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Background: There is increasing awareness of a crisis in psychiatric research and practice. Psychopathology and clinical judgment are often 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. *Aim*: The aim of this review was to examine the clinical judgment in psychiatry, with special reference to clinimetrics, a domain concerned with the measurement of clinical phenomena that do not find room in customary taxonomy. *Methods*: A MEDLINE search from inception to August 2011 using the keywords "clinical judgment" and "clinimetric" in relation to psychiatric illness for articles in English language was performed. It was supplemented by a manual search of the literature. Choice of items was based on their established or potential incremental increase in clinical information compared with use of standard diagnostic criteria. The most representative examples were selected. *Results*: Research on clinical judgment has disclosed several innovative assessment strategies: the use of diagnostic transfer stations instead of diagnostic endpoints using repeated assessments, subtyping versus integration of different diagnostic categories, staging, macro-analysis, extension of clinical information beyond symptomatic features. Evidence-based medicine does not appear to provide an adequate scientific background for challenges of clinical practice in psychiatry and needs to be integrated with clinical judgment. *Conclusions*. A renewed interest in clinical judgment may yield substantial advances in clinical assessment and treatment. A different clinical psychiatry is available and can be practiced now.

• *Clinical judgment, Clinimetrics, Evidence-based medicine, Conflict of interest, Mental disorders*

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George Engel (1) differentiated between "scientific physicians" (clinicians who fully apply the scientific method in their care of patients and in their understanding of the disease) and "physician-scientists" (physicians whose primary commitment is to scientific research pertaining to medicine and who have little or no familiarity with the clinical process). Clinical practice is the source of fundamental scientific challenges for scientific physicians, whereas the application of basic (including pharmaceutical) research is the preferred focus of physician-scientists. Part of the challenge and, at the same time, fascination of being a clinician lies in applying scientific methods in the care of patients and in understanding disease (2). Greater knowledge should result in significant benefits for the patients, and in a sense of continued development on the part of the physician. We are witnessing, however, a progressive detachment of clinicians from research, which is often accompanied by a sense of personal stagnation and tiredness (2). This detachment is mainly the reflection of an intellectual crisis that became more and more manifest in recent years (1–3). Psychiatrists are constantly reminded that genetics and neurosciences are going to transform and improve their practice. Biomarkers are considered the stairway to such a shift (4) and leading journals, such as the *American Journal of Psychiatry* and the *Archives of General Psychiatry*, are pursuing this perspective. Psychiatrists may share this optimism and wait for this event. Nothing has really come in the past two decades (5, 6), as exemplified by the field of psychiatric genetics (7), but we may be really close. 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

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than the science of psychopathology (8) and clinical judgment (9).

The proliferating connections between scientists and the industry, with ensuing conflicts of interests, have brought the credibility of clinical medicine into a crisis (10). Not surprisingly, in view of its characteristics, psychiatry has been particularly vulnerable to this loss of credibility (11, 12). Corporate interest has resulted in self-selected academic oligarchies (special interest groups) that influence clinical and scientific information (10). Members of special interest groups, by virtue of their financial power and close ties with other members of the group, have the task of systematically preventing dissemination of data that may be in conflict with their interests. The first target is to undermine the critical individual judgment of the physicians. The intellectual freedom portrayed by scientific physicians, in particular, is the worst enemy of special interest groups, and thus required massive doses of censorship. Censorship may take different forms: direct suppression of information by special interest groups who act as editors and reviewers or make choices in scientific programs; careful selection of the literature in a biased direction and manipulated interpretation of clinical trials (including those supported by public sources); self-censorship (when an investigator omits of raising questions and criticism for the fear of retaliation) (10).

Not all conflicts of interest in psychiatry are of a financial nature (personal recognition, career advancement, visibility in the media, favoring a friend or relative, the allegiance to a school of thought, political commitment, rivalry between experts, representation of a certain professional society, involvement in specific educational activities). However, the conflicts concerned with financial matters have achieved prominence in the past decade and have endangered a pluralism that existed before (10).

In this review, the detrimental effects of pharmaceutical psychiatry on shaping clinical orientations of physicians and how clinical research concerned with clinical judgment and new political attitudes may foster a renaissance of psychiatry as a medical discipline are examined.

Evidence-based medicine and clinical judgment

Chomsky's (13) mechanisms of propaganda may apply to what has occurred in medicine in the past two decades. Corporate interests have fused with academic medicine to create an unhealthy alliance that works against objective reporting of clinical research (censorship), sets up meetings and symposia with the specific purpose of selling the participants to the sponsors (engineering opinions), gets its prodigal experts into leading role in journals, medical associations and non-profit research organizations (using the public relations industry), and provides the appropriate degree of retaliation to outliers (marginalizing dissident cultures). When, in the early 1990s, these mechanisms became operational in psychiatry, there were several important obstacles: the presence of independent studies that could challenge sponsored findings, the potential influence of uncontrolled review articles and opinions by scientific physicians, the stubborn reliance of psychiatrists on clinical judgment despite evidence-based medicine, and the type of clinical research that was performed.

All four aspects were taken care of and the clinician who wanted to retain a cautious and balanced attitude felt like the person whom Chomsky depicts as sitting alone in front of the TV, thinking he/she must be crazy or outdated for not buying what comes out of the tube (13).

The pseudoscience of meta-analyses

In the mid-1990s, Alvan R. Feinstein (14) compared meta-analyses to the alchemy that existed before modern scientific chemistry. The analogy was the hope to convert existing things into something better (changing base metals into gold) and the work with material that was heterogeneous and poorly identified. Mixing together studies of different qualities and characteristics could only lead to violation of scientific principles of precision and homogeneity. It is a common belief that meta-analyses provide an objective appraisal of the state of the art in a specific field. Actually, during the developments of these analyses, there are many steps that may involve highly subjective choices (14–16): formulation of the question, collection of studies (published versus unpublished, databases, key-words, etc.), criteria for eligibility and selection of studies, evaluation of risk of bias, methods of data extraction and analysis, choice of assessment criteria, presentation of results and interpretation of data. All these issues may be affected by conflict of interest (16). However, authors of meta-analyses are only required to disclose their financial interests and are unlikely to detail the source of funding of the studies that were included (16).

The example of benzodiazepines

A recent meta-analysis that was concerned with drug treatment of generalized anxiety disorder (17) provides an illustration of how conflict of interest may affect the process. A pharmaceutical firm conceptualized and designed the study, and commissioned two of the authors, who work in a private medical communications company, to conduct the systematic review and meta-analysis, and prepare the manuscript. Two other authors, who were university employees, performed a critical review of the results and assisted in the development of the manuscript. The study was allegedly independent, yet all authors had financial ties to the funding firm and other pharmaceutical companies that manufactured drugs that were included and discussed in the meta-analysis. The expert who was commissioned to write the accompanying editorial (18)

also had financial ties with a number of the pharmaceutical companies that manufactured drugs that were included and discussed in the meta-analysis. A systematic review of randomized controlled drug trials was performed and, by use of probabilistic mixed-treatment meta-analysis, concluded that two antidepressant drugs had advantages over other treatments in generalized anxiety disorder. These conclusions were challenged by an editorial that appeared in another journal (19). Trials were selected if they could allow determination of "response" (the proportion of patients who experienced a reduction of at least 50% of their baseline score on the Hamilton Anxiety Rating Scale) and remission (the proportion of patients below a certain cut-off on the scale). The authors failed to justify the choice of outcome measures, which has the major disadvantage of being affected by different characteristics of trials, maximizing the systematic tendency of meta-analyses to violate the internal validity of the placebo comparison. The procedure excluded a great number of investigations concerned with older and low-cost medications, such as benzodiazepines, despite a large body of evidence pointing to their efficacy in generalized anxiety disorder (19). Berney et al. (20) reviewed of controlled trials on anxiety disorders that compared antidepressant drugs with benzodiazepines and could identify only one trial with newer antidepressants. They concluded that the major change of prescribing patterns from benzodiazepines to newer antidepressants in anxiety disorders occurred without any comparative evidence (20). A major drive in the change was the risk of dependence with benzodiazepines, even though withdrawal symptoms frequently occur with newer antidepressants upon tapering and discontinuation (21), even in optimal conditions, and do not necessarily subside within a few weeks (22).

The weight of meta-analyses

As often happens with innovations, the weight given to meta-analyses is likely to be reconsidered in due course: statistically significant meta-analyses of clinical trials have been found to have modest credibility and inflated effects (23). Clinical reviews which focus on the methodological appraisal of individual studies and their clinical integration in practice tend to be regarded as less "scientific" than meta-analyses, whereas just the opposite is true (14). Combining heterogeneous studies in meta-analyses may only lead to inconclusive results (24) and negative treatment trials tend to go unpublished despite registration (16). Careful analyses of individual studies, with appropriate mention to conflict of interest issues, are the actual best-evidence syntheses.

The intellectual poverty of systematic reviews

The traditional review article with one or two experts who review the literature drawing from their clinical experience tends to be substituted by systematic reviews, with increasingly complicated and cumbersome procedures that require a working team (25). Detailing literature searches and getting as close as possible to a comprehensive coverage of the literature are of course welcome targets, even though these procedures were generally endorsed by traditional reviews (disdainfully tagged as "narrative"). However, this does not necessarily occur with systematic reviews, as the following personal example concerned with bipolar disorder outlines.

Reviews on bipolar disorder

When Robert Kellner and I published a review on prodromal symptoms of affective disorders, including bipolar disorder (26), I had gone through the literature both with a computerized (Medline) and manual search, including the heavy volumes of the Index Medicus and discussed all the issues with my co-author. I had personally interviewed the patients in a specific study on prodromes of bipolar disorder (27). The conclusion was that there was high interindividual variability between patients, which did not allow recognition of a specific prodromal phase (26). However, prodromal symptoms tended to be consistent within the same individual, i.e. an affective episode tended to begin in the same way for the same patient and this allowed room for early intervention. Indeed, years later a randomized controlled trial demonstrated the feasibility of this approach (28), which was further confirmed by subsequent trials concerned with psycho-education (29). I updated the review in 1999 (30); there was no substantial change in conclusions compared with 1991, as well as it was found to be the case in an independent review that appeared in 2003 (31), but other implications were added. In 2010 (32) and 2011 (33), two systematic reviews on prodromes of bipolar disorder were published. The first paper (32) failed to cite previous reviews (26, 30), but even more importantly, did not include the investigations that were discussed in those reviews. The conclusion was typical of current systematic reviews: "More well-designed in-depth studies, including qualitative ones, are needed to characterize the initial bipolar prodrome" (32, p. 126). The same omissions took place in the other paper (33), despite the fact that one of the missing reviews had been published in the same journal (30). The authors of this 2011 paper (33) identified specific clinical features preceding bipolar disorder and ventured in postulating primary and secondary interventions. A note of caution was of course added: "Large-scale longitudinal studies are needed to validate these features and characterize their specificity and sensitivity in independent samples" (33, p. 1567). I wish these authors were simply aware of what had actually been published before advocating new studies.

Systematic or critical reviews?

I am afraid that cumbersome instructions that require a large team of authors (six in the 2011 review) do not

prevent major omissions that are functional to specific hypotheses or end up to state that the evidence is too limited and further studies are needed, as was found to be the case in more than half of Cochrane reviews (34). Laupacis & Straus (34) remark that the traditional review has its virtues: the expert interprets research findings in light of clinical experience and judgment, particularly where the evidence is limited. If he/she distinguishes between evidence and opinion, this approach can be much more helpful to clinicians and policymakers.

The reliability of reports of studies funded by the pharmaceutical industry has been seriously questioned (10). Researchers with financial conflicts of interest are more likely to publish articles (original investigations, editorials, systematic and non-systematic reviews, meta-analyses) that support the products of the companies with which the researchers have financial ties (10). Simple disclosure of financial conflicts of interest is not regarded as sufficient for original investigation funded by pharmaceutical companies, and strategies for minimizing biases have been suggested, such as ensuring that at least one author who is not employed by a commercial firm has full access to all of the data and the use of an independent biostatistician (35). Surprisingly, however, little has been proposed to minimize bias in other types of papers, and particularly systematic reviews and meta-analyses (16, 25, 35). When these latter papers have been supported by the industry, by means of funding or authors' ties, they have been found to reach conclusions that favored sponsors' interests more than independent meta-analyses (16).

Journals policies and reviews

There is the need for a reassessment of journals' policies concerned with this type of paper. In line with what has been suggested for authors of clinical practice guidelines (35), meta-analyses should only be conducted by investigators free of substantial conflicts of interest (10). The definition of conflict of interest can be, however, less stringent than that endorsed by American professional medical societies (36). It can be suggested that a researcher meets the criteria for the presence of substantial conflict of interest when he/she is an employee of a private firm, and/or is a regular consultant or on the board of directors of a firm, and/or is a stockholder of a firm related to the field of research and/or owns a patent directly related to the published work (10). The threshold for determining conflict of interest is thus based on the continuity of a financial relationship with a private company. Occasional consultancies, grants for performing an investigation, or receiving honoraria or refunds for specific occasions would not be a source of substantial conflict of interest. Rewarding those researchers who are free from binding financial ties may avoid inappropriate publication of reviews driven by financial incentives and aimed at overshadowing truly independent and high-quality individual studies. Familiarity with the clinical process and intellectual independence can make quite a difference in the way the literature is examined.

Evidence-based medicine as Leitkultur

The concept of evidence-based medicine, from its inception in the early 1990s, has achieved wide currency and enthusiastic endorsement in all areas of clinical medicine, including psychiatry. Feinstein & Horwitz (37) were among the first to warn about the dangers of excessive reliance on randomized controlled trials and meta-analyses. An issue that is neglected is the fact that, when transferred to clinical medicine from their origins in agricultural research, randomized trials were not intended to answer questions about the treatment of individual patients (37). The results may show comparative efficacy of treatment for an average randomized patient, but not for pertinent subgroups formed by characteristics such as severity of symptoms, comorbidity and other clinical nuances. Feinstein & Horwitz (37) also warned against the authoritative aura given to collections of "best available evidence", which may lead to major abuses that produce inappropriate guidelines or doctrinaire dogmas for clinical practice. The risk is particularly serious in view of the fact that financial conflicts of interest are substantial in medical societies and guidelines authors (10, 38). This has been found to apply also to the psychiatric field (39, 40).

Special interest groups are thus using evidence-based medicine to enforce treatment through guidelines, advocating what can be subsumed under the German language term of "Leitkultur", which connotes the cultural superiority of a culture, with policies of compulsory cultural assimilation. In psychiatry, such process has achieved strong prescribing connotations (41), with a resulting neglect of psychosocial treatments.

As Healy (41) remarks,

> … randomized placebo-controlled trials originated as efforts to debunk therapeutic claims, but the force field in which medicine is now practiced has transformed them into technologies that mandate action (…) Where the placebo arms of antidepressant, antipsychotic or mood stabilizer trials suggest we should not be using the drugs as readily as we do, the trials of these products, embodied in guidelines, have instead become a means to enforce treatment. (41, p. 200)

Use of clinical judgment is thus viewed as a dangerous departure from established patterns, instead of exercise of critical thinking.

The inadequacy of current research designs and strategies

Elena Tomba (42) observed that the standard randomized controlled trial design is still based on the acute disease

model and ideally evaluates therapeutic effects in untreated patients who have a recent acute onset of their disturbances. This is in sharp contrast with the fact that, particularly in psychopharmacology, the patient is likely to have experienced other treatments before and these treatments may actually modify the course and responsiveness of the individual patient (21). Under ordinary conditions, patients are included in a trial regardless of their treatment history. The heterogeneous features of these that "nowhere patients" would then affect the outcome of the trial. Meta-analyses of these nowhere groups of patients may amplify the heterogeneous nature of the patient populations (19), particularly if random effects models where endorsed (24) and trials had different rates of participation (43). Moving from the Beatles (nowhere patients) to the Talking Heads, we may add that pathophysiological studies of these patient populations end up being a "road to nowhere". The progress of neurosciences in the past two decades has often led us to believe that clinical problems in psychiatry were likely to be ultimately solved by this approach. Such hopes are understandable in terms of massive propaganda operated by biotechnology corporations (44) and reaction to a long prevalence of "brainless" approaches (45). An increasing number of psychiatrists are wondering, however, why the cures and clinical insights that neurosciences have promised have not taken place. Biological reductionism (2) has resulted in an idealistic approach, which is quite far from the explanatory pluralism required by clinical practice. Kendler (46), Van Praag (47) and Belmaker (48) have been outspoken critics of this reductionism. Neurosciences have exported their conceptual framework into psychiatry much more than serving as an investigative tool for addressing the questions addressed by clinical practice.

An example may be provided by the problems related to the loss of clinical effects during long-term antidepressant treatment (21). The return of depressive symptoms during maintenance antidepressant treatment was found to occur in 9–57% of published trials (49). Pharmacological tolerance, loss of placebo effect, increase in disease severity, change in disease pathogenesis, accumulation of a detrimental metabolite, unrecognized rapid cycling and prophylactic inefficacy have been suggested as possible explanations (49). Psychosocial factors, such as the role of life events in causing depressive relapse during maintenance treatment (50), have not been considered. Also the literature on differential neurobiological effects of psychosocial treatments compared with pharmacotherapy is scarce (51). There is virtually no exploration of the neurobiological correlates of the loss of clinical effects, despite its clinical importance and the practical implications that research in this area would entail (21). At the same time, the amount of research attempting a neurobiological characterization of a highly heterogeneous clinical phenomenon such as depression is immense. But what is its translational value?

The reveille of clinical judgment

In 1967, Alvan Feinstein dedicated a monograph to an analysis of clinical reasoning that underlies medical evaluations, such as the appraisal of symptoms, signs and the timing of individual manifestations (52). In 1982, he introduced the term "clinimetrics" (53) to indicate a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy. Such issues include the types, severity and sequence of symptoms; rate of progression in illness (staging); severity of comorbidity; problems of functional capacity; reasons for medical decisions (e.g. treatment choices), and many other aspects of daily life, such as well-being and distress (54, 55). The customary clinical taxonomy in psychiatry does not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis (56). Clinimetric research in psychiatry has yielded important insights as to the role and function of clinical judgment (56, 57).

Staging

A first strategy is concerned with staging. It differs from the conventional diagnostic practice in that it defines not only the extent of progression of a disorder at a particular point in time, but also where a person is currently along the continuum of the course of illness. Staging methods for unipolar depression, bipolar disorder, panic disorder and schizophrenia, which outlined the basic steps of development of a psychiatric disorder, ranging from the prodromal to the residual and chronic forms, in a longitudinal view of development of disturbances, have been developed (56, 58, 59), together with. specific instruments (60, 61). In two randomized controlled trials (62, 63), psychotherapeutic intervention was applied according to a staging method and was found to yield long-term benefits (64, 65).

Unitary concepts

A second approach involves building unitary concepts from apparently scattered phenomena. Tyrer and associates (66) remarked that what is shared by syndromes such as anxiety, panic, phobic disturbances and irritability may be as important as the differences between them and conditions that are apparently comorbid could be part of the same clinical syndrome. They argued that the combination of mixed anxiety and depressive disorders together

with a certain type of abnormal personality, constitute a single syndrome, the general neurotic syndrome (66), in line with the traditional concept of neurosis, in its phenomenological (67) and psychodynamic (68) traditions. The syndrome was shown to be associated with a poor response to treatment, frequent symptoms throughout the neurotic diagnostic spectrum and tendency to relapse (66). A related strategy deals with the concept of allostatic load, the cumulative effects of stressful experiences in daily life (69).

Subtyping

A complementary strategy has to do with subtyping and differentiating within a diagnostic entity. The need for subtyping major depressive disorder, since this category is too broad to yield meaningful treatment implications, has been recently underscored (70–72). The basic assumption is that clinical manifestations that share the diagnosis of major depressive disorder may display substantial differences in prognostic and therapeutic terms (70–72). If a rating scale is no more than a particular way of recording clinical judgment (73), careful symptom discrimination by interviewing may allow the attribution of differential emphasis on specific symptoms. In clinimetrics, major and minor symptoms may be discriminated, unlike in psychometrics, where all items are weighed the same (55). A recent example was provided by the use of an item of the Clinical Interview for Depression (74), reactivity to social environment, to characterize the clinical features (75) and response to treatment (76) of cyclothymic disorder.

The clinimetric perspective

The clinimetric perspective provides an intellectual home for the reproduction and standardization of the clinical intuitions (56). If associated with a broader cultural movement, it may address many of the difficulties that psychiatry is currently encountering. Pharmaceutical psychiatry is leading to a marginal role of the specialty in the medical system and to a perceived restriction of the psychiatrist's role to prescribing and signing forms, limiting opportunities to engage in the kind of integrated care that attracted many physicians to the field (77). There is increasing awareness of the limitations of current treatment strategies that are unable to provide recovery in the majority of patients (77). The case of major depression is particularly illustrative (78), including the fact that there are no significant differences between treatments provided by psychiatrists compared with primary care physicians (79).

Beyond the concept of disease: the emerging role of macro-analysis

In most instances of diagnostic reasoning in psychiatry, the process ends with the identification of a disorder, often subsumed under a rubric of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (80). A single assessment generates the prognostic and therapeutic judgments of the clinician. A DSM diagnosis (e.g. major depressive disorder), however, encompasses a wide range of manifestations, comorbidity, seriousness, prognosis and responses to treatment. The majority of patients with mood and anxiety disorders do not qualify for one, but for several axis I and axis II disorders (81).

Feinstein, when he introduced the concept of comorbidity, referred to any "additional co-existing ailment" separate from the primary disease, even in the case this secondary phenomenon does not qualify as a disease *per se* (82). Indeed, in clinical medicine, the many methods that are available for measuring comorbidity are not limited to disease entities (83). Unfortunately, in the DSM comorbidity has been used only in reference to additional diagnoses, and not to indicate significant problems, situations and subthreshold conditions.

Macro-analysis

A method has been developed in psychiatry for organizing clinical data as variables in clinical reasoning. Emmelkamp et al. (84) have introduced the concept of macro-analysis (a relationship between co-occurring syndromes and problems is established on the basis of where treatment should commence in the first place) in anxiety disorders. This method has been extended to mood disorders (56), psychosomatic assessment (85) and drug dependence (86). Macro-analysis starts from the assumption that in most cases there are functional relationships with other more or less clearly defined problem areas and that the targets of treatment may vary during the course of disturbances (56).

Diagnostic transfers

Feinstein (87) remarks that, when making a diagnosis, thoughtful clinicians seldom leap from a clinical manifestation to a diagnostic endpoint. The clinical reasoning goes through a series of "transfer stations", where potential connections between presenting symptoms and pathophysiological process are drawn. These stations are a pause for verification, or change to another direction (87). The use of diagnostic transfer stations has been suggested by the sequential treatment model (29, 88), an intensive, two-stage approach, which includes the use of one treatment (e.g. psychotherapy) after remission has been achieved with another (e.g. pharmacotherapy). The sequential model relies on repeated assessments (after each line of treatment has been completed) that may modify an initial diagnosis (e.g. pre-existing anxiety disturbances may emerge after pharmacotherapy of a major depressive episode). It recognizes that for most patients a single course of treatment is insufficient for yielding adequate improvement and that different combined or

sequential approaches may be necessary. The traditional psychiatric paradigm still endorses the conviction that psychotropic drugs work by acting on a disease process, which the propaganda translates into "curing" psychiatric disease. However, there is substantial evidence to call such views in question (89).

New research on clinical judgment

In 1967, Alvan Feinstein (52) 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, which affects clinical decision making (90), has been neglected (56). 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 (56). The use of transfer stations with repeated assessments instead of diagnostic endpoints, the building of global formulations of clinical integration, staging methods, an expansion and a better organization of clinical information, encompassing subclinical distress (30), illness behavior (91), lifestyle (92) and psychological well-being (93–95) may be an antidote to oversimplified models that derive from biological reductionism, neglect individual responses to treatment and clash with clinical reality (56). 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 and obfuscated by marketing strategies, the focus of neurobiological research is set for random effort and misunderstanding.

Research designs and strategies

An intervention can be either evaluated by a single large trial or by a series of smaller trials (96). The current standard of therapeutic trial in psychiatry nowadays is represented by the US large, multi-center, controlled, randomized trial with very specific inclusion and exclusion criteria, but little attention to the clinical history of patients (42). Not surprisingly, however, the conclusions that can be drawn by these trials are very limited and offer trivial variations on tired themes. An increasing number of researchers has no familiarity with the clinical process and their research indeed reflects their naiveté. In the meanwhile, pharmaceutical medicine is taking full advantage of the clinical vacuum, providing directions with massive doses of propaganda.

If we peruse the literature for clinical studies concerned with samples homogeneous for treatment history, we may find out that we do not even have adequate information from observational studies or open therapeutic trials (21). Borm & Donders (96) have suggested that a series of small trials with at least 30% power is preferable to a single large one. These small trials may actually provide important clinical information that is immediately helpful to the clinician encountering that specific patient. This strategy would actually constitute a paradigm shift in psychiatry. Conflicting results among randomized controlled trials can represent a spectrum of outcomes, based on different patient groups, more than bias or random variability (97).

Regaining intellectual independence

In recent years, the Leitkultur of evidence-based medicine, because of the influence of special interest groups on medical societies and their media (journals, newsletters, meetings etc.), has become the preferred tool of pharmaceutical propaganda.

Its reductionistic approach centered on the average patient hiding the wide fluctuations that may occur in treatment response.

The variability in response

Horwitz et al. (98) developed a method of clinical inquiry within randomized controlled trials that can enhance the applicability of results to clinical decision making. Re-analyzing the Beta-Blocker Heart Attack Trial, they found that propranolol reduced the risk of dying for the "average" patient who survived an acute myocardial infarction, whereas it was harmful in a subgroup of patients characterized by specific cotherapy histories. If we accept the possibility that a treatment that is helpful on average may be ineffective on some and even harmful on someone else, we may learn that a given therapy may not be of value for a particular class or subgroup of patients who are defined in terms of more detailed (compared with the RCT eligibility criteria) specifications of clinical conditions. This may stimulate further research on alternative therapies that could potentially benefit the class of patients defined by the subgroup for whom otherwise effective therapy is providing no benefit or may even be causing harm (98). Many examples may be provided in the field of psychopharmacology (2), such as with the use of atypical antipsychotic drugs (99), as well as in psychotherapy research (100). The pharmaceutical industry obviously wants to avoid the phase of disillusionment, which follows the report of toxic unwanted effects, after an initial stage of enthusiasm for the "wonder drug", which is then prescribed excessively and inappropriately (2). As a result, the pharmaceutical industry is likely to censor, with the help of special interest groups, who act as editors, reviewers and consultants

to medical journals and non-profit research organizations, any data suggesting that a specific drug may also lead to a worse outcome. Of course, subgroup analyses can entail serious methodological problems, such as multiplicity concerns (101) and advanced specification of subsets (102). Yet, these analyses are in line with the object of clinical inquiry (103).

The specificity of clinical science

Engel identified the key characteristic of clinical science in its explicit attention to humanness, where observation (outer-viewing), introspection (inner-viewing) and dialogue (inter-viewing) are the basic methodological triad for clinical assessment and for making patient data scientific (104). The exclusion of this interaction by medical science's continuing allegiance to a 17th-century scientific world view makes this approach unscientific (105). 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" (105, p. 14). Not surprisingly, the evidence-based medicine educated clinician is often not geared to tackle complex clinical problems conceptually.

A reappraisal of evidence-based medicine

Evidence-based medicine certainly gave an important historical contribution to the scientific development of medical literature in the past two decades. The time has come, however, to become aware of its considerable limitations, overall reductionism, insufficient consideration of problems related to financial conflicts of interest, disregard of the patient–physician relationship (including patient's preferences) and the need for integration with clinical judgment. Not only do guidelines need to be individualized (106), but alternative ways of assessing evidence should be explored. For instance, in discussing treatment options in depression, the choice of the main evidence-based treatment ingredients in depression (pharmacotherapy and psychotherapy) can be placed in the context of clinical judgment (107), outlining the advantages and disadvantages that each treatment selection carries.

The role of scientific societies

The scientific societies that underlie the guideline-making process do not provide an adequate background for intellectual independence (10). Furthermore, society meetings are still held on an annual basis, causing major ecological wastes due to thousands of people travelling for reaching the sites, and reflect a 20th-century communication paradigm, where meetings were of the main source of scientific novelties compared with printed journals. At a time of information available to scientific community through the web system, scientific meetings should offer the opportunity for in-depth discussions of scientific physicians with no substantial conflict of interest as defined elsewhere (10). This process of regaining intellectual independence not only involves researchers, but each clinician and society member. I recently refused to pay the American Psychiatric Association annual dues, because of the dramatic inadequacy of the society in handling the issues related to conflict of interest and clinical challenges. Such stands have personal costs, but are in line with the expression of intellectual freedom.

Conclusions

Often, in their clinical practice, psychiatrists use sophisticated forms of clinical judgment that are suitable for clinical challenges, but are not addressed by current research strategies. A renewed interest in the process of clinical judgment (56) and in psychopathology as a science (8) may entail solution to the current impasse of psychiatric research and practice. The notion of psychiatric disease is not in line with the changed spectrum of health and the complex interplay of biological and psychosocial factors (56). Evidence-based medicine leads to undertreatment, overtreatment or mistreatment, and is not geared to the complexity of clinical situations. Alternative models that articulate the clinical process may pave the way to a renewal of the appraisal of clinical judgment in psychiatry.

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