	0.38	0.16-0.59	53	8-76	4.72
Psychotherapy vs. placebo	11	0.37	0.11-0.64	68	41-83	4.85

Ncomp - number of comparisons, NNT – number needed to treat

Table 4 Long-term follow-up effects in included studies: definitions of positive outcome and relative risk associated with each outcome

Study	Outcome	Follow-up (months)	RR	95% CI
Barlow et al (29)	CGI response	6-8	1.52	1.07-2.16
Barlow et al (29)	CGI response	9-12	1.39	0.75-2.58
Barlow et al (29)	PDSS response	6-8	1.52	1.07-2.16
Barlow et al (29)	PDSS response	9-12	1.31	0.69-2.45
Bellack et al (30)	<10 on BDI + HAMD	6-8	1.30	0.53-3.16
Blanco et al (34)	remission	3-5	2.07	1.08-3.96
Blanco et al (34)	response	3-5	1.61	1.09-2.37
Hautzinger et al (46)	response	9-12	1.91	1.07-3.39
Hellerstein et al (47)	remission	3-5	0.62	0.23-1.66
Hellerstein et al (47)	response	3-5	1.53	0.74-3.14
Hollon et al (48)	no relapse	9-12	1.87	0.99-3.52
Hollon et al (48)	no relapse	13-24	1.73	0.90-3.32
Keller et al (50)	no relapse	3-5	1.01	0.95-1.08
Loerch et al (54)	FQ<10	6-8	1.17	0.79-1.74
Loerch et al (54)	FQ>50% improvement	6-8	1.17	0.79-1.74
Lynch et al (55)	BDI<9	6-8	1.29	0.43-3.88
Lynch et al (55)	HAMD<7	6-8	2.35	1.07-5.16
Maina et al (57)	CGI success	6-8	1.55	0.62-3.86
Maina et al (57)	HAMD response	6-8	1.16	0.47-2.86
Maina et al (57)	YBOCS response	6-8	0.77	0.38-1.58
Mitchell et al (60)	HAMD<9	3-5	2.08	1.13-3.82
Mitchell et al (60)	HAMD<9	9-12	1.76	1.01-3.08
Mitchell et al (60)	HAMD<9	13-24	1.42	0.91-2.23
Murphy et al (61)	no relapse	9-12	1.71	0.61-4.80
Mynors-Wallis et al (62)	recovered	9-12	1.18	0.81-1.73
Prasko et al (65)	no relapse	3-5	1.62	0.89-2.95
Prasko et al (65)	no relapse	9-12	2.16	0.81-5.77
Prasko et al (65)	no relapse	13-24	1.94	0.71-5.31
Reynolds et al (67)	no relapse	3-5	9.58	2.09-43.94
Sharp et al (71)	FQ-AG: clinically significant change	6-8	1.60	0.88-2.91
Sharp et al (71)	HAMA: clinically significant change	6-8	1.64	0.95-2.82
Sharp et al (71)	SRT: clinically significant change	6-8	2.50	0.88-7.07
van Apeldoorn et al (76)	remission	6-8	1.48	0.63-3.47
van Apeldoorn et al (76)	remission	9-12	1.93	0.87-4.27
Wiborg & Dahl (78)	no DSM relapse	9-12	3.20	1.45-7.05
Wiborg & Dahl (78)	remission	9-12	3.20	1.45-7.05

BDI – Beck Depression Inventory, CGI – Clinical Global Impression, FQ – Fear Questionnaire, FQ-AG – Fear Questionnaire, Agoraphobia Subscale, HAMA – Hamilton Anxiety Rating Scale, HAMD – Hamilton Depression Rating Scale, PDSS – Postpartum Depression Screening Scale, RR – relative risk, SRT – Kellner and Sheffield Symptom Rating Scale, YBOCS – Yale-Brown Obsessive Compulsive Scale

difference between pharmacotherapy and placebo, psychotherapy (with or without a pill placebo) and placebo, as well as between combined treatment and placebo. With these effect sizes we could estimate the contribution of pharmacotherapy and psychotherapy to the effects of combined treatment.

The results of the analyses are presented in Table 3. The effects of combined treatment compared with placebo are large (g = 0.74; 95% CI: 0.48-1.01; NNT = 2.50), with moderate to high heterogeneity ($I^2 = 65$; 95% CI: 33-82). In these 11 studies, the effect size of pharmacotherapy compared with placebo was g = 0.35 (95% CI:0.21-0.49) and

Table 5 Long-term effects of combined therapy for anxiety and depressive disorders compared with antidepressive medication only: relative risk of having a positive outcome

	Ncomp	RR	95% CI	I^2	95% CI	NNT
3-5 months after end of treatment	6	1.60	1.03-2.48	75	43-89	3.41
6-8 months after end of treatment	7	1.40	1.13-1.73	0	0-71	6.90
9-12 months after end of treatment	10	1.51	1.25-1.84	13	0-56	4.52
13-24 months after end of treatment	4	1.49	1.12-1.98	0	0-85	4.35
All long-term outcomes pooled	19	1.48	1.23-1.78	55	25-73	4.29

Ncomp – number of comparisons, NNT – Number needed to treat, RR – relative risk

that of psychotherapy compared with placebo was g = 0.37 (95% CI: 0.11-0.64). This suggests that the effects of psychotherapy and those of pharmacotherapy are largely independent of each other, and each add about 50% to the overall effects of combined treatment. The independence of the effects of the two kinds of treatments is further supported by the effect sizes of pharmacotherapy versus combined treatment (g = 0.37 in this sample), and those of psychotherapy versus combined treatment (g = 0.38).

Long-term differences between pharmacotherapy and combined treatment

Long-term differences between pharmacotherapy and combined treatment were reported in 19 studies, with follow-up periods varying from 3 to 24 months. Because the way positive outcomes were defined differed from study to study, we have reported the definition of a positive outcome at each of the follow-up points in Table 4.

The RR of having a positive outcome for all follow-up periods together was 1.48 (95% CI: 1.23-1.78; NNT = 4.29), and ranged from RR = 1.40 to 1.51 (NNTs: 3.41 to 6.90) for the four follow-up periods we distinguished. In each of the four follow-up periods, combined treatment was significantly more effective than pharmacotherapy alone (Table 5).

DISCUSSION

In this meta-analysis, we found clear evidence that combined treatment with psychotherapy and antidepressant medication is more effective than treatment with antidepressant medication alone. This difference was significant for major depression, panic disorder, and OCD. A trend indicated possible superior effects in SAD. We did not find sufficient evidence for a significant difference in dysthymia, PTSD and GAD, but this could be due to the small number of studies and associated lack of statistical power for these disorders. The superior effects of combined treatment remained significant at one to two-year follow-up.

We found that the superior effects of combined treatment may have been overestimated by publication bias, which is in line with earlier research on pharmacotherapy (81) as well as psychotherapy (82), showing evidence of publication bias in both fields. However, even after adjusting for publication bias, the superiority of combined treatment was still statistically significant.

We also found some indications that the difference between pharmacotherapy and combined treatment was especially high in clinical samples compared with samples that were (in part) recruited from the community. Although this difference was only marginally significant ($p<0.1$), it does suggest that patients actively seeking treatment may benefit more from combined treatment than people who are recruited from the community.

Research up to now has not been able to answer the question of how large the effects of combined treatment are compared with pill placebo only. We found indications that the effects of combined treatment compared with placebo only were about twice as large as those of pharmacotherapy compared with placebo only.

Until now it has not been established well whether the effects of pharmacotherapy and those of psychotherapy are complementary to each other, whether they have effects independent from each other, or whether combined treatments lead to higher effects than the sum of the two treatments alone (83,84). The present study indicates that the effects of psychotherapy and pharmacotherapy may be largely independent from each other and additive, not interfering with each other, and both contribute about equally to the effects of combined treatment.

From a clinical point of view, this paper suggests that combined treatment should be used in more patients than is currently done in clinical practice. Most patients receive either pharmacotherapy or psychotherapy (16,17), and only a minority receives combined therapy. Combined treatment is especially given to more severe and chronic cases. Our data suggest that the superior effects of combined treatment are not associated with baseline severity, at least in depression. Because the effects of the two treatments seem to be largely independent from each other, combined treatment may also be beneficial in less severe cases.

This study has some limitations. First, it is not possible to blind comparisons of pharmacotherapy to combined treatment and this may have introduced a bias in the outcomes. Second, because patients refusing antidepressants may not have been willing to be enrolled in trials, there may have been a sampling bias that could limit the generalizability of these findings. Third, we found considerable levels of heterogeneity among the studies, which could not fully be explained by moderator analyses. Another limitation was the relatively small number of included studies for some disorders. A final limitation is that we considered psychotherapy and

pharmacotherapy as monolithic treatments, while in fact several different treatments were used in the included studies.

In sum, the present study found superior effects of combined treatment over pharmacotherapy alone, which are significant and relevant up to two years after treatment. These results thus support the use of combined treatment for common mental disorders rather than monotherapy with psychotropic medication without psychotherapy.

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A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial

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In depression, the ability to experience daily life positive affect predicts recovery and reduces relapse rates. Interventions based on the experience sampling method (ESM-I) are ideally suited to provide insight in personal, contextualized patterns of positive affect. The aim of this study was to examine whether add-on ESM-derived feedback on personalized patterns of positive affect is feasible and useful to patients, and results in a reduction of depressive symptomatology. Depressed outpatients (n=102) receiving pharmacological treatment participated in a randomized controlled trial with three arms: an experimental group receiving add-on ESM-derived feedback, a pseudo-experimental group participating in ESM but receiving no feedback, and a control group. The experimental group participated in an ESM procedure (three days per week over a 6-week period) using a palmtop. This group received weekly standardized feedback on personalized patterns of positive affect. Hamilton Depression Rating Scale – 17 (HDRS) and Inventory of Depressive Symptoms (IDS) scores were obtained before and after the intervention. During a 6-month follow-up period, five HDRS and IDS assessments were completed. Add-on ESM-derived feedback resulted in a significant and clinically relevant stronger decrease in HDRS score relative to the control group ($p<0.01$; −5.5 point reduction in HDRS at 6 months). Compared to the pseudo-experimental group, a clinically relevant decrease in HDRS score was apparent at 6 months ($B=-3.6$, $p=0.053$). Self-reported depressive complaints (IDS) yielded the same pattern over time. The use of ESM-I was deemed acceptable and the provided feedback easy to understand. Patients attempted to apply suggestions from ESM-derived feedback to daily life. These data suggest that the efficacy of traditional passive pharmacological approach to treatment of major depression can be enhanced by using person-tailored daily life information regarding positive affect.

Key words: Ecological momentary assessment, experience sampling method, intervention study, psychological feedback, depressive disorder, positive affect

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According to the World Health Organization, depression is among the leading causes of disability (1). Improving the efficacy of pharmacotherapy and psychotherapy is considered a priority. Enlarging the window of observation of depressive symptomatology to out-of-the-office situations could result in a more detailed and personalized assessment of contextual influences on symptomatology, and hence may add to the effect of existing treatments.

Self-monitoring, comprising once-a-day retrospective paper-pencil assessments of mood, has been shown to reduce depressive symptomatology (2-4). However, because retrospectively obtained self-assessments are biased by mood-congruent emotional and cognitive biases (5), the use of prospective in-the-moment daily life assessments may be used to improve reliability, providing a much more fine-grained film of the dynamics of depressive symptomatology, which may aid in optimizing treatment decisions. Furthermore, digital instead of paper-and-pencil assessments have the advantage that data are immediately available.

Digitalized prospective, in-the-moment monitoring is commonly used in medical disciplines. Continuous monitoring, for example, is used in the treatment of hypertension and diabetes (i.e., 24h blood pressure or plasma glucose monitoring). In the field of mental health, however, this area remains to be explored. For mental health outcomes, the equivalent of mobile ambulatory assessment of medical outcomes has recently become available in the form of electronic momentary assessment techniques. These techniques represent the combination of experience sampling methodology (ESM) with new electronic tools, such as the PsyMate (6), allowing for direct electronic recording of the data. ESM consists of repeated assessments of affective experience and context in the flow of daily life (7-9).

Until recently, ESM has been used only in the context of research to identify moment-to-moment patterns and mechanisms of psychopathology (10-14). With the advent of personal digital assistants (PDAs) and web-based applications, however, real-life data are immediately available to patients and professional caregivers. This creates the possibility for ESM interventions (ESM-I) that can transform implicit real-life dynamic patterns to explicit, visualized and quantifiable configurations, through which dysfunctional patterns become modifiable. ESM-I has the additional benefit that it can be easily implemented in standard mental health care and does not require much additional investment of clinicians (6,11). Therefore, ESM-I constitutes a

new viable approach to improve personalized mental health care and stands to become a widely used mobile-health tool in clinical practice (10-13,15).

A new and exciting development is the use of real-life self-monitoring with ESM-I in depressed patients to gain insight in personalized patterns of positive affect and the context in which they are experienced. Numerous recent studies (16-19) have shown the importance of the reward system and positive affect experience in resilience against depression. It was demonstrated that especially positive affect – more than its counterpart, negative affect – is crucial and necessary in predicting recovery from depression (20-23). Furthermore, a recent randomized controlled trial showed that allocation to an intervention that increased real-life positive affect experience was associated with a significant decline in depressive symptoms (22). Therefore, the next step in the treatment of depression is to examine whether self-monitoring can be used as an intervention to increase insights in personalized patterns of positive affect. Personalized feedback focused on positive affect and its context may help both the patient and the professional carer in their search for custom opportunities to increase the experience of that affect, thus enabling recovery from depression.

Although the above arguments suggest that ESM-I represents a novel approach with a potential to improve treatment in mental health care, feasibility and patient preference need to be considered as well. There is a need to know how patients experience this procedure and whether they are able and willing to participate.

Therefore, the aims of the current study were to examine whether: a) ESM-derived personalized feedback can be used, in combination with standard antidepressant medication, as an effective add-on treatment for depressive symptoms designed to increase patients' resources with regard to positive affective experience; b) ESM-I is considered feasible and useful by patients.

To our knowledge, this is the first randomized controlled trial using ESM as a novel therapeutic intervention in depressed patients, with a view to improve personalized treatment.

METHODS

Participants and design

Consecutively presenting depressed outpatients attending mental health care facilities serving the catchment areas of the Dutch cities of Eindhoven and Maastricht were approached by their health care professionals and recruited into the study. In addition, recruitment in the same catchment areas was also carried out independent of contact with mental health care services by distributing posters and flyers in health care facilities and local media. Recruitment occurred between January 2010 and February 2012.

Inclusion criteria were: age 18-65 years; a DSM-IV-TR diagnosis of depressive episode with a current total score on the Hamilton Depression Rating Scale - 17 (HDRS) (24) of at least 8 (i.e., above remission cut-off and including residual depressive states); receiving pharmacological treatment with antidepressants or mood stabilizers; adequate vision; sufficient Dutch language skills; no current or lifetime diagnosis of non-affective psychotic disorder, and no (hypo)manic or mixed episode within the past month.

The study protocol was approved by the Medical Ethics Committee of Maastricht University Medical Centre. Informed consent was obtained from all participants. The trial was registered at Netherlands Trial Register (Identifier: NTR1974).

A randomized controlled trial was conducted with three treatment arms. After baseline, patients were randomly allocated to the experimental, pseudo-experimental or control group. In addition to treatment as usual (TAU), the experimental group participated in an ESM procedure (three days per week over a 6-week period) using a palmtop. This group received weekly standardized feedback on personalized patterns of positive affect. Feedback was given to both the patient and the mental health professional. The pseudo-experimental group also participated in the ESM procedure (three days per week over a 6-week period) in addition to TAU, but without feedback. The control group received no additional intervention during TAU.

Randomization (allocation ratio 1:1:1) was stratified according to duration of antidepressant pharmacotherapy (new/switch vs. maintenance, i.e. receiving antidepressant or mood stabilizing medication for less vs. longer than 8 weeks prior to study entry), and current psychotherapy (yes or no). The randomization sequence in blocks of six (using the sequence generator on the Internet site random.org) was generated by the first author of this paper. An independent research assistant wrote the randomization code into sealed numbered envelopes. After completion of all baseline assessments, the interviewer allocated participants to their treatment condition based on the randomization code in the sealed envelope (opened in order of sequence). Interviewers were not blind to the patients' treatment allocation.

Procedure

Figure 1 shows participant flow and procedure throughout the trial. The study protocol consisted of a telephone interview, a screening, a baseline assessment (week 0), a six-week intervention period (weeks 1 to 6), a post assessment (week 7), and five follow-up assessments (at weeks 8, 12, 16, 20, 32). From baseline (week 0) onward, the overall study duration was 32 weeks.

The recruitment process started with a short telephone interview conducted by a psychologist or psychiatrist to establish whether inclusion criteria were likely met. During the screening, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (25), the HDRS, and the 30-item

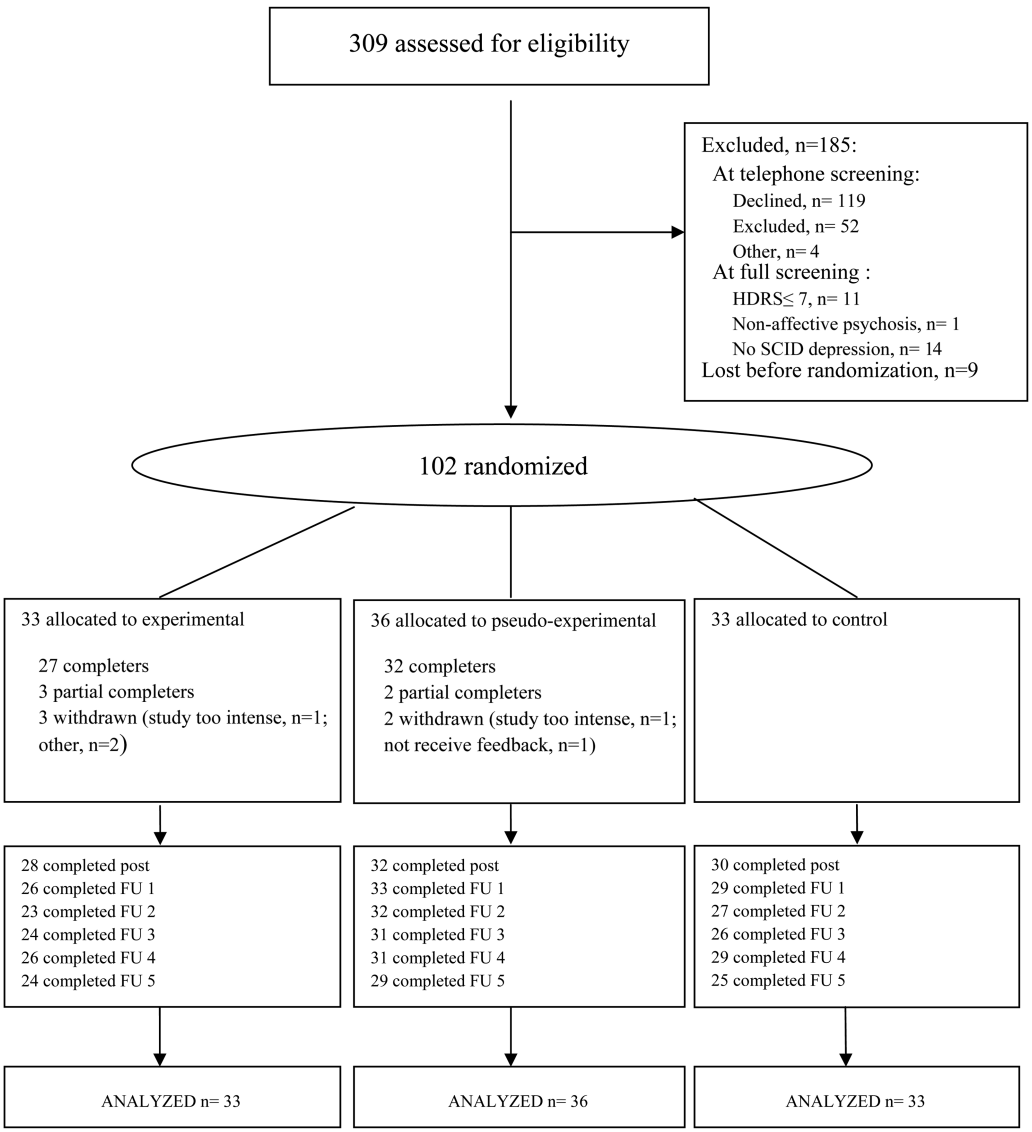

Figure 1 Flowchart of the study. HDRS - Hamilton Depression Rating Scale - 17, SCID - Structured Clinical Interview for DSM-IV Axis I Disorders, post - immediate post assessment, FU - follow-up assessment

Inventory of Depressive Symptoms (IDS-SR) (26) were administered. The HDRS semi-structured interview and the IDS self-report questionnaire, both assessing the severity of depressive symptoms, were completed at baseline, at post assessment and at follow-up. The IDS was used as a measure that is independent from the interpretation of the interviewer. ESM assessments took place as part of the baseline assessment (week 0), during the 6-week intervention period (weeks 1 to 6), and at the post assessment (week 7). The feasibility of the ESM measurement procedure and the desirability of the ESM-derived feedback on positive affect were evaluated through specific questions, with items rated on 7-point Likert scales (1="not at all" to 7="very").

ESM was carried out according to previous studies (7,27-29). The recently developed PsyMate, a palmtop, was used to digitally collect daily life momentary assessments of positive affect in relation to momentary context and activity. The PsyMate was programmed to emit a beep 10 times per day at random intervals in each of ten 90-min time blocks between 7.30 and 22.30. At each beep, participants used the PsyMate to digitally complete a brief beep-questionnaire including current affect (four positive affect and six negative affect items) as well as current context and activities ("daily life activities", "persons present", "physical activity", and "events"). PsyMate positive affect indicators included the adjectives "cheerful", "satisfied", "enthusiastic" and "relaxed" (22). Negative affect was indexed by the adjectives "down", "suspicious", "guilty", "irritated", "lonely" and "anxious". The self-assessments were rated on 7-point Likert scales (ranging from 1="not at all" to 7="very"). Participants were instructed to complete the beep-questionnaire as quickly as possible after the beep.

During both the 5-day ESM baseline assessment and the 5-day ESM post assessment, 10 beep-questionnaires were generated per day. The total number of beep-questionnaires therefore was 50 for both the ESM baseline and ESM post assessments. During the 6-week intervention period, participants completed 10 beep-questionnaires per day for three consecutive days ($10 \times 3 \times 6 = 180$ beep-questionnaires).

The ESM procedure was explained in an initial briefing session, and a practice run was performed to ensure that the participants understood the questions and the device. The debriefing to assess aspects of feasibility of the ESM procedure with PsyMate was scheduled immediately after the ESM baseline assessment.

Intervention

The experimental group received standardized ESM-derived feedback. Feedback sessions immediately followed the weekly ESM procedure. In these face-to-face sessions, feedback was provided by the researcher (a psychologist or psychiatrist). The feedback on participants' momentary affective state in specific daily life contexts and the association with depressive symptoms was given verbally, in writing and graphically (Figure 2). Feedback showed actual levels of positive affect (the mean of the items "cheerful", "satisfied", "enthusiastic" and "relaxed") in the context of daily life activities (Figure 2a and 2b), events and social situations. The second part of the feedback showed changes in positive affect level (Figure 2c) and the number of depressive complaints over the course of the ESM intervention.

The ESM-derived feedback was divided in three modules. In each module, a novel element of feedback was added cumulatively. The first feedback sessions (1 and 2) were focused on positive affect experienced during activities. Feedback sessions 3 and 4 additionally focused on positive affect experienced after daily events, differentiating between affect experienced during events appraised with an internal vs. external locus of control. Finally, feedback sessions 5 and 6 additionally focused on positive affect experienced during social interactions in daily life.

Participants' opinion about the feedback procedures was evaluated at the post assessment.

The pseudo-experimental group was similar in procedure to the experimental group except that no feedback was given. To prevent any effects of different duration of the sessions, this group's sessions were filled with an alternative activity (an additional HDRS interview).

Statistical analysis

Statistical analyses were conducted using STATA 12.1 (30). The data had a hierarchical structure, because multiple assessments of HDRS and IDS depressive symptoms were clustered within patients.

First, to examine the impact of treatment allocation on course of depressive symptoms, mean HDRS total scores were plotted over time (in weeks from baseline to last follow-up) for each of the three groups. The best fit was provided by a linear model (time) for the experimental and control group and a polynomial model (time and time^2) for the pseudo-experimental group.

Next, the XTMIXED command was used to perform a multilevel regression analysis with the two-way interaction between time (in weeks) and treatment allocation as fixed effects, patients as random intercept and a random slope for time. The covariance was set to unstructured. The LINCOM command was used to calculate estimated between-group effects. A difference of three or more points on the HDRS was *a priori* considered as clinically relevant (31,32).

Power calculations using the STATA (30) SAMPSI command were based on previous work (33), and led to an initial sample size of 120 with a power of 84% to detect a 3-point difference in HDRS score (31,32). However, because many participants were excluded, inclusion rate was lower than expected. The eventual number of patients who participated in the trial was 102.

RESULTS

The characteristics of the included subject sample at screening are shown in Table 1. There were no large or significant differences in socio-demographic characteristics between the groups, but at screening there were some differences in clinical features. Compared to the pseudo-experimental and control group, patients in the experimental group used lithium more often and displayed lower HDRS and IDS total scores (Table 1). Group differences in HDRS and IDS or lithium use were non-significant at baseline (two weeks later, i.e., just before start of the intervention) ($F(2;98) = 1.00$, $p = 0.37$; $F(2;98) = 1.52$, $p = 0.22$, and $\chi^2(2) = 4.65$, $p = 0.10$, respectively).

Of the 102 randomized patients, 93 completed at least one HDRS assessment during the post-intervention assessment period of approximately 6 months. There were no large or significant between-group differences in completion of at least one HDRS assessment during this period ($\chi^2(2) = 0.93$, $p = 0.62$). Similar findings were obtained for the IDS ($\chi^2(2) = 0.93$, $p = 0.62$).

Of the 69 patients allocated to the experimental or pseudo-experimental group, 59 (85.5%) completed the 6-week intervention period, comprising 6×3 ESM assessment days and six corresponding intervention sessions. There was no large or significant difference in baseline depressive symptoms between patients who fully completed the intervention period and those who did not (HDRS: $B = 0.76$, $p = 0.72$; IDS: $B = 1.03$, $p = 0.80$). The average number of completed beep-questionnaires in these 59 patients was 135.5 ± 16.5 out of 180, indicating a completion rate of 75.3%. There were no significant differences between the

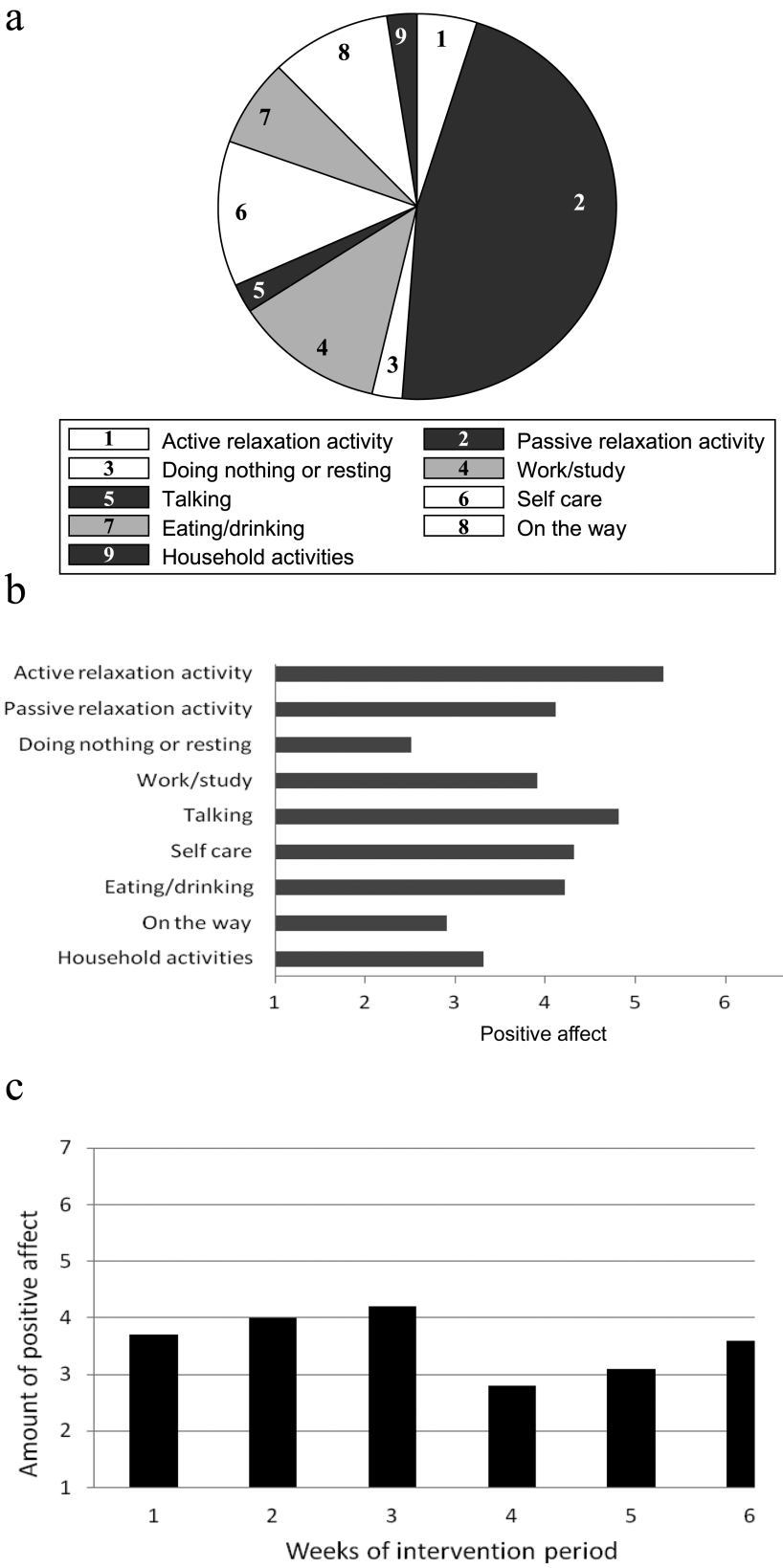

Figure 2 Examples of feedback graphs. (a) Amount of time spent doing different types of activities. (b) Amount of positive affect experienced per type of activity. (c) Mean level of positive affect over the 6-weeks intervention period

Table 1 Demographic and clinical characteristics of the study sample at screening

	Total (n=102)	Experimental (n=33)	Pseudo-experimental (n=36)	Controls (n=33)	Test parameter	df	p
Age (mean±SD)	48.0±10.2	48.7±10.2	46.7±9.6	48.9±10.9	χ^2=2.06	2	0.36
Sex (M/F)	46/56	17/16	14/22	15/18	χ^2=1.11	2	0.57
Educational level							
Low	25	6	9	10			
Middle	38	12	14	12	χ^2=1.73	4	0.79
High	39	15	13	11			
Full or part-time work	35	13	10	12	χ^2=1.12	2	0.57
Living with partner/own family	53	18	17	18	χ^2=0.50	2	0.78
Bipolar disorder	9	5	2	2	χ^2=2.43	2	0.39
DSM-IV Axis I comorbidity	40	12	16	12	χ^2=0.64	2	0.73
HDRS total score (mean±SD)	15.8±4.6	14.1±4.5	16.2±4.8	17.0±4.3	*F*=3.64	2;99	0.03
IDS total score (mean±SD)	36.2±10.4	32.9±10.2	36.4±10.0	39.2±10.5	*F*=3.19	2;99	0.045
GAF symptoms (mean±SD)	56.3±7.7	58.0±7.5	55.9±7.6	55.0±7.8	*F*=1.35	2;95	0.26
GAF disability (mean±SD)	54.6±10.9	54.0±10.5	55.9±11.5	53.9±10.9	*F*=0.34	2;95	0.71
Antidepressant							
Start/switch	19	5	6	8	χ^2=1.04	2	0.66
Maintenance	83	28	30	25			
Current use of benzodiazepines	30	7	10	13	χ^2=2.70	2	0.27
Current use of antipsychotics	26	6	8	12	χ^2=3.18	2	0.24
Current use of hypnotics	22	5	9	8	χ^2=1.19	2	0.55
Current use of lithium	11	7	1	3	χ^2=6.23	2	0.049
Current psychotherapy	10	4	4	2	χ^2=0.77	2	0.77

HDRS – Hamilton Depression Rating Scale, IDS – Inventory of Depressive Symptoms, GAF – Global Assessment of Functioning
Educational level – low: no/primary/low secondary, middle: high school/low vocational, high: higher vocational/university

experimental vs. the pseudo-experimental group in either the mean number of completed beep-questionnaires over the entire intervention period (t=0.91, df=57, p=0.18), or the number of patients who completed all six intervention sessions ($\chi^2(1)=0.69$, p=0.50). Feedback sessions lasted significantly longer (mean: 48.9±11.2 min, range 27-105 min) compared to the pseudo-experimental interview sessions (mean: 39.5±12.9 min, range 15–90 min) (B=9.57, p<0.001).

Figure 3 displays the results of the multilevel regression analysis of the interaction between treatment allocation and time on HDRS and IDS scores. The experimental group demonstrated a significantly greater weekly decline in depressive symptoms over the complete study period compared to the control group (HDRS: B=−0.15, p<0.001; IDS: B=−0.29, p=0.002). Between-group comparisons demonstrated that the decline in depressive symptoms in the experimental group compared to the control group became significant at week 8 (IDS) and 11 (HDRS) and lasted until the end of the study (week 32). Over time, differences between the experimental and control group became stronger, reaching a −5.5 HDRS point difference and a −13.1 IDS point difference at week 32.

The pseudo-experimental group followed a different pattern: it displayed significantly lower HDRS and IDS scores compared to the control group, starting directly after the intervention period (week 7). However, the initial decrease in depressive symptoms did not persist until the last assessment: after week 26 (HDRS) and week 28 (IDS), the difference in depressive symptoms between the pseudo-experimental group and the control group was no longer significant (Figure 3). Compared to the pseudo-experimental group, patients in the experimental group demonstrated clinically relevant lower HDRS scores, *a priori* defined as a decrease of 3 or more points (31,32), at the end of the study (weeks 31 and 32) (B=−3.1, p=0.08 and B=−3.6, p=0.053, respectively).

Patients in the control group did not demonstrate a change in HDRS and IDS scores over the course of the study (B=–0.02, p=0.56, and B=0.01, p=0.92, respectively).

Table 2 displays the results of the patient estimated feasibility of ESM-I. Results indicated that the procedure was not very stressful with respect to number of beeps per day, time to fill out a beep-questionnaire, or sound of the beep. Instructions on how to use the PsyMate were rated as very clear. Table 2 also displays the results regarding participants'

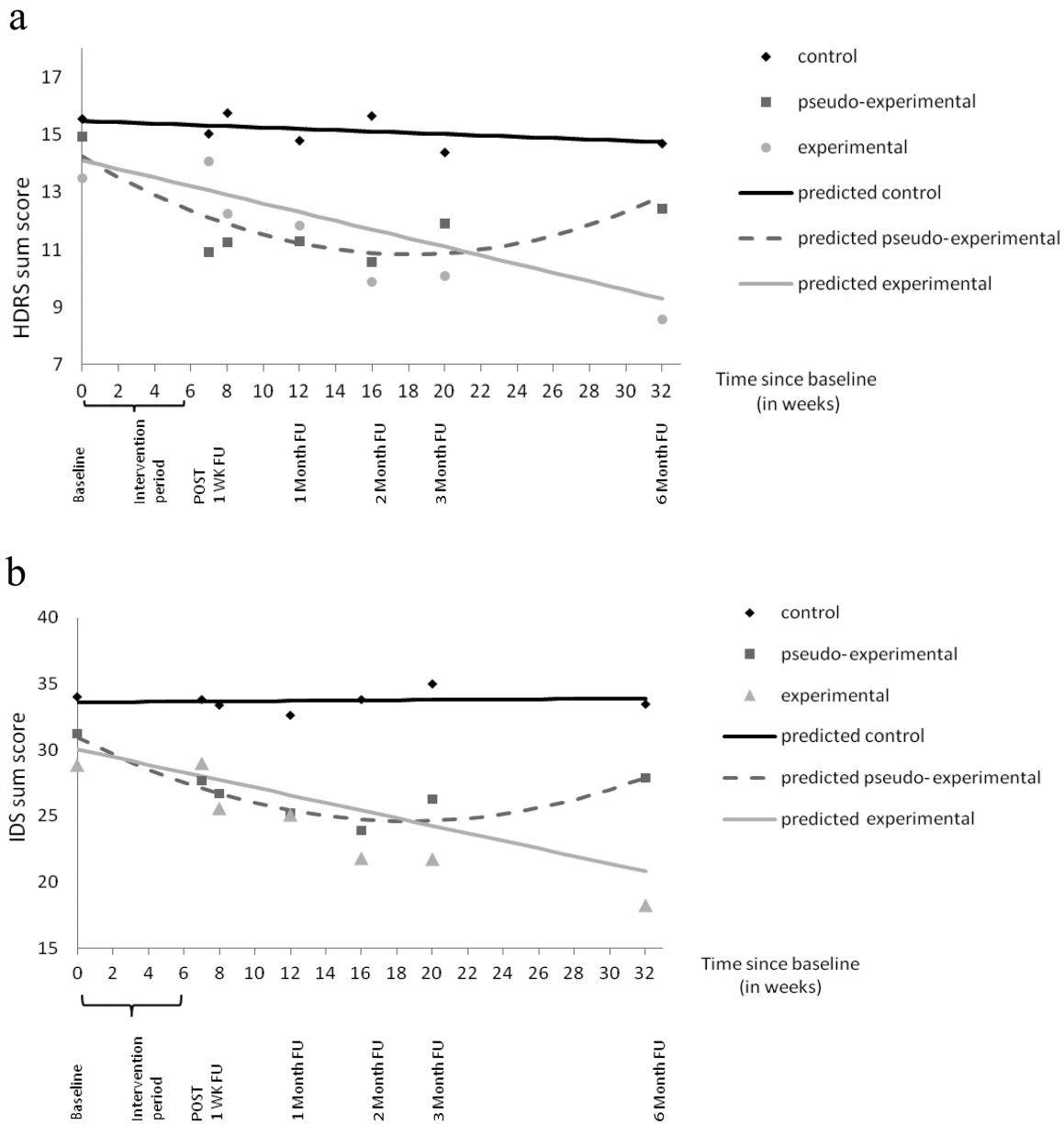

Figure 3 Mean depression scores and predicted lines plotted over time. (a) Hamilton Depression Rating Scale (HDRS). (b) Inventory of Depressive Symptoms (IDS). POST – immediate post assessment, FU – follow-up assessment

opinions on ESM-derived feedback, indicating that feedback on positive affect was relatively easy to understand. Also, participants appreciated getting ESM-derived feedback and tried to apply the suggestions from the feedback to their daily lives.

DISCUSSION

This study shows that the use of add-on momentary assessment technology may be effective as a therapeutic tool to complement standard antidepressant treatment. Allocation to the intervention group with ESM-derived feedback on positive affect was associated with a linear decrease in HDRS depressive symptoms over time that persisted until the last follow-up six months later. The difference with the pseudo-experimental group was clinically relevant and borderline significant.

Although the use of ESM-derived feedback in the treatment of depression has been suggested before (8,10,11,34,35), the present endeavor is, to our knowledge, the first randomized controlled trial that systematically examined ESM-I as a therapeutic tool to provide depressed patients with insight into personalized patterns of positive affect. Relative to receiving passive pharmacological treatment only, depressed patients who received additional feedback on

Table 2 Patient estimated feasibility of the procedure and opinions on the feedback

		Mean (min-max) (scale 1-7)	SD	N (subjects)
Feasibility of the procedure				
	Was the text on screen readable?	5.8 (2-7)	1.4	102
	Was it difficult to switch PsyMate on?	1.6 (1-6)	1.2	102
	Was the PsyMate difficult to control?	1.4 (1-5)	0.8	102
	Were the verbal instructions you received about using the PsyMate clear?	6.6 (3-7)	0.7	102
	Were the written instructions you received with the PsyMate clear?	6.5 (1-7)	1.0	96
	Were the questions you answered on the PsyMate difficult or unclear?	2.6 (1-6)	1.5	102
	Did you find it annoying or stressful to use the PsyMate?			
	With respect to the number of beeps per day?	3.1 (1-7)	1.6	102
	With respect to the time it took to answer the questions for a single beep?	2.5 (1-7)	1.5	102
	With respect to the noises/sound volume?	2.0 (1-7)	1.5	102
ESM-derived feedback				
	I found it easy to understand the explanation given with the feedback	6.1 (4-7)	0.6	25
	The researcher was able to answer my questions well when there was something I didn't understand	6.4 (6-7)	0.5	24
	I was annoyed that I wasn't allowed to get answers about (help) questions that were about my specific problems	2.3 (1-6)	1.6	22
	Would you like to have received more specific advice following the feedback you were given?	3.2 (1-6)	2.0	25
	I appreciated getting a summary of the feedback	6.2 (5-7)	0.7	25
	I found it easy to understand the feedback summary	6.2 (3-7)	0.9	25
	I was happy to get feedback in the form of graphs	6.5 (4-7)	0.7	24
	I found it easy to understand the information in the graphs	6.3 (3-7)	0.9	25
	I have tried to apply the suggestions from the feedback in my daily life	5.4 (3-7)	1.1	25
	The amount of information in the feedback was exactly right	5.4 (4-7)	0.9	25
	The duration of the contact reserved for feedback was exactly right	6.2 (4-7)	0.4	25

personalized opportunities for positive affect demonstrated a clinically relevant and persistent decrease in depressive symptomatology. This could reflect increased insight and accompanying change towards behavioral patterns increasing positive affect. In contrast, the effects in the pseudo-experimental group (self-monitoring without feedback) did not appear to persist. Because these patients may have thought that they were receiving the experimental intervention, this could reflect a placebo response. Another speculation is that these findings result from a short-lived behavioral activation effect attributable to the weekly in-the-office appointments in the intervention period. Moreover, these appointments, in which patients had the opportunity to share their depressive feelings, may have been experienced as more supportive than the experimental feedback appointments, which would explain the stronger immediate reduction in symptoms in this group. Finally, although speculative, the effect of continuous self-monitoring (i.e. without ESM-derived feedback) on depressive symptoms may also be explained by an increased momentary emotional awareness (36). This may make ESM-I an interesting tool to use in mindfulness based cognitive therapy, as suggested by Telford et al (36).

Although interventions based on momentary assessment technology have been developed for several mental disorders and health promoting behaviors (15,37-43), actual implementation in mental health care is still limited (12). Examples are interventions directed to practice anxiety reducing techniques (39), remind patients to use previously learned skills (43), or remind patients about medication adherence (41). Interventions that provided insights derived from momentary assessments were developed for attention deficit-hyperactivity disorder (38) and migraine attacks (44).

Mild to severely depressed patients (45,46) were able and motivated to complete ESM measurements for a longer period of time (18 days), and became actively involved in their recovery process by trying to implement suggestions derived from ESM-feedback into their personal daily life. So, the current results suggest that ESM interventions as an add-on treatment may be both feasible and effective for

patients suffering from mild to severe depressive disorder, including residual depressive states that are associated with substantial morbidity (47-52).

A first limitation of this study is that neither patients nor researchers were blind with regard to treatment allocation. If knowledge of allocation resulted in biased depression ratings by the patient one would, in contrast to the current results, expect that the experimental group (relative to the control group) demonstrated the largest decrease in HDRS depression at the post-intervention assessment. Knowledge of allocation by researchers did not result in biased HDRS depression ratings, because analyses using the IDS self-rating depression scale yielded similar results. Second, although we showed clinically significant effect size differences between the experimental and the pseudo-experimental group, these differences were not conclusive by conventional alpha. This may relate to the fact that the sample was somewhat smaller (n=102) compared to the sample size (n=120) required to obtain power of >0.80. Finally, given that more face-to-face time may reduce depressive complaints, the longer duration (approximately 10 min) of the feedback sessions may have had an influence on the results. However, given the resemblance between the two groups with respect to weekly ESM assessments and subsequent weekly face-to-face contact with the researcher, it is unlikely that this had a large impact on the results.

Using ESM-I in mental health care has the potential to bridge the gap between the therapist office and patients' daily life, by bringing the patients' daily life into the therapist office, and creating the opportunity to extend the therapeutic setting to patients' daily life. The latter may be achieved by a web-based interactive ESM-I application that provides in-the-moment feedback based on previously assessed individual patterns of affect and behavior. This may result in helpful person-tailored insights that not only foster individualized therapy but also the diagnostic process, monitoring of early change in response to medication alterations, or identifying individual affective patterns indicating recovery or relapse (53). This approach could be integrated with cognitive behavior therapy (54) and may create a 24/7 access to and provision of care. Currently, web-based interactive ESM-I applications are in development and studies are required to examine treatment efficacy as well as cost-efficiency.

Although the present findings suggest that providing ESM-derived feedback to depressed patients is feasible and leads to a lasting decrease in depressive symptomatology, these results need to be replicated.

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RESEARCH REPORT

A newly identified group of adolescents at "invisible" risk for psychopathology and suicidal behavior: findings from the SEYLE study

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This study explored the prevalence of risk behaviors (excessive alcohol use, illegal drug use, heavy smoking, reduced sleep, overweight, underweight, sedentary behavior, high use of Internet/TV/videogames for reasons not related to school or work, and truancy), and their association with psychopathology and self-destructive behaviors, in a sample of 12,395 adolescents recruited in randomly selected schools across 11 European countries. Latent class analysis identified three groups of adolescents: a low-risk group (57.8%) including pupils with low or very low frequency of risk behaviors; a high-risk group (13.2%) including pupils who scored high on all risk behaviors, and a third group ("invisible" risk, 29%) including pupils who were positive for high use of Internet/TV/videogames for reasons not related to school or work, sedentary behavior and reduced sleep. Pupils in the "invisible" risk group, compared with the high-risk group, had a similar prevalence of suicidal thoughts (42.2% vs. 44%), anxiety (8% vs. 9.2%), subthreshold depression (33.2% vs. 34%) and depression (13.4% vs. 14.7%). The prevalence of suicide attempts was 5.9% in the "invisible" group, 10.1% in the high-risk group and 1.7% in the low-risk group. The prevalence of all risk behaviors increased with age and most of them were significantly more frequent among boys. Girls were significantly more likely to experience internalizing (emotional) psychiatric symptoms. The "invisible" group may represent an important new intervention target group for potentially reducing psychopathology and other untoward outcomes in adolescence, including suicidal behavior.

Key words: Risk behaviors, adolescents, media consumption, sedentary behavior, reduced sleep, psychiatric symptoms, suicidal behavior, SEYLE

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Risk behaviors (1,2) and psychiatric symptoms (3,4) among youth are a major public health concern. Adolescents establish patterns of behavior and make lifestyle choices that affect both their current and future health and well-being (5-8). It has been shown that some of these choices have a strong association with mental disorders in adulthood (9,10). Given the importance of this transitional period and the acute need for targeted preventive efforts, it is essential to gather information regarding the prevalence of both healthy and risk behaviors, as well as psychiatric symptoms, based on a robust methodology (6,11-14).

Detailed information regarding adolescent risk behaviors is regularly collected in the United States through the Youth Risk Behavior Surveillance System (YRBSS) for the purpose of helping to shape policy and to identify areas for further research. Data from the YRBSS indicate that many pupils engage in behaviors that place them at risk for the leading causes of morbidity and mortality (15,16). These include tobacco, alcohol and substance use (17-19), underweight (20), obesity (21), sedentary behavior (22), unhealthy sleep patterns (23), and truancy (24). Many of these behaviors and conditions frequently co-occur in the same individuals (25). Similar information is not systematically collected and available for other regions of the world, including Europe.

The European School Survey Project on Alcohol and Other Drugs (ESPAD, 26) and the European Monitoring Centre for Drugs and Drug Addiction (27) regularly provide European Union Member States with an overview of alcohol and drug problems in the continent. However, these projects focus primarily on substance abuse, with limited attention to other risk behaviors and lifestyles. Studies that provide a comprehensive picture of adolescent risk behaviors, therefore, are critically needed in Europe (25). There is also recent evidence of an association in adolescents between mental health status, risk behaviors and lifestyles (28-32). To date, no comprehensive cross-national study has been conducted to test associations between risk behaviors, lifestyles and psychiatric symptoms in European adolescents.

The Saving and Empowering Young Lives in Europe (SEYLE) project (33) was developed by a consortium of

twelve European countries (Sweden, Austria, Estonia, France, Germany, Hungary, Ireland, Israel, Italy, Romania, Slovenia, Spain) and supported with funding by the European Commission (grant agreement HEALTH-F2-2009-22309). One of the aims of SEYLE was to gather information about European adolescents' health and well-being. Here we report the main epidemiological findings regarding alcohol and illegal drug use, smoking, sleep behavior, nutrition, physical activity, and sensation seeking, including their associations with self-destructive behaviors and psychiatric symptoms. The hypothesis being tested was that the prevalence of these behaviors varies by age and gender and that behaviors cluster in identifiable subgroups of adolescents suitable for targeted intervention.

METHODS

High school pupils (N=12,395; mean age 14.91±0.90, 83 missing; M/F: 5,529/6,799, 67 missing) were recruited in randomly selected schools (n=179) in eleven European countries. At each country study site, a list of all eligible schools was generated according to specific inclusion and exclusion criteria (33). Ethical approval was obtained from each local ethical committee. Data regarding the study sites, the representativeness of the sample and consent/participation rates of schools and pupils were previously analysed, showing that each study site is reasonably representative of the respective country and that the external validity of the sample is high (34).

A structured self-report questionnaire was administered to adolescents in the participating schools. It covered socio-demographic items, such as sex, age, country of birth of the adolescent and his/her parents, parental employment status, and belonging to a religious group. Risk behaviors were assessed through the Global School-based Student Health Survey (GSHS, 35), which is the international version of the Youth Risk Behavior Survey questionnaire (36). Psychiatric symptoms were assessed by the Beck Depression Inventory (BDI-II, 37), the Zung Self-Rating Anxiety Scale (Z-SAS, 38), the Strengths and Difficulties Questionnaire (SDQ, 39), the Paykel Suicide Scale (PSS, 40) and the Deliberate Self-Harm Inventory (DSHI, 41). The officially translated and validated versions of these instruments were used when available. If the instruments were not available in the required language, they were translated (and back-translated) and linguistically adapted. Internal reliability for all instruments was assessed through Cronbach's alpha, which was high or very high for all of them (34). All the assessment instruments were administered in a single classroom session.

The GSHS items were recoded to identify nine areas of risk behaviors: excessive alcohol use (drinks at least twice a week), illegal drug use (used illegal drugs at least three times during life), heavy smoking (smokes more than 5 cigarettes per day), reduced sleep (sleeps 6 hours per night or less), overweight (body mass index (BMI) above the 95th percentile for age (42)), underweight (BMI below the 5th percentile for age (42)), sedentary behavior (performs physical activity less than once a week), high media use (uses Internet, TV and videogames for reasons not related to school or work for 5 hours or more per day), truancy (skips school at least once a week without being ill or having another legitimate excuse). A dichotomous variable was generated for each risk behavior.

Psychopathological symptoms were recoded to stratify pupils into dichotomous categories: subthreshold depression (BDI-II score <20 and positive on items assessing core symptoms of depression, i.e., sadness and loss of pleasure (43)); depression (BDI-II score ≥ 20); anxiety (Z-SAS score ≥ 60); subthreshold anxiety (Z-SAS score between 45 and 59 (43)); emotional symptoms (SDQ subscale ≥ 7); conduct problems (SDQ subscale ≥ 5); hyperactivity (SDQ subscale ≥ 7); peer problems (SDQ subscale ≥ 6), lack of prosocial behavior (SDQ subscale ≤ 4); non-suicidal self-injury (DSHI score ≥ 3); suicidal ideation (positive on at least one PSS item); and suicide attempter (lifetime history of suicide attempts). All psychopathological measures, with the exception of lifetime suicide attempt, referred to the past two weeks. All measures regarding risk behaviors and psychopathology were further stratified by gender and age. On the basis of the recruited sample, three age groups were identified: 14 years or less (n=4,007), 15 years (n=5,350), 16 years or more (n=2,955).

A chi-square test of independence was used to statistically define the differences between genders and age groups for socio-demographics, risk behaviors and psychopathology.

Latent class analysis (LCA) was applied without any *a priori* assumption about the nature of the latent categorization, thus identifying and characterizing clusters of pupils with similar risk behavior profiles. In order to account for the effect of age on different risk behaviors, a latent class logistic regression (LCLR) test was used with age as a covariate (44). The LCLR models were fitted starting with a two-class model, increasing the number of classes up to four. The Bayesian information criterion (BIC) was compared across models. The lowest BIC was used to identify the most parsimonious and best fitting model. LCLR was applied to the nine risk behaviors in a subsample of 9,035 pupils with no missing information for any risk behaviors. A chi-square test was used to identify significant differences in the socio-demographic and psychopathology variables between the different latent classes of risk identified by the LCA.

A multivariate multinomial logistic regression model adjusted for gender and age group was developed to describe the relationship between belonging to a latent class, selected as the dependent variable, and levels of psychopathology.

For all analyses, a critical value of $p<0.05$ was considered to be statistically significant. All statistical analyses were run in STATA IC 9.0 for Windows.

Table 1 Prevalence (%) of risk behaviors in the adolescent sample

	14 years and below (n=4,007)			15 years (n=5,350)			16 years and above (n=2,955)			All age groups (n=12,328)		
	Male (n=1,833)	Female (n=2,167)	Both genders	Male (n=2,183)	Female (n=3,160)	Both genders	Male (n=1,490)	Female (n=1,456)	Both genders	Male (n=5,529)	Female (n=6,799)	Both genders
Excessive alcohol use	6.4*	4.1	5.2**	10.0*	5.3	7.3	17.7*	10.2	14.1	10.9*	6.0	8.2
Illegal drug use	3.2*	2.0	2.6**	5.8*	2.7	3.9	8.6	7.8	8.2	5.7*	3.6	4.5
Heavy smoking	4.6	6.1	5.4**	10.5*	8.0	9.0	25.0*	16.7	21.0	12.4*	9.2	10.7
Reduced sleep	9.7*	14.6	12.3**	11.4*	17.6	15.1	19.9	21.4	20.7	13.1*	17.4	15.5
Overweight	4.8*	2.5	3.5**	5.4*	1.6	3.1	6.1*	2.3	4.2	5.4*	2.0	3.5
Underweight	3.0	2.8	2.9	3.6	2.4	2.9	4.1	3.4	3.8	3.5	2.8	3.1
Sedentary behavior	9.4*	16.8	13.5**	14.2*	23.4	19.6	17.7*	29.3	23.5	13.6*	22.6	18.5
High media use	10.8*	7.2	8.8**	10.6*	8.8	9.6	14.1*	11.3	12.7	11.7*	8.8	10.1
Truancy	2.8*	1.9	2.3**	4.2*	2.3	3.1	9.3*	4.5	7.0	5.1*	2.6	3.8

*Significant difference between males and females of the same age ($p<0.05$), **significant difference across ages in both genders ($p<0.05$)

RESULTS

Risk behaviors

The prevalence of the nine identified areas of risk behaviors is reported in Table 1.

Less than ten percent (8.2%) of adolescents reported drinking alcohol at least twice a week. More than one-third (35.9%) of those who reported drinking had at least three drinks in one sitting; 14.2% reported having experienced being "really drunk", and 7.7% reported having had a hangover. Alcohol use was higher among males and increased significantly with age.

Less than five percent (4.5%) of the total sample reported having used illegal drugs three times or more during their lifetime. Illegal drug use was higher among males and increased with age. More than ten percent (10.7%) of the sample reported smoking at least 5 cigarettes per day and more than forty-five percent (45.8%) reported smoking cigarettes at least once in their lifetime. Slightly more than ten percent (10.3%) of the sample reported having started smoking when they were eleven years old or younger.

More than fifteen percent (15.5%) of the adolescents reported sleeping 6 hours per day or less. Reduced sleep was more frequent among females and among older age pupils. More than forty percent (41.8%) reported sleeping less than 8 hours per day; slightly more than one-third (34.2%) reported waking up often or being always tired in the morning, a finding significantly more common among females (37.1% vs. 31.7%, $p<0.05$); approximately twenty-five percent (25.4%) of adolescents reported the habit of taking a nap in the afternoon, with a statistically significant higher prevalence among females than males (27.8% vs. 23.4%, $p<0.05$).

More than three percent (3.5%) of pupils had a BMI above the 95th percentile for age (42), with the prevalence of overweight being higher among males and increasing with age. Three percent (3.1%) of adolescents had a BMI below the 5th percentile for age (42), with no significant gender or age differences. More than one fourth (26.5%) of the sample did not regularly have breakfast, a behavior significantly more common in females than males (30.8% vs. 21.2%, $p<0.05$). Six percent (6.1%) reported never eating fruit or vegetables, while 62.5% reported eating them at least once every day. Less than twenty percent (18.5%) reported performing physical activity less than once a week. Sedentary behavior was more common among females and increased with age. More than two thirds (68.8%) of the adolescents reported performing sports on a regular basis, with a significant gender difference (77.3% males vs. 61.8% females, $p<0.05$).

Approximately ten percent (10.1%) of the adolescents reported spending at least 5 hours per day watching TV, playing videogames or surfing the Internet for reasons not related to school or work. This percentage was significantly higher in males and increased with age. Almost seventy-five percent (74.5%) of the adolescents reported using their own computer to surf the Internet, while 2.5% of the sample reported having never used the Internet.

Less than four percent (3.8%) of the adolescents reported often missing school without permission. This behavior was significantly more frequent among older pupils and among males. Ten percent (10.4%) reported having been in a physical fight in the past 12 months and almost half of them (45.2%) reported having started the fight. Approximately one-sixth (16.9%) of the pupils reported having been a passenger in a vehicle with a driver who had been drinking. Ten percent of the 14-year olds, 19% of the 15-year olds and

Table 2 Prevalence (%) of psychiatric symptoms in the adolescent sample

	14 years and below (n=4.007)			15 years (n=5.350)			16 years and above (n=2.955)			All age groups (n=12.328)		
	Male (n=1,833)	Female (n=2,167)	Both genders	Male (n=2,183)	Female (n=3,160)	Both genders	Male (n=1,490)	Female (n=1,456)	Both genders	Male (n=5,529)	Female (n=6,799)	Both genders
Subthreshold depression	25.7*	32.0	29.1**	24.8*	35.4	31.1	27.1*	35.0	31.0	25.8	34.2	30.4
Depression	3.8*	9.2	6.7**	4.2*	10.6	8.0	7.4*	12.8	10.1	4.9	10.6	8.1
Subthreshold anxiety	14.0*	26.6	20.8**	14.7*	30.8	24.2	19.7*	31.1	25.3	15.8	29.5	23.3
Anxiety	1.6*	4.6	3.2**	2.4*	6.9	5.1	3.2*	8.8	6.0	2.3	6.6	4.7
Emotional symptoms	3.0*	9.9	6.7**	2.3*	11.0	7.4	4.3*	13.6	8.9	3.0	11.2	7.5
Conduct problems	10.7*	7.5	9.0**	11.4*	8.6	9.8	16.1*	9.3	12.7	12.5	8.4	10.3
Hyperactivity	10.9	9.1	9.9	8.6	9.0	8.8	9.6	9.8	9.6	9.6	9.2	9.4
Peer problems	3.1	2.7	2.9**	3.7*	2.7	3.1	7.0*	3.3	5.1	4.4	2.9	3.6
Lack of prosocial behavior	9.5*	3.1	6.0**	9.9*	4.0	6.5	12.7*	4.7	8.7	10.6	3.9	6.9
Non-suicidal self-injury	6.8*	10.7	8.9**	7.6	8.8	8.3	9.7	12.2	11.0	7.9	10.2	9.1
Suicidal ideation	21.2*	35.4	28.9**	23.5*	39.3	32.8	30.1*	42.5	36.2	24.5	38.7	32.3
Suicide attempts	2.2*	4.2	3.3**	2.8*	4.7	3.9	4.1*	7.5	5.8	3.0	5.1	4.2

*Significant difference between males and females of the same age ($p<0.05$), **significant difference across ages in both genders ($p<0.05$)

42.9% of the 16-year olds reported having had a sexual intercourse, with a significantly higher prevalence among males in each age group. Less than four percent (3.3%) of those engaging in sexual intercourse reported never or seldom having used a condom, with no significant age differences.

Psychiatric symptoms

The prevalence of psychiatric symptoms is reported in Table 2.

Approximately one third (30.4%) of pupils experienced subthreshold depression, with girls having a significantly higher prevalence than boys (34.2% vs. 25.8%, $p<0.05$). Approximately eight percent (8.1%) of the sample was categorized as depressed, with a significantly higher prevalence in females (10.6% vs. 4.9%, $p<0.05$). The prevalence of depressive symptoms increased with age.

More than twenty percent (23.3%) of pupils experienced subthreshold anxiety, with the prevalence increasing with age and being significantly higher among females (29.5% vs. 15.8%, $p<0.05$). Almost five percent (4.7%) of pupils reported severe to extreme anxiety, with the prevalence increasing with age and being significantly higher among girls (6.6% vs. 2.3%, $p<0.05$).

Emotional symptoms were reported by 7.5% of the sample. Their prevalence increased with age and was significantly higher among girls (11.2% vs. 3.0%, $p<0.05$).

Conduct problems occurred in 10.3% of the sample. Their prevalence increased with age and was significantly higher among boys (12.5% vs. 8.4%, $p<0.05$). Symptoms of hyperactivity were present in 9.4% of the pupils and did not differ significantly by gender.

More than three percent (3.6%) of the sample experienced peer problems; the prevalence increased with age and was significantly higher among boys (4.4% vs. 2.9%, $p<0.05$). Nearly seven percent (6.9%) of the sample reported lack of prosocial behavior; the prevalence increased with age and was significantly higher among boys (10.6% vs. 3.9%, $p<0.05$).

Suicidal ideation was present in approximately one third of the sample (32.3%), with a significantly higher prevalence in older pupils and among girls (38.7% vs. 24.5%, $p<0.05$). More than four percent (4.2%) of the sample reported attempting suicide during their lifetime, with a significantly higher prevalence among girls (5.1% vs. 3.0%, $p<0.05$). The frequency of suicide attempts for both genders increased with age.

Classes identified through LCA and their correlates

LCLR models were fitted to the nine risk behaviors reported above. A three-class model best fit the data. Figure 1 presents the patterns of response probability profiles for each of the three classes. The first class ("low-risk"), comprising 57.8% of the sample (M/F=2,557/3,497), included

Figure 1 Results of the latent class analysis

students with no or very low frequency of risk behaviors. The second class ("high-risk"), comprising 13.2% of the sample (M/F=622/562), included pupils who scored high on all risk behaviors. The third class, comprising 29% of the sample (M/F=687/1,109), included pupils who were positive for high media use, sedentary behavior and reduced sleep. This class was labelled "invisible risk", as these behaviors are generally not obvious or recognized by observers, including parents and teachers, to be associated with mental health problems.

Table 3 describes the relationship between the classes identified through LCA and socio-demographic variables. The percentage of pupils not born in the study site country was significantly higher in the high-risk compared to both the invisible- and the low-risk groups (10.0% vs. 6.9% and 4.8%, $p<0.05$). A similar pattern was observed for pupils with parents not born in the study site country. Having someone in the family who had lost his/her job during the previous year was significantly more frequent in the high- and invisible-risk groups than in the low-risk one (11.6% and 12.1% vs. 8.3%, $p<0.05$). Living with a single parent was significantly more frequent in the high-risk than in the invisible-risk group (31.1% vs. 23.6%, $p<0.05$).

Table 3 Socio-demographic features (%) by latent class risk groups

Socio-demographic features	Low-risk class n=6,054 (M/F=2,557/3,497)	High-risk class n=1,184 (M/F=622/562)	Invisible-risk class, n=1,796 (M/F=687/1,109)
Females*	57.8	47.5	61.8
Not born in the country*	4.8	10.0	6.9
Parents not born in the country*	15.1	27.0	20.6
Doesn't belong to a religious denomination	31.2	34.0	31.3
Someone in your family lost job last year**	8.3	11.6	12.1
Single parent household*	17.5	31.1	23.6

*The three groups differ significantly from each other ($p<0.05$), **the high-risk and the invisible-risk groups differ significantly from the low-risk group ($p<0.05$)

Table 4 Psychiatric symptoms (%) by latent class risk groups

Psychiatric symptoms	Low-risk class, n=6,054 (M/F=2,557/3,497)	High-risk class, n=1,184 (M/F=622/562)	Invisible-risk class, n=1,796 (M/F=687/1,109)
Subthreshold depression**	29.4	34.0	33.2
Depression**	4.2	14.7	13.4
Subthreshold anxiety**	19.0	31.3	31.0
Anxiety**	2.5	9.2	8.0
Emotional symptoms*	5.8	9.0	11.6
Conduct problems*	6.4	23.2	11.5
Hyperactivity*	6.1	18.6	11.8
Peer problems***	2.3	3.0	5.0
Lack of prosocial behavior**	4.5	9.9	8.1
Non-suicidal self-injury*	5.5	22.3	12.4
Suicidal ideation**	27.1	44.0	42.2
Suicide attempter*	1.7	10.1	5.9

*The three groups differ significantly from each other ($p<0.05$), **the high-risk and the invisible-risk groups differ significantly from the low-risk group ($p<0.05$), ***the low-risk and the invisible-risk groups differ significantly from the high-risk group ($p<0.05$)

Table 5 Results of multivariate multinomial logistic regression of latent class variables by gender, age group and psychopathological scores (n=8,579)

	Invisible-risk vs. low-risk class RRR (95% CI)	High-risk vs. low-risk class RRR (95% CI)
Gender (male/female)	0.95 (0.84, 1.08)	0.51* (0.44, 0.60)
Age group 15 years/ 14 years or younger	2.41* (2.08, 2.79)	4.50* (3.55, 5.69)
Age group 16 years or older/14 years or younger	7.88* (6.67, 9.30)	27.62* (21.66, 35.23)
Subthreshold depression	1.10 (0.96, 1.27)	1.21* (1.02, 1.43)
Depression	1.97* (1.50, 2.58)	1.82* (1.30, 2.53)
Subthreshold anxiety	1.62* (1.40, 1.88)	1.58* (1.32, 1.90)
Anxiety	1.81* (1.31, 2.52)	1.93* (1.31, 2.86)
Emotional symptoms	0.80 (0.63, 1.02)	0.47* (0.34, 0.65)
Conduct problems	1.24 (1.00, 1.52)	2.74* (2.21, 3.40)
Hyperactivity	1.59* (1.29, 1.95)	2.49* (1.99, 3.13)
Peer problems	1.23 (0.89, 1.70)	0.47* (0.29, 0.74)
Lack of prosocial behavior	1.60* (1.26, 1.74)	1.54* (1.17, 2.03)
Non-suicidal self-injury	1.40* (1.13, 1.74)	2.99* (2.37, 3.79)
Suicidal ideation	1.29* (1.12, 1.48)	1.30* (1.09, 1.55)
Suicide attempter	1.69* (1.22, 2.35)	2.62* (1.83, 3.74)

RRR – relative risk ratio, *p=0.05 (two-tailed tests)

As shown in Table 4, the prevalence of depressive and anxiety symptoms (both severe and subthreshold) and of suicidal ideation was very similar in the invisible- and the high-risk groups, and significantly higher in each of these groups compared with the low-risk one ($p<0.05$). Emotional symptoms and peer problems were significantly more prevalent in the invisible-risk than in the high-risk group, and more frequent in both these groups than in the low-risk one ($p<0.05$). Conduct problems, hyperactivity, non-suicidal self-injury and lifetime suicide attempts were significantly more prevalent in the high-risk group compared with both the invisible- and the low-risk ones ($p<0.05$).

Multivariate multinomial logistic regression

Results from the multivariate multinomial logistic regression model of psychiatric symptoms and latent classes, adjusted for gender and age, are presented in Table 5. Symptoms of depression, anxiety, lack of prosocial behavior and suicidal ideation were associated with significant and similarly increased relative risk ratios of being in both the invisible- and the high-risk groups. Having symptoms of hyperactivity, non-suicidal self-injury or having attempted suicide were associated with significantly increased relative risk ratios of being in the high-risk group and, even if at a lower level, of being in the invisible-risk group.

DISCUSSION

The results of this study indicate that the prevalence of risk behaviors and psychopathology among European adolescents is relatively high. Almost all studied risk behaviors show an increase with age and most of them are significantly more frequent among boys. The only exceptions are sedentary behavior and reduced sleep, which are more frequent among girls, who also have more internalizing (emotional) psychiatric symptoms, such as depression, anxiety and suicidal ideation.

In this large sample, LCA identified three groups of adolescents. The first group, representing 13.2% of the adolescents, scored high on all examined risk behaviors and can be called "high-risk group". Most interventions today target this population (45,46). The largest group, comprising almost two thirds (57.8%) of the adolescents, scored low on most risk behaviors and has accordingly been called "low-risk group". Even pupils in this low-risk group, however, reported suicide attempts (1.7%), suicidal ideation (27%), subthreshold depression (29%) and subthreshold anxiety (19%). These findings highlight the need for large-scale preventive interventions and outreach in schools, as reported in previous studies (43,47).

Most importantly, this study also identified, for the first time, a third group labelled the "invisible-risk" group, which includes 29% of the adolescents. These pupils clustered on three specific risk behaviors (reduced sleep, low physical activity and high media use), while simultaneously having significantly increased prevalence of psychiatric symptoms. The level of psychiatric symptoms found in this "invisible" group is, in many cases, very similar to the high-risk group. The group includes adolescents who spend an excessive amount of time watching TV, being on the Internet or playing videogames, including going to sleep late in order to prolong the use of these media activities and who, perhaps as a direct consequence, neglect other healthy activities such as sports. Adult observers (e.g., parents, teachers and mental health professionals) do not generally perceive these behaviors as particularly harmful or reasons for concern. Nevertheless, the high- and the invisible-risk groups have a very similar prevalence of depressive symptoms, anxiety symptoms and suicidal thoughts. In comparison with pupils in the high-risk group, those in the invisible-risk group have a higher prevalence of emotional symptoms and peer problems but a lower prevalence of conduct problems and hyperactivity. The differences between the high- and invisible-risk groups do not depend on gender representation in these groups, as multivariate analyses indicated that these associations remained significant when adjusting for age and gender.

Adolescents in the invisible- and high-risk groups have different patterns compared with the low-risk group concerning country of origin (adolescent or one of his/her parents born outside study site country), belonging to a single parent household, or a family where a parent lost his/her

job in the previous year. Interestingly, belonging to a religious denomination (as perceived by adolescents), which is generally considered protective (48), did not confer any difference in risk group membership. These findings suggest that adolescents in the invisible group may more likely have a lower socioeconomic status and thus, perhaps, be even more invisible to existing interventions and outreach activities.

A major strength of this study is the large sample of adolescents (n=12,395), recruited from randomly selected schools across study sites in eleven European countries, which are reasonably representative of the respective European country (34). The students were recruited and evaluated with homogeneous procedures across countries in terms of inclusion and exclusion criteria and outcome measures. Furthermore, the study comprised a very large geographic area. One potential limitation of this study is that all data were collected through self-report. Although it has been shown that data acquired through self-report are reasonably reliable (36,49,50), the prevalence of risk behaviors and psychopathology may have been underestimated. Another limitation is that only one site per country was chosen for study participation. Even though study sites were shown to be reasonably representative of the respective country, inclusion of more than one site per country might have improved representation of the urban and rural areas and possibly allowed stratification of risk groups by population density.

The results of this study are in agreement with the classical distinction between internalizing and externalizing disorders (51), with the former (emotional) being more common among girls and the latter (behavioral) among boys. Similar patterns of age- and gender- related differences have been previously reported in American studies, such as the Study of Disruptive Behavior Disorders in Puerto Rican Youth (5), the NIMH Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) Study (13) and the YRBSS (15). Until now, investigations conducted in Europe, such as the ESPAD study (26), focused exclusively on substance abuse and did not include a wider range of risk behaviors as in the SEYLE study. Regarding substance abuse, however, SEYLE results are in line with previous findings, confirming the high burden of substance abuse among European adolescents and its relationship with various types of psychopathology (52). In general, SEYLE results indicate that it would be a great advantage to establish within Europe a system to routinely collect data regarding adolescents' mental health and lifestyles, as regularly done in the United States with the YRBSS.

Because specific age- and gender-related differences change over time, monitoring them may have important implications for the prevention of risk behaviors. The increase in risk behaviors and psychopathology by age, as observed in this study, is very steep but in agreement with other investigations (53,54). Importantly, in the SEYLE data, a simultaneous increase in the prevalence of each assessed risk behavior was observed for each single increase in years of age. However, data about the longitudinal life-time trajectory of these risk behaviors and their predictive value and potential consequences for subsequent psychopathological and psychosocial outcomes are not yet available. Nonetheless, the cross-sectional correlations between the high- and invisible-risk groups and psychopathological variables, as presented here, warrant the development of systematic psychosocial support and intervention for these pupils.

In summary, the results of this study confirm the need for early prevention and intervention in the mental health field (55,56). The most common risk behaviors among girls are a reduced number of hours of sleep and a sedentary lifestyle, while drug and alcohol use are more common among boys. Thus, preventive interventions should be tailored specifically for boys and girls. The most important findings of this study arise from the LCA. In addition to the classical low- and high- risk groups, we identified a third group, accounting for almost one third of the adolescents, who engage in behaviors that are easily overlooked as they are generally not perceived by adults, including mental health professionals, as troublesome. Pupils in this invisible-risk group show high rates of depression, anxiety and suicidal ideation, which are at the same level as among pupils belonging to the high-risk group. While most parents, teachers and clinicians would react to an adolescent using drugs or getting drunk, they may easily overlook adolescents engaging in unobtrusive behaviors such as watching too much TV, not playing sports, or sleeping too little. The causality of the relationships between these risk behaviors and psychopathology remains unclear. However, common psychiatric disorders, such as depression, are already known to often show bidirectional relationships with reduced sleep (57), low levels of activity (58) and high media consumption (59). Thus, our findings have implications for gatekeepers delivering information and education about adolescent health and lifestyle to pupils and parents, as well as for policy makers and clinicians. While discussions with adolescents often focus on substance abuse and delinquency, the risk behaviors identified here need to be considered, and special attention given to encouraging sufficient sleep, participation in sports and using new media moderately.

These data afforded a unique opportunity to profile typical schools throughout Europe serving regular pupils. However, a number of unanswered questions remain. For example, not having more specific individual socio-economic data on the participating adolescents precluded better identification of the relationship of these factors with risk behaviors and psychiatric symptoms. An epidemiologic household study should be conducted, including detailed socioeconomic data collection, to help explore the correlations between psychopathology, risk behaviors and the general socio-economic status. Moreover, this study evaluated psychiatric symptoms cross-sectionally in the general population through psychometric self-report instruments. Diagnostic interviews would allow a better understanding of the relationship between psychiatric disorders and risk behaviors.

Regardless of these limitations, the SEYLE study established an important multi-national cohort of European adolescents that ideally will be studied longitudinally, in order to identify the trajectories from risk behaviors to psychopathology and thus help to elucidate causality. Such a study would also allow for the assessment of the course and prognostic trajectories of various adolescent risk behaviors.

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Gene-environment interaction in evolutionary perspective: differential susceptibility to environmental influences

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By tradition, psychiatrists have been concerned with the nature, origins, sequelae and treatment of mental disorders. When it comes to etiology and the role of genetics, psychiatric geneticists have focused on genotype-phenotype associations, that is, direct links between particular polymorphisms and particular disorders, as well as genetic vulnerability to adversity, as revealed in studies of gene-environment interaction.

Here we offer a new way of looking at these psychiatric-genetic issues. Rather than conceptualizing some genetic polymorphisms as genes *for* some disorder or as functioning as "risk genes", increasing the likelihood that disorder will emerge in the face of contextual adversity, we contend that many genes which have been the focus of psychiatric-genetic research may actually make people more vs. less sensitive to the environment and thus differentially susceptible to developmental experiences and environmental exposures.

Moreover, and contrary to prevailing thinking, we argue that select polymorphisms should be conceptualized as "plasticity" rather than "vulnerability" genes (1), making individuals not just more likely to succumb to mental disorders when they experience adversity, but more likely to benefit from supportive conditions *and* to be adversely affected by negative ones (2,3).

This way of conceptualizing gene-environment interaction derives from an evolutionary analysis of human development (1,3,4), one which explicitly acknowledges that there are both costs and benefits of plasticity, with some costs related to the fact that the future is inherently uncertain; as a result, sometimes, when prior developmental experience shapes later functioning, a costly "mismatch" will ensue, as the world encountered later in development proves inconsistent with that experienced at an earlier – and influential – point in time. This suggests that natural selection would have "hedged its bets", making some individuals more and other less – or hardly at all – developmentally plastic. This further implies that developmental plasticity should be regarded as a phenotype or individual-difference construct in its own right (4).

As it turns out, many gene-environment interaction findings prove consistent with this view that some individuals are more affected – due to their genetic make-up – by environmental exposure in a "for-better-and-for-worse" manner (2), depending on the environment to which they are exposed. For illustrative purposes we here focus on two widely studied polymorphisms.

TWO PLASTICITY GENES?

Like other polymorphisms, the serotonin transporter gene, 5-HTTLPR, and the dopamine receptor gene, DRD4, have long been regarded by psychiatric geneticists as "vulnerability genes" predisposing carriers of particular alleles to depression and attention-deficit/hyperactivity disorder (ADHD), respectively, in the face of adversity. Ever more evidence indicates, however, that they might better be regarded as "plasticity genes", making carriers of the putative risk alleles especially susceptible to environmental influences – for better and for worse.

Regarding 5-HTTLPR, individuals carrying one or more short alleles have been found to show greater "for-better-or-for-worse" plasticity when the rearing predictor and child outcome are, respectively, maternal responsiveness and moral internalization, child maltreatment and antisocial behavior, and supportive parenting and positive affect. Such differential-susceptibility-related findings also emerge (among male African-American adolescents) when perceived racial discrimination is used to predict conduct problems; when life events are used to predict neuroticism and life satisfaction of young adults; and when retrospectively reported childhood adversity is used to explain aspects of impulsivity among college students. In fact, a recent meta-analysis reveals that, in the case of Caucasian children under 18 years of age, short-allele carriers are more susceptible than long-allele carriers to both positive and negative developmental experiences (5).

Regarding DRD4, heightened if not exclusive susceptibility has emerged in the case of carriers of the 7-repeat allele in contexts where the environmental predictor and developmental outcome were, respectively, maternal positivity and prosocial behavior; early nonfamilial childcare and social competence; contextual stress and support and adolescent negative arousal; childhood adversity and young-adult persistent alcohol dependence; and newborn risk status (i.e., gestational age, birth weight for gestational age, length of stay in the hospital) and observed maternal sensitivity. Notable again is that a meta-analysis of gene-environment interaction research involving dopamine-related genes found that children 8 and younger respond to positive and negative experiences in a manner consistent with differential susceptibility (6).

FUTURE RESEARCH DIRECTIONS

Despite ever-growing gene-environment interaction evidence consistent with the plasticity-genes' view under consideration, many issues remain to be explored or illuminated.

In addition to 5-HTTLPR and DRD4, there is evidence that other well studied polymorphisms may operate as plasticity factors (e.g., brain-derived neurotrophic factor, BDNF; monoamine-oxidase A), rendering some individuals more susceptible to environmental influences – for better and for worse (4). Especially important to appreciate is that most polymorphisms that have emerged as potential plasticity factors derive from psychiatric-genetic studies guided by vulnerability thinking. Researchers should thus expand their list of candidate genes beyond such polymorphisms associated with disturbed functioning, ideally to ones thought to influence plasticity. A recent example of such an effort yielding evidence of differential susceptibility focused on the CHRNA4 genotype, because of its role in acetylcholine production, a component strongly related to plasticity and learning (7).

Rather than regarding some individuals as plastic or malleable (e.g., 5-HTTLPR short-allele carriers) and others as not (e.g., homozygous long-allele carriers), it probably makes more sense to think of a gradient, with some being especially malleable, some reasonably malleable, some less so, and some not at all. Certainly that is suggested by work using multiple plasticity genes, as it reveals a dose-response relation between number of plasticity genes and the extent to which individuals are affected by environmental exposures in a for-better-and-for-worse manner (4). Future work of this kind should be guided by a "system-level genetic approach" involving the compositing of putative plasticity genes based on knowledge of particular biological processes or pathways, such as the dopaminergic or serotonergic system, or neurological morphology.

Furthermore, most differential-susceptibility-related research has been observational in character. This can challenge interpretation because environmental experiences may be selected rather than randomly assigned, creating the possibility that gene-environment correlation masquerades as gene-environment interaction. One solution to this problem involves conducting intervention experiments with random assignment of participants to experimental or control conditions, a work still in its early stages (4,8). Even though such efforts are limited to examining just the "for-better" side of plasticity, they still enable evaluation of whether allelic variants observed to make individuals especially vulnerable to adversity in observational research also predispose carriers to benefit disproportionately from intervention efforts designed to promote positive functioning. Just as importantly, such intervention work can determine whether, as presumed by differential-susceptibility thinking, allelic variants associated with resilience in the face of adversity lead carriers to benefit less – or not at all – from interventions designed to foster positive functioning.

Consideration of the notion that developmental plasticity be regarded as an individual-difference construct raises the issue of whether plasticity is domain general or domain specific. That is, are more malleable individuals especially responsive to and influenced by a wide variety of environmental conditions and developmental exposures and other individuals not particularly influenced by the same large set of experiences? Or are individuals mostly "mosaics" of plasticity, being highly sensitive to some contextual conditions but not others and/or with respect to some developmental outcomes but not others?

However surprising it might seem, there is some evidence for the domain general view. Consider the results of two interventions which used strikingly dissimilar methods to promote different aspects of development. In one case the intervention sought to foster sensitive parenting in order to reduce toddler's externalizing behavior (9) and cortisol-related stress reactivity (10), whereas in the other a computerized instructional program was employed to foster preschooler's phonemic awareness and, thereby, early literacy (11). Despite the dramatic differences in the interventions and in the features of development studied, it was children carrying 7-repeat DRD4 allele who benefited disproportionately, if not exclusively, from both. Before it can be concluded, however, that plasticity is more domain general than domain specific, far more work is required. We suspect that some individuals will be on the extremes of plasticity – highly responsive or virtually unaffected by almost all contextual conditions – but that most might fall somewhere between these extremes.

CONCLUSIONS

An evolutionary perspective led us not only to appreciate the costs as well as benefits of developmental plasticity but, as a result, why individuals should vary in their susceptibility to environmental influences. Moreover, this framework led us to expect – and find – that individuals long regarded as especially vulnerable to adversity due to their genetic make-up disproportionately benefit from supportive experiences – due to the very same genetic factors. This led to re-conceptualizing some presumed vulnerability genes as putative plasticity genes.

Despite the evidence summarized here and elsewhere (1,4), much still needs to be learned about when and why genetic factors operate as plasticity rather than just vulnerability factors. Nevertheless, the study of differential susceptibility to environmental influences has already highlighted both the benefits of considering human development from an evolutionary perspective and the drawbacks of focusing disproportionately on contextual risk, dysfunctional development and vulnerability – in that it makes it difficult to discover that the very genetic factors that might be related to dysfunction when individuals experience contextual adversity can also

be related to especially competent functioning when they encounter supportive developmental contexts.

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The evolution of psychoeducation for bipolar disorder: from lithium clinics to integrative psychoeducation

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Coping and living with bipolar disorder is complex and sometimes counterintuitive. It demands a number of attitudes and aptitudes that include a huge emotional insight, healthy and regular lifestyle, skills to identify subtle changes and motivation to reach full treatment adherence. Patients' engagement and proactive attitude are a must for a successful therapeutic outcome. This may partly explain the therapeutic impact of psychoeducational programs in this disorder.

However, the history of group psychoeducation in bipolar disorder is full of ups and downs. Interestingly enough, worldwide-respected opinion leaders in group therapy were initially not very enthusiastic with the use of such strategy with bipolar patients. I. Yalom, for instance, defined a bipolar patient as "one of the worst calamities that could befall group therapy" (1). Since then, the practice of psychoeducation has been evolving together with the conceptualization of bipolar disorder.

THE PIONEERS: LITHIUM CLINICS

The ancestors of psychoeducation have to be found in the so-called "lithium clinics", which appeared both in Europe and the US in the 1970s, and were typically run by a team consisting of a psychiatrist and support staff (nurses and sometimes psychologists). The focus was on pharmacological treatment monitoring, although some information and mutual support was also offered. This would correspond to a 100% biological understanding of the disorder which, perhaps, was trying to counterbalance psychodynamic views in the pre-lithium era. The efficacy of such a setting has been described in several reports (e.g., 2), unfortunately without an appropriate comparative methodology.

INFORMATION-BASED PSYCHOEDUCATION

After the era of lithium clinics, several reports of information-based psychoeducation appeared in the literature, mainly produced in the US and in the Netherlands, a country with a long tradition of both bipolar psychoeducational efforts and self-help and advocacy groups. The studies by E. van Gent (3) showed, initially, a remarkable effect on stigma and self-esteem and, later on, in a three-year follow-up, a significant decrease of adherence problems and hospitalizations amongst patients receiving psychoeducation. However, this information-based view of psychoeducation reflected a poorly integrated approach to bipolar disorder, where proactiveness was not seen as a core issue in the treatment.

ATTITUDES & APTITUDES PSYCHOEDUCATION PROGRAM

In 2003, our group (4) published the first randomized controlled trial of the efficacy of psychoeducation in the prevention of recurrences in bipolar disorder. The model used stressed the importance of illness awareness, self-management, early-warning signs identification, habits regularity, treatment adherence and avoiding drug misuse. It has been defined as "behavioural psychoeducation", but we rather think of it as an "attitudes & aptitudes" psychoeducation program. This definitely corresponded to a view of bipolar disorder as a complex condition involving not only biological etiological factors but also psychological and social variables that may act as triggering factors, modulators or mediators. The Barcelona Psychoeducation Program showed a huge efficacy in preventing all sort of recurrences both at two-year and five-year follow-up (5). This study has been successfully replicated using exactly the same intervention, showing excellent results regarding admission prevention (6).

THE LIMITATIONS OF THE CURRENT MODEL

However, even this highly disseminated program had some relevant limitations which, perhaps, may reflect the view regarding the disorder that we had when the program was started (middle 1990s). The program hardly promoted physical health – by means of prescribing a regular diet, promoting regular exercise, etc. – an issue that nowadays is well known to be essential in the management of any chronic psychiatric condition, and bipolar disorder and schizophrenia in particular, due to the increased risk of obesity and metabolic syndrome (e.g., 7). Moreover, recent studies showed that a behavioral weight-loss intervention significantly reduced weight over a period of 18 months in

overweight and obese adults with serious mental illness (8), although the effect of physical exercise on mood is limited according to a recently published controlled trial (9).

Furthermore, the program did not contemplate the importance of illness progression or sensitization. Although in the middle 1990s kindling theories (10) were an outstanding research topic, the current knowledge on cognitive impairment and illness staging (see 11) was yet to be achieved. Interestingly, many psychological interventions – including psychoeducation, cognitive-behavioral therapy and family psychoeducation – lose efficacy when implemented in patients with a high number of previous episodes. In a 18-month follow-up randomized controlled trial, Scott et al (12) did not find significant differences in terms of recurrences between two groups of patients with severe and recurrent bipolar disorder, receiving respectively 22 sessions of cognitive-behavioral therapy and treatment as usual. A post-hoc analysis demonstrated that adjunctive cognitive-behavioral therapy was effective compared with treatment as usual only in those patients with fewer than 12 previous episodes.

The importance of introducing psychological interventions as soon as possible has also been highlighted in a subanalysis by Colom et al (13), showing the lack of efficacy of group psychoeducation in patients with more than 15 previous episodes who were euthymic at the study onset. Both the likelihood of suffering from cognitive impairment and the difficulties of changing habits may be more common in more veteran patients, which could contribute to the lack of efficacy of psychoeducation in this subgroup. Similarly, Reinares et al (14) showed that, despite the general good outcomes associated with family group psychoeducation, its efficacy seemed to be limited to patients in the initial stages of the illness (15). There may be a progressive impairment of coping abilities in patients in advanced stages, increasing vulnerability and decreasing resilience as the illness progresses. These coping abilities could possibly be resumed with a proper intervention.

PSYCHOLOGICAL TREATMENTS OF TOMORROW: TOWARDS INTEGRATIVE PSYCHOEDUCATION

The integrative approach to bipolar disorder should target both syndromal and functional recovery. Unfortunately, most of the available treatments – both pharmacological and psychological – are usually more successful at reaching just clinical rather than full recovery. Interestingly enough, the first randomized controlled trial of the efficacy of a brand new therapy labeled "functional remediation" has been recently published (16). This is a 21-session group program that includes neurocognitive techniques, training, psychoeducation on cognition-related issues and problem solving, aiming to avoid problems with generalizability of similar programmes adopted in the field of schizophrenia. The mentioned study was a three-arm multicenter trial comparing the efficacy of functional remediation with psychoeducation and with treatment as usual, including a total of 268 outpatients. Functional remediation had a large effect on functioning – mostly on occupational and interpersonal domains – and did differ from treatment as usual, but did not significantly differ from psychoeducation, which however had a smaller effect on functioning.

An integrative model of psychoeducation should, hence, include strategies which are useful not only to patients in earlier stages of the illness but also to those with some impairment. It should also promote healthy habits, including the regular practice of physical exercise. Moreover, given the problems in social cognition which persist even when the patient is asymptomatic (17), a more significant effort to address these issues should be made.

On the other hand, functional remediation and psychoeducation may take different places in the available arsenal of psychotherapies for bipolar disorders. Whilst psychoeducation may be the first choice treatment as a prophylactic add-on for many bipolar patients (mostly for those in early and medium stages of the illness), functional remediation is the treatment of choice for patients showing a clear cognitive and functional impairment who would probably respond poorly to psychoeducation.

There is a need to better clarify what works for whom in the field of bipolar therapies, also considering the impact on preventing manic vs. depressive episodes. Polarity index is a novel and validated metric depicting the relative antimanic vs. antidepressive prophylactic efficacy of an intervention in the maintenance treatment of bipolar disorder (18) and may apply both to pharmacological and non-pharmacological treatments. According to this index, patient group psychoeducation, although being the most balanced intervention, may have a greater effect in preventing depressive episodes, whilst caregiver psychoeducation may have a greater effect in preventing manic episodes (19).

In conclusion, since psychoeducation is inspired both by the current understanding of bipolar disorder and by our sensitivity to our patients' needs, it cannot be a static and unchangeable treatment, but rather a dynamic program which will evolve following the evolution of that understanding and those needs.

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Moving beyond intelligence in the revision of ICD-10: specific cognitive functions in intellectual developmental disorders

A lower level of intelligence, as measured by IQ, has historically been the central defining criterion of mental retardation (MR). The use of IQ scores in terms of standard deviation units from the mean is the basis for defining MR in the ICD-10 and DSM-IV-TR, and more recently for defining intellectual disability (ID) in the DSM-5. Similarly, ID is defined by the American Association on Intellectual and Developmental Disabilities as an IQ score approximately two standard deviations below the mean (1).

However, in recent years, an increasing number of researchers and clinicians have expressed the view that measurements of IQ fail to capture individual differences in cognitive dysfunction. The heterogeneity of cognitive dysfunction and consequent adaptive behavior profile in persons with MR is one of the reasons leading the working group in charge of this issue within the revision of the ICD-10 to propose a new definition for intellectual developmental disorders (IDD) in the upcoming 11th edition of the diagnostic system (2).

In 2011, the WPA Section on Psychiatry of Intellectual Disability started a mini-Delphi process with an international panel of experts to produce a consensus document on this issue. The present letter reports the results of the systematic mapping (3) of the international literature included in this process, focusing on current models of intelligence, multi-component and specific cognitive functions, and the relationship between intellectual and affective assessment, as relevant for defining IDD.

A total of 7,948 articles matched the key words. After titles were checked, 3,179 were selected. After abstracts were read, 2,497 were excluded as they were not relevant to the mapping topic, and 114 were excluded because they were not in English. After reading the remaining articles in full, 177 papers were included as relevant to search questions.

The mapping of current theoretical approaches identified limitations of IQ as an indicator of the adaptive complexity and dynamism of human intellectual functioning and pointed out the need for a shared model and comprehensive definition of intelligence. Of the available approaches, the most frequently used refers to a unitary capacity, articulated in complex functions. A second evolving group of theories identifies a key role of interdependent but specialized factors, such as specific cognitive functions. There is a neuro-bio-psychological evidence in support of both approaches, but multi-component models seem to prevail. Experimental data indicate that the same IQ score can correspond to very different cognitive profiles, and that functional limitations and problem behaviors associated with IDD correlate with impairment of specific cognitive functions more than with IQ (4,5).

To address the limitations of the current conceptualization of MR, the ICD-11 working group proposed revised diagnostic criteria for IDD, based on a more articulated model of cognitive impairment. This approach juxtaposes a new concept of cognitive characterization to that of intelligence and complements the measurement of IQ with the assessment of specific cognitive functions and a contextualised description of consequent adaptive and learning difficulties (2).

Within this new approach, cognitive skills should be assessed through tests, semi-structured observations, and direct clinical examination. The tests should combine the measurement of IQ with that of several aspects of executive functioning, including perceptual reasoning, processing speed, verbal comprehension, as well as the assessment of attention, perception and working memory. The evaluation should aim to identify the cognitive dysfunctions that have the greatest negative impact in terms of behavior, adjustment, autonomy, and above all quality of life, across the lifespan. The instruments to assess specific cognitive functions should have a low cost, in order to allow fast assimilation by professionals practicing in low-income countries (6). Production and distribution by international non-profit organizations could greatly facilitate this effort.

In conclusion, within the proposed ICD-11 framework for characterization of IDD, there is a need for neuropsychological measures that can be readily adapted to different levels of severity, and that are easy to apply in clinical and research practice. The evolving understanding of how environmental and cultural factors influence development should promote a continuing search for assessment models and practices that capture developmental pathways of cognition in persons with IDD. Naturalistic, multidisciplinary and multicentric studies could provide useful data to this purpose (7).

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Extreme attributions predict suicidal ideation and suicide attempts in bipolar disorder: prospective data from STEP-BD

Individuals with bipolar disorder (BD) experience high rates of suicide, with previous reports indicating that 25 to 50% of people with this disorder have a lifetime history of a suicide attempt (1). Few studies of patients with BD have evaluated psychosocial predictors of suicidal ideation and suicide attempts (2,3).

Negative life events and hopelessness often precipitate suicide attempts (2), but not all individuals who experience negative events go on to make a suicide attempt. In BD and major depressive disorder, the tendency to make "extreme" rigid, black-or-white attributions about the causes of life events (e.g., "I'm a total failure") is associated with a poorer course of illness (4-6). However, whether extreme attributions are linked to suicidal ideation and suicide attempts in BD remains unexplored.

The present study evaluated the relationship between extreme attributions, history of suicide attempts, and the occurrence of suicidal ideation among depressed patients with BD.

Study participants were 100 depressed patients with DSM-IV bipolar I (61%) or II (39%) disorder. This was a subsample of the 293 outpatients enrolled in the randomized, controlled trial (7) comparing the efficacy of psychotherapy and collaborative care treatment as part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (7), who had received an assessment of attributional style and had valid data about lifetime suicide attempt history.

Diagnoses of BD and evaluation of suicide attempts were made by study psychiatrists using the Affective Disorders Evaluation (8). The Clinical Monitoring Form (9) was used to evaluate mood symptoms, including presence of suicidal ideation, at each visit over a one-year period.

The Attributional Style Questionnaire (ASQ, 10) was used to measure extreme attributions. Participants rated the perceived cause of twelve hypothetical life events on 7-point Likert scales in terms of internality ("due to me" vs. "due to others"), stability ("always" vs. "never present"), and globality ("all situations" vs. "only this situation"). Consistent with prior studies (4-6), we computed variables representing total attributional style (ASQ total) and the number of "extreme" attributions (ratings of 1 or 7). Internal consistency was good (alpha=.76).

Of the 100 participants, 31% had a previous history of a suicide attempt. Seventy-one percent experienced the occurrence of suicidal ideation across up to a year of follow-up.

Logistic regression analyses indicated that, after controlling for bipolar status (I vs. II), patients who made more extreme attributions were more likely to have a history of making a suicide attempt (OR=1.06, p=0.04, ΔR^2=0.06). This effect remained significant when controlling for initial symptoms of depression and mania, bipolar type, gender, age, age of onset of BD, presence of comorbid anxiety disorder, number of lifetime anxiety disorders, number of comorbid psychiatric disorders, and sleep (OR=1.08, p=0.02, ΔR^2=0.07), but was reduced to non-significance when controlling for number of lifetime episodes of depression and mania/hypomania (OR=1.06, p=0.12, ΔR^2=0.03). In contrast, general attributional style did not significantly predict history of suicide attempts (OR=1.01, p=0.61, ΔR^2<0.01).

Hierarchical logistic regressions indicated that there was a significant interaction between extreme attributions and history of a suicide attempt in predicting the occurrence of suicidal ideation during the study's prospective period, above and beyond initial depression severity (OR=1.20, p=0.03, ΔR^2=0.07). Extreme attributions predicted a significantly greater likelihood of the occurrence of suicidal ideation among patients with a suicide attempt history (t=2.08, p=0.04), but not among patients without a suicide attempt history (t=-0.64, p=0.52). These results remained significant when controlling for psychosocial treatment condition, initial symptoms of mania, number of psychosocial treatment sessions, days in the study, bipolar I or II status, age, gender, education, number of lifetime episodes of depression and mania/hypomania, number of comorbid psychiatric diagnoses, psychiatric medication load, and age at onset of BD (interaction term: OR=1.37, p=0.01). In contrast with extreme attributions, general attributional style did not significantly predict the occurrence of suicidal ideation, either as a main effect or in interaction with suicide attempt history (OR=1.01, p=0.89, ΔR^2<0.01).

Our findings suggest that evaluating extreme thinking styles may be important in identifying which bipolar patients are at risk for suicide. Limitations of this study include that the sample was receiving psychosocial treatment for bipolar depression, so that the extent to which these results generalize to patients not in psychotherapy remains to be explored. Due to the low base rate, we could not evaluate suicide attempts prospectively, so that the causal direction between extreme attributions and suicide attempts is not clear.

In conclusion, clinicians should consider evaluating extreme attributions in BD, as they may be relevant to understanding and potentially reducing the substantial burden of suicide in this disorder.

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Fasting during Ramadan is associated with a higher recurrence rate in patients with bipolar disorder

Fasting during the Ramadan month is a cornerstone of Islam. Several disturbances of biological rhythms have been reported in fasters during that month (1), but there is no consensus on the impact of fasting on patients with bipolar disorder (2,3).

We conducted a study in 170 patients with stabilized bipolar disorder (DSM-IV criteria), including 111 fasters and 59 non-fasters, targeting the Ramadan month of two successive years (2011 and 2012). Participants were recruited among outpatients at the Casablanca Ibn Rushd University Psychiatric Center. They were assessed for depression by the Hamilton Depression Rating Scale, for mania by the Bech-Rafaelsen Scale, for anxiety by the Hamilton Anxiety Rating Scale, for stress by the Perceived Stress Scale (4), for religiosity by the Religious Practices Index (5). Sleep and eating patterns, use of stimulants and other drugs, and plasma lithium levels were also assessed. The evaluations were conducted one week before the month of Ramadan (W−1), on the second and fourth week of Ramadan (W2 and W4), and two weeks after the end of the Ramadan month (W+2).

The mean age of patients was 36.2±12.0 years; 51.2% were women; 62.4% were single; 51.8% were professionally active. The number of mood episodes per year was 0.72± 0.45. All patients were under mood stabilizers; 81.2% were also receiving antipsychotics; 21 patients were also receiving antidepressants.

The relapse rate among fasters was 33.3% (37/111), including 14 relapses at W2 (7 manic and 7 depressive), 9 more at W4 (6 manic and 3 depressive) and 14 more at W+2 (13 manic and one depressive). The relapse rate among non-fasters was 15.3% (9/59), including 3 manic relapses at W2, 4 more relapses at W4 (1 manic and 3 depressive) and two more at W+2 (one manic and one depressive). The difference between fasters and non-fasters was statistically significant (χ^2=6.38, p=0.012). Fasting during the Ramadan month increased the risk of relapse among bipolar patients by 2.77 fold in comparison to non-fasters (95% CI: 1.233 to 6.254, p=0.014).

The number of sleeping hours decreased more significantly during the month of Ramadan among fasters (from 9.39±1.45 at W−1 to 7.34±1.64 at W4) as compared to non-fasters (from 9.92±1.28 at W−1 to 8.59±2.17 at W4) (p<0.0001). Coffee consumption during the month increased in fasters (from 1.47±1.51 cups at W−1 to 1.94±1.94 at W4) more than in non-fasters (from 1.61±1.59 cups at W−1 to 1.76±1.75 at W4), but the difference was not statistically significant. Serum lithium levels did not differ significantly between fasters (mean: 0.57±0.65 mEq/l at W−1 and 0.65± 0.71 mEq/l at W4) and non-fasters (mean: 0.57±0.11 mEq/l at W−1 and 0.64±0.75 mEq/l at W4). After controlling for the number of sleeping hours, coffee consumption and serum lithium levels, the recurrence rate remained higher in fasters than in non-fasters.

This study suggests that fasting during the month of Ramadan may have a negative impact on patients with bipolar disorder. This could lead to preventive measures against relapses for persons with bipolar disorders in Muslim countries (more than 1 billion people worldwide). Studies on larger samples are needed to replicate these findings.

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This is why there is hope for psychiatry

In the past twenty years there has been a growing concern that psychiatry as a profession is in crisis (1-3) and that there is a shortage of psychiatrists worldwide (4), which may have an impact on the delivery of effective mental health care. Attempts to counterbalance this trend have been on the agenda of many international associations, including the WPA, the European Psychiatric Association (EPA) and the American Psychiatric Association, amongst others (5-7). Many of these associations have established specific workstreams aimed at addressing the educational needs of early career psychiatrists, and identifying the reasons behind low levels of interest and recruitment into psychiatry among medical students (e.g., 8).

The WPA was one of the first associations to give attention to early career psychiatrists, with a specific young psychiatrist scientific track made available at World Congresses, starting from Hamburg in 1999 up to Buenos Aires in 2011. At these meetings a range of activities were dedicated to early career psychiatrists, including scholarships, training seminars, scientific symposia, and informal get-together meetings.

The WPA Executive Committee, in the triennium 2008-2011, placed great emphasis on developing and inspiring early career psychiatrists, with one of the Action Plan goals being "to promote the professional development of early career psychiatrists worldwide" (9). A WPA Council of Early Career Psychiatrists was appointed, with 60 countries from all continents each nominating an early career psychiatrist to participate and represent their peers. The Council has implemented a specific action plan aimed at identifying problems concerning early career psychiatrists and promoting their professional development through a series of activities (10,11).

Three surveys have been conducted by this group: one dealing with training in psychotherapy (12), one with training and practice of early intervention in mental health (13), and one dealing with the transition from psychiatric training to independent practice (14), which represents a crucial step in the professional development of every psychiatrist.

Also based on this experience within the WPA, early career psychiatrists are now being considered equal partners in research activities as well. For example, within a large European Commission funded project, the ROAMER, a survey was conducted on priorities for mental health research, with the participation of different categories of stakeholders (15). Associations of psychiatric trainees were included, as well as associations of psychiatrists, of other mental health professionals, and organizations of users and/or carers. Moreover, the European Federation of Psychiatric Trainees (EFPT) and the Early Career Psychiatrists Committee of the EPA have recently created a task force on research, with several projects carried out so far (6), and many others still ongoing.

The importance of supporting early career psychiatrists is now well recognized worldwide, and the majority of national psychiatric associations have now a section for this category of psychiatrists, with its own rules and by-laws. There are also some transnational groups, for example in East Africa, Asia and Europe, whose common interest is the professional development of early career psychiatrists (16-18).

Many educational activities worldwide are now co-organized with early career psychiatrists, who have identified the areas where they have the most significant educational needs and gaps, including psychopathology, forensic psychiatry, leadership and research skills, and comorbidity of mental disorders with physical diseases (6,7,19-21). Several actions have been taken to address these educational needs, including the organization of scientific events and the production of books (22) and educational modules. For example, the EPA runs a highly successful annual summer school that brings together many early career psychiatrists working in Europe every year. Other courses have been organized in collaboration with various EPA sections, such as those on philosophy and psychiatry and on consultation and liaison psychiatry. A further educational activity, run by the Association for the Improvement of Mental Health Care Programmes, includes courses on leadership and research skills, and promotes research projects conducted by early career psychiatrists (e.g., 23). Among the educational activities of the WPA (24), the Section on Education, which has several early career psychiatrists among its members, is currently promoting a range of initiatives aimed to improve the availability and quality of psychiatric education.

An important challenge for early career psychiatrists today is the promotion of the public image of psychiatry (25,26). The specific skills needed to interact effectively with families, administrators, journalists and the legal system should become a formal component of post-graduate training and continuing medical education of every early career psychiatrist (6).

Many further activities promoted by or devoted to early career psychiatrists could be listed here. However, what we wanted to highlight with this letter is that psychiatry is still alive, growing and developing and will certainly survive the current "crisis". We should consider the present one as a developmental phase, that can help us improve our training, research and practice. This in turn will take us further towards our ultimate aim – that of improving the health and well-being of our patients.

The WPA, with its early career psychiatrists' programmes and initiatives, has played a crucial role in these

developments. Early career psychiatrists are ready to contribute to further activities.

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A hidden face of community mental health care in Africa: specialist care from private providers in Kenya

In their systematic review of community mental health care in Africa, published in *World Psychiatry*, Hanlon et al (1) point out that "in the low-income countries of the Africa region, community mental health care is largely restricted to mental health care delivered by primary care workers, with specialist mental health workers (usually psychiatrists and psychiatric nurses) tending to provide care through hospital-based outpatient clinics". An article by McDaid et al (2), also published in the journal, notices that non-governmental organizations can support primary care by "building on social capital in communities". A hidden face of community mental health care in Africa, however, is specialist care from private providers, especially psychiatrists and psychiatric nurses. A good example is Kenya, where three quarters of doctors and two thirds of nurses work in the private sector (3).

We administered a structured interview, between July and September 2012, to 11 private mental health specialists (8 psychiatrists, 3 psychiatric nurses), sampled using snow-balling. Five of them were from Nairobi and six – including all nurses – from central province. Three of them were women. Their average age was 46 years, and time in private sector 9.2 years. Respondents had a mean active case load of 128 mental health patients, and the mean number of mental health patients seen per clinic day was 5.

The leading diagnosis for which 55% of people attended private clinics was common mental disorders, while 25% had severe mental disorders, 15% substance use disorders, and 5% epilepsy, child mental disorders or mental retardation. Slightly over half (56%) were women, representing a departure from psychiatric hospitals, where the majority are men affected by psychosis (4). In a context where the term "mental" is associated with psychotic behaviour, a private clinic in the community may offer a less stigmatizing option of care. Privately owned clinics are also more "private" to clients in that care can be sought with greater confidentiality.

Private clinics operated on average 24 hours per week (range 12-40), and specialists saw their patients for an average of one hour on the first visit (range 50-90 minutes) and half an hour at follow-up (range 15-45 minutes). Typical wait time was 20 minutes (range 3-60 minutes). Patients were followed up on average monthly (maximum every 8 weeks). In the previous month, respondents referred a mean of 13% of clients for hospitalization. Two out of the three psychiatric nurses ran general health clinics, with only 5% of patients seen for mental health reasons. The third ran an exclusively mental health clinic.

The mean fee of Int$ 13.0 (Ksh 500) charged by psychiatric nurses represents approximately 2.5 days work by an unskilled agricultural labourer (5) – a significant, but not unattainable sum. The average psychiatrist fee of Int$ 55.3 (Ksh 2,100) (higher in Nairobi than the province) represents one month's salary for the same agricultural worker, making it inaccessible to most. Nearly two thirds of respondents modulated fees, based on session length and ability to pay, judged in part by patient occupation.

We found a large cross-over between private and public sectors: eight out of the eleven private specialists split their time with the public sector. Six of them said the care they offered in private practice was different – mainly with a greater choice of drugs, especially atypical antipsychotics. One respondent noted: "At government clinics, prescriptions are dictated by the available medications". Continuity of care was also highlighted: "I am able to constantly follow the client". In a context of under-paying public health providers, private employment may be seen as cross-subsidizing public health care.

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The WPA website (www.wpanet.org): a living platform to improve the identity and image of the organization

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In a previous article (1), we reviewed the development of the WPA website since it was renewed in April 2010. In this paper, we provide an update of its content, performance and impact in the light of the latest statistics, and discuss the perspectives to improve its efficiency.

The WPA website (along with the WPA News, the quarterly official news bulletin of the WPA), has been playing an important role in improving the organizational image and identity of the Association, in line with its Action Plan of 2008-2011 and that of 2011-2014. It was reconstructed both in its content and aesthetics in April 2010, with a general perspective of reaching elegancy in simplicity.

The WPA Secretary General, as the editor of these media channels, monitored this route with the collaboration of the WPA Executive Committee members, the WPA Secretariat staff, and the IT staff, responsible for the technical administration. This process of renewal and reconstruction allowed to host many organizational and educational material and to achieve high performance and impact.

CONTENT

The WPA website hosts now more than 3,500 items. These cover news on the activities of the WPA components and information on WPA Secretariat activities, scientific meetings, publications, scientific sections, and educational activities (see 2-5). Furthermore, information on the structure and work of the WPA Committees and the WPA normative instruments are posted. In addition, educational and training material of interest to clinicians, researchers and educators working in the field of psychiatry and mental health can be read.

A highly visited section of the website hosts World Psychiatry, the WPA official journal, which has now an impact factor of 8.974. Current and all past issues of this journal, now ranking no. 5 out of 126 psychiatric journals, can be read and freely downloaded not only in English but also in various languages. Either full issues or individual papers or abstracts are available in Spanish, Chinese, Russian, French, Arabic, Turkish, Japanese, Polish, Romanian, and Italian.

A WPA e-learning programme was developed and implemented in 2010. This program covers videos and slide sets of prominent scientific lectures and presentations from the WPA Congresses, starting with a selection from the WPA International Congress 2009, Florence. Currently, 33 lectures in video and synchronized .ppt format are uploaded.

Four guidance papers, produced during the past triennium, are available on the website in several languages. They deal with steps, obstacles and mistakes to avoid in the implementation of community mental health care, how to combat stigmatization of psychiatry and psychiatrists, mental health and mental health care in migrants, and protection and promotion of mental health in children of persons with severe mental disorders. Three sets of slides, based on WPA books, are available in 18 different languages, dealing with the recognition, epidemiology, pathogenesis, cultural aspects, medical costs and management of the comorbidity of depression with diabetes, heart disease and cancer. An educational module on physical illness in patients with severe mental disorders is also available on the website in several languages.

Furthermore, an online public education program, aiming to provide high-quality and reliable scientific information on mental health and psychiatry to non-professionals, is also hosted in the website. The content of these pages is in the process of improvement in collaboration with the relevant scientific sections. Results of two surveys, conducted in collaboration with WPA member societies, exploring their views about various issues concerning diagnosis and classification of mental disorders and strategies to reduce the treatment gap for mental disorders, appeal the interest of the visitors, as well as information on WPA-WHO collaborative activities (see 6,7) and WPA-funded research projects (e.g., 8).

The WPA website also hosts some essential documents for the benefit of improving the ethical and scientific quality standards of our profession: the Madrid Declaration on Ethical Standards; the WPA template for undergraduate and postgraduate education in psychiatry and mental health; recommendations for relationships of psychiatrists, health care organizations working in the psychiatric field, and psychiatric associations with the pharmaceutical industry, and recommendations on best practices in working with service users and family carers.

PERFORMANCE

The performance of the website is followed closely with periodic analysis. During the period between April 12, 2010 and November 12, 2013, 298,741 people have visited the WPA website, making 430,079 visits. These visits came from 218 countries/territories, practically covering all parts of the world. It is remarkable that the number of countries in which WPA has national member societies is 118.

Hence, the WPA is even reaching over its organizational limits by its website. The average number of visits per day was 328, and the average number of pages per visit was 3.32.

The website is continuously visited by new people, with the proportion of new visitors being nearly 70%. This is also reflected in the fact that 67% of the visitors of the website reach it via "searchengines", while 18% via "referring sites", and 15% using "direct traffic".

It is interesting to check the days of the week that people prefer to visit the WPA website. During the first three days of the week (Monday through Wednesday), visits are more frequent than the other four days, with an increasing trend, while from Thursday to Sunday it decreases continuously. It seems the visitors start their week by visiting the pages of the WPA website.

IMPACT

One of the widely used criteria to measure the impact of a website is "page rank check", a free service provided by Google. The page rank value indicates the importance of a particular website/page. Being an objective measure of its citation significance, it also corresponds well with people's subjective idea of importance.

Currently, the page rank of the WPA website is 7/10 (that is, the page rank value is 7 from 10 possible points), which reflects a high impact compared to many other similar websites.

FUTURE PERSPECTIVES

Currently, the WPA website is a highly active electronic platform fulfilling two main functions at the same time: as an international "news channel" on psychiatry and mental health, and as an "archive" of training and educational materials, and basic reference documents. Considering its international character, these two functions could be improved to become more comprehensive and interactive. This is possible via advances in the relations with other international organizations in the fields of mental health and psychiatry. Giving high priority to international solidarity in psychiatry may enhance this process. In fact, a website is a highly flexible living platform, a work in progress where we can explore further improvements continuously.

As the editor and the WPA Secretary General, I have been facilitating this process with the cooperation of the WPA Executive Committee members of 2008-2011 and of 2011-2014, and our past and current secretariat staff, Anna Engstrom, Francesca Sotgiu and Pamela Atiase, and our IT staff at the Istanbul-based agency SaglikBahcesi. Their enthusiasm, support, and skilful efforts are highly appreciated.

I hope the visitors of the WPA website will continue to support us in improving its quality by sending their contributions and comments.

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Following the development of ICD-11 through *World Psychiatry* (and other sources)

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The World Health Organization (WHO) is developing the 11th edition of the International Classification of Diseases and Related Health Problems (ICD-11), whose publication is currently expected in the year 2015. The WPA is partnering with the WHO in the production of the chapter on mental and behavioural disorders.

The principles guiding the development of that chapter have been summarized by the International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders in a paper published in *World Psychiatry* in June 2011 (1). That paper emphasizes that the chapter is being produced in consultation with relevant stakeholders, including WHO member countries, several professional groups, and users of mental health services and their families. Attention to the cultural framework is being a key element. The revision is seen as an opportunity to improve the classification's clinical utility, particularly in primary care settings and in low- and middle-income countries (see also 2,3).

The ICD-11 classification will remain based on descriptions of the prototypes of the various mental disorders rather than on operational diagnostic criteria.

The advantages and possible limitations of this approach have been discussed in several *World Psychiatry* articles and commentaries (e.g., 4-11). A major argument in favour of this approach is that it is congruent with the spontaneous clinical process, which does not involve checking in a given patient whether each of a series of symptoms is present or not, but rather checking whether the characteristics of the patient match one of the templates of mental disorders that the clinician has built up in his/her mind through his/her training and clinical experience (see also 12). Moreover, some recent research focusing on various classes of mental disorders (i.e., personality, eating, anxiety and mood disorders) suggests that a diagnostic system based on refined prototypes may be as reliable as one based on operational criteria, while being more user friendly and having greater clinical utility (e.g., 13,14).

Eleven Working and Consultation Groups have been appointed by the WHO for the development of the ICD-11 chapter on mental and behavioural disorders. These groups include several WPA officers and experts among their chairpersons and members (see 15,16). Several of these groups have recently published background papers or preliminary reports on their activities.

Highlights of the expected convergences and divergences between the ICD-11 and DSM-5 approaches to the classification of mood disorders have been presented in several papers in various journals (e.g., 17,18) and in a supplement to *World Psychiatry* (19). Among the convergences are the inclusion of activation/energy as a defining symptom for mania, and the acknowledgement 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, the ICD-11, as the DSM-5, will allow the clinician to record the occurrence of a subsyndromal anxiety syndrome in a patient with a major depressive episode, by using a specifier. Bipolar II disorder is expected to be recognized as a distinct diagnostic entity in the ICD-11, 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. Furthermore, the ICD-11 is going to exclude from the diagnosis of depressive episode, in line with the ICD-10 but differently from the DSM-5, "normal bereavement reactions appropriate to the culture of the individual concerned" (see 20-26).

Highlights of the expected convergences and divergences between the ICD-11 and the DSM-5 in the classification of stress-related disorders have been presented in a recent *World Psychiatry* paper (27). In the ICD-11, the proposed new grouping of "disorders specifically associated with stress" will include adjustment disorder (whose description will undergo a major revision, involving an increased specification of symptoms), post-traumatic stress disorder (PTSD) (whose diagnosis is going to be based on three well-identified core symptoms), and complex PTSD (a new category marked by disturbance in the domains of affect, self-concept and relational functioning in addition to the three core features of PTSD). Acute stress reaction will be conceptualized as a normal reaction and thus classified in the chapter corresponding to ICD-10 "Factors influencing health status and contact with services" (while "acute stress disorder" is still included in the section on trauma- and stress-related disorders in the DSM-5).

Proposals for the ICD-11 section on feeding and eating disorders have been summarized in another *World Psychiatry* article (28). These include a broadening of the category of anorexia nervosa through dropping the requirement for amenorrhoea, extending the weight criterion to any significant underweight, and extending the cognitive criterion to include developmentally and culturally relevant presentations. Furthermore, a severity qualifier "with dangerously low body weight" is expected to distinguish the severe cases of anorexia nervosa that carry the riskiest prognosis. The bulimia nervosa category is likely to be extended to include subjective binge eating, and binge eating disorder will be included as a specific diagnostic category, in agreement with the DSM-5.

The input of the ICD-11 Working Group on Intellectual Developmental Disorders has been presented in a paper published in *World Psychiatry* in 2011 (29) and is further discussed in this issue of the journal (30). Intellectual developmental disorders (a term replacing "mental retardation") are proposed to be defined as "a group of developmental conditions characterized by significant impairment of cognitive functions, which are associated with limitations of learning, adaptive behaviour and skills". The Working Group further advised that intellectual developmental disorders be incorporated in the larger grouping of neurodevelopmental disorders, that current subcategories based on clinical severity be maintained, and that problem behaviours be described as associated features.

The Chairman of the ICD-11 Working Group on Psychotic Disorders recently reported (31) about the expected convergences and divergences in the ICD-11 and DSM-5 approaches to the classification of those disorders. In the ICD-11, as in the DSM-5, Schneider's first-rank symptoms are going to be deemphasized in the description of schizophrenia, and the subtypes of the disorder are going to be omitted. These subtypes will be replaced by six symptom specifiers (positive symptoms, negative symptoms, depressive symptoms, manic symptoms, psychomotor symptoms, and cognitive impairment). Contrary to the DSM-5, 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.

Preliminary reports about the development of the ICD-11 sections on mental disorders in children and adolescents (32), somatic distress and dissociative disorders (33) and personality

disorders (34) are also available in the recent literature. A more general discussion of diagnostic topics related to DSM-5 and ICD-11 classifications can be found in recent issues of *World Psychiatry* (35-45).

Internet-based field testing of proposals for ICD-11 will be implemented through the Global Clinical Practice Network, currently consisting of more than 7,000 individual mental health and primary care practitioners (www.globalclinicalpractice.net).

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